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Clinical Protocol CA209915

A Phase 3, Randomized Study of Adjuvant Immunotherapy with Nivolumab Combined with Ipilimumab Versus Nivolumab Monotherapy after Complete Resection of Stage IIIb/c/d or Stage IV Melanoma

(CheckMate 915: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 915)

Revised Protocol Number: 03
Incorporates Administrative Letters 04 and 05

Study Director / Medical Monitor
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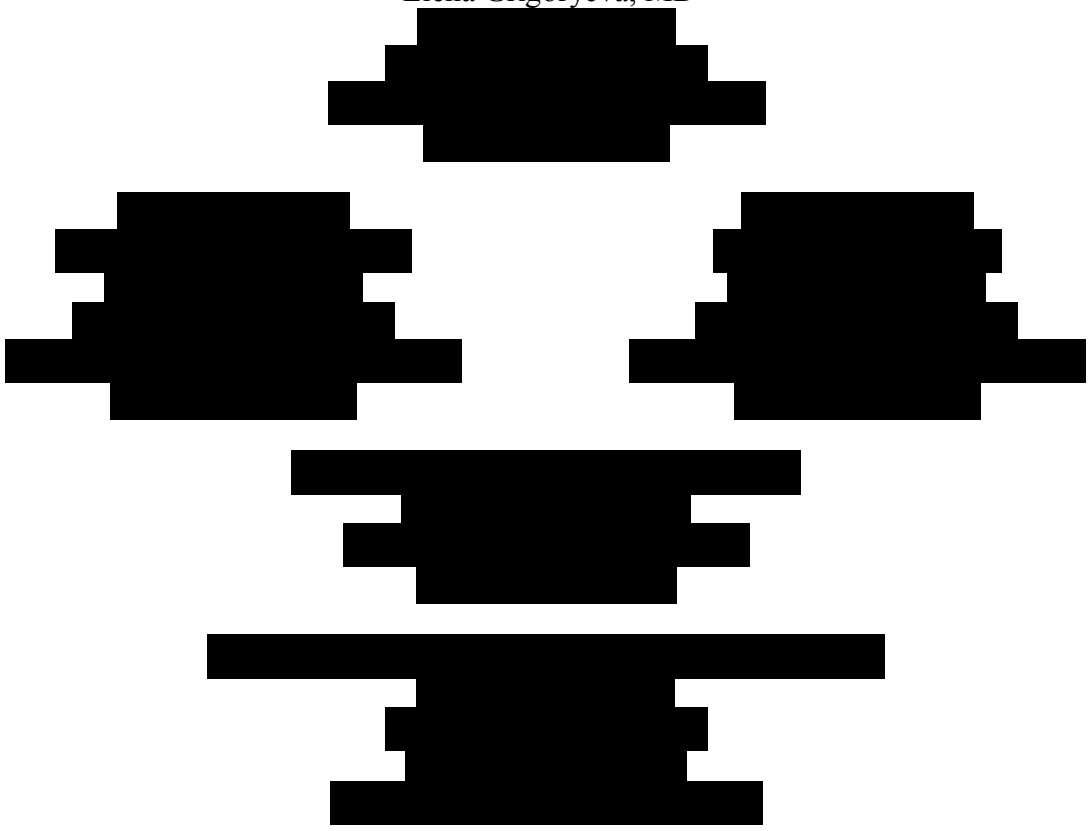

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Replace all previous version(s) of the protocol with this revised protocol and please provide a copy of this revised protocol to all study personnel under your supervision, and archive the previous versions.

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 03	11-Mar-2019	Incorporates administrative letters 04, and 05. Updates to this protocol include, additional medical monitor, continued treatment for malignant melanoma in situ, modification of the statistical design to evaluate RFS after a sufficient period of minimum follow-up, evaluation of the surrogate endpoint Progression-Free Survival 2 (PFS2), and assessment of quality of life for 4 years in survival follow up.
Administrative Letter 05	22-May-2018	The purpose of this letter is to advise of an additional Medical Monitor for the study, to clarify the criteria for treatment resumption and discontinuation, to add *phosphate* to laboratory test done during On-Treatment visits and clarify the laboratory assessments done during follow-up visits.
Administrative Letter 04	23-Feb-2018	This Administrative Letter is to clarify the study design regarding the age of adolescents and dosing of Nivolumab including the date of implementation of this design change. In addition, this letter corrects inconsistencies and typographical errors.
Revised Protocol 02	12-Dec-2017	The purpose of this revised protocol is to modify the study design based on changes in the knowledge in the management of melanoma, and possible similarities in the pattern of efficacy by PD-L1 expression in adjuvant and metastatic settings. To understand the impact on sequencing of therapies the exploratory objective of evaluation of investigator-assessed outcomes on next-line therapies was added. In addition, the protocol now clarifies the Schedule of Activities for participants during Arm C open label visits. Also incorporates Administrative Letter 03
Administrative Letter 03	18-Aug-2017	This Administrative Letter is to clarify the study visits that will need to be completed by the subjects randomized to Arm C after they are un-blinded (per Amendment 6) and a decision is made to continue treatment with ipilimumab 10 mg/kg or to switch to nivolumab 480 mg every 4 weeks. Also an inconsistency regarding the duration of the ipilimumab infusion will be clarified.
Revised Protocol 01	20-Jul-2017	Incorporates Amendment 06 and Administrative Letters 01 and 02
Amendment 06	20-Jul-2017	This purpose of this amendment is: • Remove treatment Arm C for Ipilimumab 10 mg/kg. • Reduce infusion time for Ipilimumab from 90 minutes to 30 minutes • Clarify the duration of post-treatment contraception

Document	Date of Issue	Summary of Change
Administrative Letter 02	05-Apr-2017	This Administrative Letter clarifies the Inclusion Criteria for participants with prior anti-cancer therapy which is currently reflected only in the Exclusion Criteria, Prior/Concomitant Therapy. Also inconsistencies about study procedures are clarified.
Administrative Letter 01	09-Mar-2017	This administrative letter clarifies the laboratory assessment for performing TSH with reflexive Free T4 and Free T3 if TSH is abnormal from D1Wk1 to D1Wk9. Also clarifies to perform thyroid panel, ACTH and Cortisol as indicated in the Schedule of Assessments (Section 2) but not mentioned in the table of laboratory assessments in Section 9.4.4. Urinalysis assessment is not needed for this protocol and has been removed from the table of laboratory assessments indicated in Section 9.4.4.
Original Protocol	20-Dec-2016	Not Applicable

[redacted]

[redacted]

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03

Section Number & Title	Description of Change	Brief Rationale
Title Page	Revised for additional Medical Monitor.	[redacted]
Section 2, Schedule of Activities, Table 2-2, On-Treatment Assessments Week 1 - Week 9 (CA209915) (Participants on Arm A or Arm B), Laboratory Tests	Phosphate was added to the list of laboratory assessments performed with 72 hours prior to dosing. Previously written: Within 72hrs. prior to dosing to include CBC w/differential, AST, ALT, ALP, T.Bili, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, Glucose, TSH (with reflexive FreeT4 and FreeT3 if TSH is abnormal) Albumin, ACTH, cortisol, amylase, and lipase as clinically indicated. Changed to: Within 72hrs. prior to dosing to include CBC w/differential, AST, ALT, ALP, T.Bili, BUN or serum urea level, creatinine, Ca, **Phosphate**, Mg, Na, K, Cl, LDH, Glucose, TSH (with reflexive FreeT4 and FreeT3 if TSH is abnormal) Albumin, ACTH, cortisol, amylase, and lipase as clinically indicated.	[redacted]
Section 2, Schedule of Activities, all tables excluding Table 2-1 and Table 2-8.	Regarding Outcome Research Assessments, added the following: Adolescents should only complete the EQ-5D and not the EORTC QLQ-C30 or AI:GH.	[redacted]

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03

Section Number & Title	Description of Change	Brief Rationale
Section 2, Schedule of Activities, Table 2-10, Follow-up Procedural Outline, Adverse Events Assessment	Previously written: Immune-mediated adverse reactions should be followed until stabilization. Nonimmunemediated adverse reactions should be followed until resolution or stabilization. Changed to: Record at each visit. Collect continuously throughout the treatment period and for a minimum of 100 days following discontinuation of dosing.	[redacted]
Section 2, Schedule of Activities, Table 2-10, Follow-up Procedural Outline, Laboratory Test: Notes	Previously written: CBC w/ differential, chemistry panel, thyroid test for Follow-up Visit 1 (repeat at Visit 2 if toxicities are present) Changed to: CBC w/ differential, chemistry panel, thyroid test for Follow-up Visit 1 (repeat at Visit 2 if toxicities are present). **Refer to Section 9.4.4 Clinical Safety laboratory Assessments for list of laboratory test**.	[redacted]
Section 2, Schedule of Activities, Table 2-10, Follow-up Procedural Outline, Outcomes Research Assessment: Notes for EQ-5D-3L	Previously written: Every 3 months (±14 days), maybe accomplished by visit or phone contact for up to 2 years after follow up visit 2 Changed to: Every 3 months (±14 days), maybe accomplished by visit or phone contact for up to **4** years after follow up visit 2	[redacted]
Section 3.2, Background, under heading title Nivolumab + Ipilimumab Combination in Metastatic or Unresectable Melanoma	A paragraph was added regarding the new secondary endpoint of PFS2.	[redacted]
Section 4, Objectives and Endpoints, Table 4-1, and Synopsis, Objectives and Endpoints	Secondary Objectives and Endpoints, and [redacted] Endpoints were revised.	[redacted]

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03

Section Number & Title	Description of Change	Brief Rationale
Section 5.1, Overall Design, second dashed-bullet item, and Synopsis, Overall Design	Previously written: For adolescents between 12 and 18 years of age the dosing of nivolumab is body weight based dosing as follows: Q2 week dosing - 3 mg/kg IV Q2 weeks up to a maximum of 240 mg; Q4 week dosing - 6 mg/kg Q4 weeks up to a maximum of 480 mg. The change will be implemented upon IRT modification. Changed to: For adolescents between 12 to <18 years of age the dosing of nivolumab is body weight based dosing as follows: Q2 week dosing - 3 mg/kg IV Q2 weeks up to a maximum of 240 mg; Q4 week dosing - 6 mg/kg Q4 weeks up to a maximum of 480 mg. This will be applicable for participants enrolled after IRB approval of Revised Protocol 02 and will be implemented upon IRT modification.	[redacted]
Section 5.1, Overall Design, under Follow-up Phase, bullet 6	Previously written: Participants will be followed for drug-related toxicities until these toxicities resolve, return to baseline or are deemed irreversible. All toxicities will be documented for a minimum of 100 days after the last dose of study medication Changed to: Participants will be followed for drug-related toxicities according to the Section 9. All toxicities will be documented for a minimum of 100 days after the last dose of study medication	[redacted]
[redacted]	[redacted]	[redacted]

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03

Section Number & Title	Description of Change	Brief Rationale
Section 7.1, Treatments Administered, paragraph 1 under Arm A (Nivolumab + Ipilimumab) Dosing; paragraph 1 under Arm B (Nivolumab) Dosing; paragraph 1, under For Participants who switch to Nivolumab 480 mg, Open-label; and Table 7.1-1, Dosing Schedule for Study CA209915, footnote b; Synopsis, Treatment Arms and Duration	Previously written: For adolescents between 12 and 18 years of age the dosing of nivolumab is body weight based dosing as follows: Q2 week dosing - 3 mg/kg IV Q2 weeks up to a maximum of 240 mg; Q4 week dosing - 6 mg/kg Q4 weeks up to a maximum of 480 mg. The change will be implemented upon IRT modification. Changed to: For adolescents between 12 to <18 years of age the dosing of nivolumab is body weight based dosing as follows: Q2 week dosing - 3 mg/kg IV Q2 weeks up to a maximum of 240 mg; Q4 week dosing - 6 mg/kg Q4 weeks up to a maximum of 480 mg. This will be applicable for participants enrolled after IRB approval of Revised Protocol 02 and will be implemented upon IRT modification.	[redacted]
Section 7.2, Method of Treatment Assignment, first dash item under bullet regarding Participants will be stratified by; and Section 7.3, Blinding, last paragraph	Added text allowing that the statistician may be unblinded to the participant's PD-L1 status results.	[redacted]
Section 7.3, Blinding, paragraph 2	Added sentence to paragraph 2: The actual task of unblinding can be delegated by the investigator to a designee assigned the task on the Delegation of Authority	[redacted]
Section 7.3, Blinding, last paragraph	Added text allowing that the statistician may be unblinded to the participant's PD-L1 status results.	[redacted]

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03

Section Number & Title	Description of Change	Brief Rationale
Section 7.4.3, Criteria to Resume Treatment	Previously written: Participants with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the BMS Medical Monitor. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement. Changed to: Participants with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the BMS Medical Monitor. Adrenal insufficiency ≥ **Grade 3** requires discontinuation regardless of control with hormone replacement.	[redacted]
Section 7.7.1, Prohibited and/or Restricted Treatments	Added sentence to bullet 4: Use of marijuana and its derivatives for treatment of symptoms related to cancer or cancer treatment are permitted if obtained by medical prescription or if its use (even without a medical prescription) has been legalized locally Added bullet 5: Any live/attenuated vaccine (eg, varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella (MMR)) during treatment and until 100 days post last dose.	[redacted]
Section 8.1, Discontinuation from Study Treatment	Bullet 3 under Treatment should be permanently discontinued for the following: Myocarditis was added.	[redacted]
Section 8.1, Discontinuation from Study Treatment	Treatment should be permanently discontinued for the following: Previously written: Persistent Grade 2 or 3 immune-mediated adverse drug reactions that last 12 weeks or longer. Changed to: Persistent Grade 2 or 3 immune-mediated adverse drug reactions that last 12 weeks or longer **with exception for Grade 2 endocrinopathies**.	[redacted]

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03

Section Number & Title	Description of Change	Brief Rationale
Section 9.2.1, Time Period and Frequency for Collecting AE and SAE Information	Paragraph 5 (eg, a follow-up skin biopsy) was added	[redacted]
Section 9.2.2, Method of Detecting AEs and SAEs	Added sentence: Every adverse event must be assessed by the investigator with regard to whether it is considered immune-mediated. For events which are potentially immune-mediated, additional information will be collected on the participant's case report form.	[redacted]
Section 9.3, Overdose	Changed to Appendix 5	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03

Section Number & Title	Description of Change	Brief Rationale
Section 10.1, Sample Size Determination, Section 10.1.1.1, RFS in All Randomized Participants with PD-L1 Expression Level < 1%, Section 10.1.1.2, RFS in All Randomized Participants, Section 10.1.2 Overall Survival; and Synopsis, Number of Participants	Section revised regarding RFS.	[redacted]
Section 10.3.1.1, Primary Endpoint Analysis, paragraph 1; Table 10.3.1.1-1, Censoring Scheme for Primary Definition of RFS	Revised to include melanoma *in situ*.	[redacted]
Section 10.3.1.1, Primary Endpoint Analysis	Revisions were made to paragraphs 2, 3, and 4 regarding RFS testing strategy and alpha adjustment	[redacted]
Section 10.3.1.2, Secondary Endpoint Analyses	Headings for "Overall Survival" and "Association between PD-L1 expression and RFS" were added in this section. Added section titled, Investigator-Assessed Outcomes on Next-Line Therapies".	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Section 10.3.4, Interim Analyses and Hierarchical Testing	Revised section regarding RFS testing strategy.	[redacted]
[redacted]	[redacted]	[redacted]
Appendix 4, Study Governance Considerations	Revised language regarding a potential breach of the conditions and principles of Good Clinical Practice. Updated text regarding Study Treatment Records.	[redacted]

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03

Section Number & Title	Description of Change	Brief Rationale
Appendix 5, Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow Up and Reporting	Clarified text regarding: the definition of AE Events, events NOT meeting the AE definition, and the definition of SAEs.	[redacted]
[redacted]	[redacted]	[redacted]
Appendix 8, Revised Protocol Summary of Change History, Summary of Key Changes for Revised Protocol 02, Row 1, Column 3	[redacted]	[redacted]
All	Minor formatting and typographical corrections	[redacted]

[redacted]

TABLE OF CONTENTS

1 SYNOPSIS

Protocol title: A Phase 3, Randomized Study of Adjuvant Immunotherapy with Nivolumab Combined with Ipilimumab Versus Nivolumab Monotherapy after Complete Resection of Stage IIIb/c/d or Stage IV Melanoma (CheckMate 915: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 915)

Study Phase: 3

[redacted]

Study Population:

1) Males and Females, at least 12 years of age, except where local regulations and/or institutional policies do not allow for participants <18 years of age (pediatric population) to participate. For those sites, the eligible participant population is ≥18 years of age.

Inclusion Criteria

a) All participants must be either stage IIIb/c/d or Stage IV AJCC (AJCC Cancer Staging, 8th edition; see also Appendix 1) and have histologically confirmed melanoma that is completely surgically resected in order to be eligible. All melanomas, except ocular/uveal melanoma, regardless of primary site of disease will be allowed; mucosal melanomas are eligible. Participants must have been surgically rendered free of disease with negative margins on resected specimens.

When T is....	And N is.....	And M is....	The pathological stage is...
T0	N1b, N1c	M0	IIIB
T0	N2b, N2c, N3b, N3c	M0	IIIC
T1a/b-T2a	N1b/c or N2b	M0	IIIB
T2b/T3a	N1a-N2b	M0	IIIB
T1a-T3a	N2c or N3a/b/c	M0	IIIC
T3b/T4a	Any N ≥N1	M0	IIIC
T4b	N1a-N2c	M0	IIIC
T4b	N3a/b/c	M0	IIID
Ant T, Tis	Any N	M1	IV

i) If stage III melanoma (whether Stage IIIb or IIIc or IIId) the participants should have clinical or radiographic evidence of regional metastases, either in the regional lymph nodes or locoregional metastases manifesting as satellite or in-transit metastases, or microsatellites discovered at the time of microscopic evaluation of the primary tumor diagnostic biopsy. Participants must have pathological evidence of regional metastases, regional lymph node and/or microsatellite/satellite/in-transit metastases, and no distant metastasis. The pathology report for stage IIIb, IIIc, and IIId must be reviewed, signed and dated by the investigator; this process will be confirmed during the IRT randomization call.

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

iii) For CNS lesion(s), documentation indicating that there has been complete resection of CNS lesion(s) will suffice as confirmation of negative margins

b) Complete resection of stage III disease that is documented on the surgical and pathology reports or complete resection of stage IV disease with margins negative for disease that is documented on the pathology report

c) Complete resection must be performed within 12 weeks prior to randomization

d) All participants must have disease-free status documented by a complete physical examination and imaging studies within 4 weeks prior to randomization. Imaging studies must include CT or MRI scans of the chest, abdomen, pelvis and all known sites of resected disease, and brain magnetic resonance (MRI) or CT (brain CT allowable if MRI is contraindicated or if there is no known history of resected brain lesions). Participants with equivocal lymph nodes ≥ 10 mm and <15 mm in a short axis may be eligible if confirmation with histology/cytology is available. If risk of biopsy is too high or biopsy is not feasible, two sequential CT or MRI scans should be available and showing no progressive and measureable disease or PET/CT demonstrating no FDG uptake. The second scan should occur at least 4 weeks after the initial scan. Lymph nodes ≥ 15 mm in a short axis are defined as pathological.

e) The complete set of baseline images must be available before randomization

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

g) Tumor tissue from the resected site of disease must be provided for biomarker analyses (preferably collected within 12 weeks of assessment time). In order to be randomized, a participant must have quantifiable PD-L1 expression (< 1% or 1%-< 5% or ≥ 5% tumor cell membrane staining) or be classified as PD-L1 indeterminate. If insufficient tumor tissue content is provided for analysis, acquisition of additional archived tumor tissue (block and /or slides) for the biomarker analysis is required.

h) Participants must not have received anti-cancer therapy (for example but not limited to systemic, local, radiation, radiopharmaceuticals) for their melanoma except:

i) Surgery for the melanoma lesion(s)

ii) Adjuvant radiation therapy (RT) after neurosurgical resection for central nervous system (CNS) lesions

iii) Prior adjuvant interferon if completed ≥ 6 months prior to randomization

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

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

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

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

Exclusion Criteria

a) History of ocular/uveal melanoma

b) Weight ≤ 40 kg *"Not applicable as per amendment 07"*

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

d) 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.

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

f) Pregnant or nursing women

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

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

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

i) Treatment with botanical preparations (eg herbal supplements or traditional Chinese medicines) intended for general health support or to treat the disease under study within 2 weeks prior to randomization/treatment.

Objectives and Endpoints:

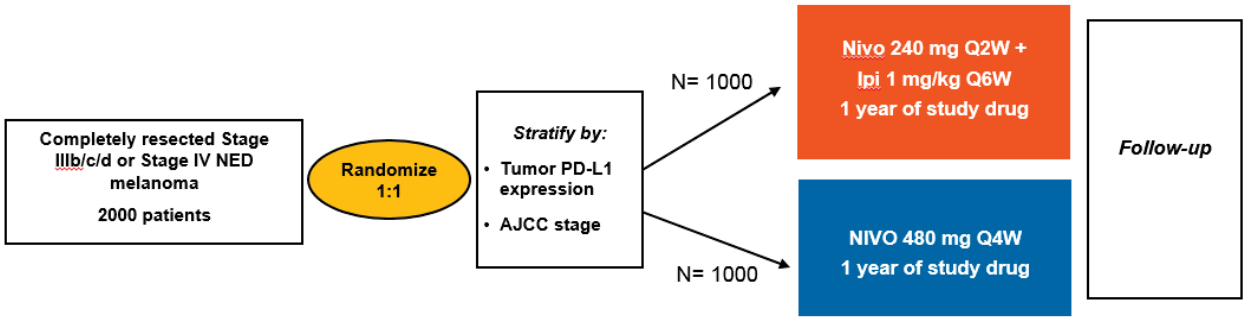
Endpoints: This should be a high level description of the assessments.

Objective	Endpoint
Primary	
• To compare the efficacy, as measured by recurrence free survival (RFS), provided by nivolumab plus ipilimumab versus nivolumab monotherapy in participants with completely resected stage IIIb/c/d or stage IV no evidence of disease (NED) melanoma (in all randomized participants with PD-L1 expression level < 1%. and all randomized participants)	• Recurrence-free survival, RFS
Secondary	
• To compare the overall survival provided by nivolumab plus ipilimumab versus nivolumab monotherapy in participants with completely resected stage IIIb/c/d or stage IV NED melanoma (in all randomized participants with PD-L1 expression level < 1%. and all randomized participants)	• Overall survival (OS)
• To evaluate the association between PD-L1 expression and RFS	• PD-L1 expression • Objective response rates (if applicable) • Duration of treatment on next-line therapies • PFS2 defined as time from randomization to second recurrence/objective disease progression, or death from any cause, whichever occurs first.
To evaluate investigator-assessed outcomes on next-line therapies	End-of-next-line-treatment: To be used for situations where PFS2 cannot be reliably determined. Event defined as end or discontinuation of next-line treatment, second objective disease progression, or death from any cause, whichever occurs first.
[redacted]	
[redacted]	[redacted]

Objective	Endpoint
[redacted]	[redacted]

Overall Design:

This is a Phase 3, randomized, double blind study designed to compare nivolumab plus ipilimumab vs nivolumab monotherapy participants (≥ 12 years) with completely resected stage IIIb/c/d or stage IV no evidence of disease (NED) melanoma.



Participants will be treated with one of the following:

- Arm A: nivolumab 240 mg IV Q2 weeks plus ipilimumab 1 mg/kg IV Q6 weeks (for 1 year of study drug treatment)
- Arm B: nivolumab 480 mg IV Q4 weeks (for 1 year of study drug treatment) with nivolumab placebo on Weeks 3, 7, 11, 15, 19, 23, 27, 31, 35, 39, 43, & 47 and ipilimumab placebo on Weeks 1, 7, 13, 19, 25, 31, 37, 43, & 49
  - The original study design included an ipilimumab monotherapy arm (Arm C). Randomization into Arm C was discontinued upon implementation of Amendment 06. Sites who have randomized participants to the ipilimumab arm will be unblinded to that information and the participants will be allowed to continue as open-label on either ipilimumab 10 mg/kg IV Q3 weeks for 4 doses, then Q12 weeks starting at Week 24 or switch to the nivolumab 480 mg IV Q4 weeks in 8 weeks after the last dose of ipilimumab. The change will be implemented upon IRT modification.
  - For adolescents between 12 to < 18 years of age the dosing of nivolumab is body weight based dosing as follows: Q2 week dosing - 3 mg/kg IV Q2 weeks up to a maximum of 240 mg; Q4 week dosing - 6 mg/kg Q4 weeks up to a maximum of 480 mg. This will be applicable for participants enrolled after IRB approval of Revised Protocol 02 and will be implemented upon IRT modification.

Number of Participants:

Approximately 2000 participants will be randomized in a 1:1 ratio to nivolumab plus ipilimumab versus nivolumab monotherapy and stratified by PD-L1 status (PD-L1 expression < 1% or indeterminate, 1%-<5%, ≥5% tumor cell surface expression) and American Joint Committee on Cancer (AJCC) stage IIIb vs stage IIIc/d vs stage IV (Appendix 1). Accrual will be stopped when approximately 600 participants with PD-L1 expression level < 1% will be randomized in a 1:1 ratio to nivolumab plus ipilimumab and nivolumab respectively. The prevalence of participants with PD-L1 expression level < 1% is expected to be around 30% of all randomized participants. Therefore, it is estimated that approximately 2000 participants will be randomized in a 1:1 ratio to nivolumab plus ipilimumab and nivolumab respectively. No more than 1400 participants with PD-L1 expression level ≥ 1% will be randomized to nivolumab plus ipilimumab and nivolumab respectively In addition, there will be a number of participants that were already randomized to the ipilimumab arm under the original protocol.

The sample size of the study is based on a comparison of the RFS distribution between participants randomized to nivolumab plus ipilimumab and participants randomized to nivolumab. RFS will be evaluated for treatment effect using the following testing strategy: RFS will be compared first in the all randomized participants with PD-L1 expression level < 1% subgroup with an alpha allocation of 0.03 (two-sided); and if significant, the alpha allocated to this subgroup will be recycled to the treatment comparison in the overall population (all randomized participants). Thus RFS will be compared in all randomized participants with an alpha allocation of 0.05 (two-sided). If the treatment comparison in all randomized participants with PD-L1 expression level < 1% is not significant, RFS will be compared in all randomized participants with an alpha allocation based on the method published by Spiessens and Debois[1]. This method takes into account the correlation between the test statistics for the overall and the subgroup analysis, and is essentially the same as the method used when dealing with interim analyses, ie, group sequential method. The alpha allocated to the overall analysis will be calculated based on the fraction of information in the subgroup, relative to the overall population, which is determined by the ratio of events observed in the two groups. For example, if 257 events are observed in the PD-L1 expression level < 1% subgroup, and 651 events are observed in the overall population (ie, about 40% of all events in the PD-L1<1% subgroup), the alpha allocated to the overall analysis is 0.0265.

The sample size is driven by the comparison of RFS between all randomized participants with PD-L1 expression level < 1% randomized to receive nivolumab plus ipilimumab vs nivolumab. Approximately 600 participants with PD-L1 expression level < 1% will be randomized in a 1:1 ratio to nivolumab plus ipilimumab and nivolumab respectively. Approximately 257 RFS events in all randomized participants with PD-L1 expression level < 1% will provide approximately 90% power to detect an average hazard ratio (HR) of 0.65 with an alpha level of 0.03 (two-sided). In case the 257 RFS events would be reached at a timepoint earlier than 13 months of minimum follow-up (from the randomization of the last participant), analysis of RFS will be conducted when there would be a minimum follow up of 13 months (ie, at the time when 257 events are reached or a minimum follow-up of 13 months, whatever occurs later).

Approximately 2000 participants will be randomized in a 1:1 ratio to nivolumab plus ipilimumab and nivolumab respectively. Approximately 700 participants with PD-L1 expression level < 1% were randomized in a 1:1 ratio to nivolumab plus ipilimumab and nivolumab respectively.

Approximately 651 RFS events in all randomized participants will provide approximately 90% power to detect an average hazard ratio (HR) of 0.76 with an alpha level of 0.0265 (two-sided).

The analysis of RFS in the all randomized participants with PD-L1 expression level < 1% subgroup will be performed at the time when 257 RFS events are observed in this subgroup or a minimum follow-up of 13 months is reached, whatever occurs later.

If the treatment comparison in the all randomized participants with PD-L1 expression level < 1% subgroup is significant, RFS will be compared in all randomized participants with an alpha allocation of 0.05. In this case, two analyses, an interim and a final, will be conducted in all randomized participants. The interim analysis will take place at the same time as the RFS analysis for the PD-L1 expression level < 1% subgroup. The final analysis will take place when 560 RFS

events are observed in the overall population. The stopping boundaries at the interim and final analyses will be derived based on the exact number of RFS events using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries.

If the treatment comparison in all randomized participants subjects with PD-L1 expression level < 1% subgroup is not significant, RFS will be compared in the overall population with an alpha allocation based on the method published by Spiessens and Debois.[1] In this case, no interim analysis is planned. The final RFS analysis for the overall population will be conducted when approximately 651 RFS events are observed.

In case the events come slower than projected, final analysis of RFS for the overall population will be conducted when the minimum follow up from randomization of the last participant reaches 30 months.

Given actual accrual rates so far and estimated accrual rates of 157 participants per month for the coming months, it is estimated that accrual of 2000 participants (ie, 1000 participants in a 1:1 ratio in the nivolumab plus ipilimumab and nivolumab arms each) and the participants in the ipilimumab arm that has already taken place, will take approximately 17 months. Given actual accrual rates, accrual took approximately 13.5 months.

Treatment Arms and Duration:

In this protocol, investigational products are nivolumab and ipilimumab.

Table 1-1: Study treatments for CA209915

Product Description/ Class / Dosage Form	Potency	IP/Non-IMP	Packaging / Appearance	Storage Conditions
BMS-936558 Nivolumab Solution for Injection	100 mg (10 mg/mL) or 40 mg (10 mg/mL)	IP	10 mL per vial (5 or 10 vials per carton) or 4 mL/vial (240 mg kits: 2-100 mg vials and 1-40 mg vial)	Store at 2° - 8° C Protect from light and freezing
Ipilimumab Solution for Injection	200 mg (5 mg/mL)	IP	40 mL/vial (4 vials/carton)	Store at 2° - 8° C Protect from light and freezing
Placebo	Placebo for Nivolumab or Ipilimumab will be considered as drug diluent alone, either Normal Saline or Dextrose 5%. Preparation of placebo, blinding and labeling will be outlined in the CA209915 pharmacy manual.			

Arm A (Nivolumab + Ipilimumab) Dosing:

Participants randomized to Arm A will receive treatment with nivolumab at a dose of 240 mg as a 30-minute infusion on Day 1 every 2 weeks plus ipilimumab 1 mg/kg as a 30-minute infusion every 6 weeks until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first with a maximum of 1 year total duration of study medication. For adolescents between 12 to < 18 years of age, use the body weight-based dosing for nivolumab of 3 mg/kg Q2W up to a maximum of 240 mg. This will be applicable for participants enrolled after IRB approval of Revised Protocol 02 and will be implemented upon IRT modification. Participants should begin study treatment within 3 calendar days of randomization.

Arm B (Nivolumab) Dosing:

Participants should receive nivolumab at a dose of 480 mg as a 30-minute infusion on Day 1 of each treatment cycle every 4 weeks until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first with a maximum of 1-year total duration of study medication. For adolescents between 12 to < 18 years of age, use the body weight-based dosing for nivolumab 6 mg/kg Q4W up to a maximum of 480 mg. This will be applicable for participants enrolled after IRB approval of Revised Protocol 02 and will be implemented upon IRT modification. Participants should begin study treatment within 3 calendar days of randomization.

In order to maintain the blind, nivolumab placebo will be administered on D1WK3, D1WK7, D1WK11, D1WK15, D1WK19, D1WK23, D1WK27, D1WK31, D1WK35, D1WK39, D1WK43 and D1WK47. Ipilimumab placebo will be administered on D1WK1, D1WK7, D1WK13, D1WK19, D1WK25, D1WK31, D1WK37, D1WK43, and D1WK49. (See Table 7.1-1 in the protocol)

For participants who have been randomized to Arm C: (Ipilimumab) before the implementation of Amendment:

Sites who have randomized participants to the ipilimumab arm will be unblinded to that information and the participants will be allowed to continue as open-label on either ipilimumab 10 mg/kg or switch to nivolumab 480 mg. The change will be implemented upon IRT modification.

For participants who continued on Ipilimumab 10 mg/kg.

Open-label.

Participants should continue receiving ipilimumab at a dose of 10 mg/kg as a 90-minute IV infusion, on Day 1 of each treatment cycle every 3 weeks for 4 doses, then every 12 weeks beginning at Week 24, until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first with a maximum of 1-year total duration of study medication. Participants should begin study treatment within 3 calendar days of randomization. (See Table 2-8)

For Participants who switched to Nivolumab 480 mg.

Open-label.

The first dose of nivolumab 480 mg should occur 8 weeks after the last dose of ipilimumab 10 mg/kg. Participants should receive nivolumab at a dose of 480 mg as a 30 minute IV infusion of each treatment cycle every 4 weeks until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first with a maximum of 1-year total duration of study medication starting from first dose of ipilimumab 10 mg/kg. (See Table 2-9) For adolescents between 12 to < 18 years of age, use the body weight-based dosing for nivolumab 6 mg/kg Q4W up to a maximum of 480 mg. The change will be implemented upon IRT modification.

Dosing calculations should be based on the body weight assessed at baseline. It is not necessary to re-calculate subsequent doses if the participant weight is within 10% of the weight used to calculate the previous dose. All doses should be rounded up or to the nearest milligram per institutional standard.

Dose reductions or dose escalations are not permitted. All dose modification rules apply to all arms given the blinded nature of this study.

Dose delay criteria apply for all drug-related adverse events regardless of whether or not the event is attributed to nivolumab, ipilimumab, or both. All study drugs must be delayed until treatment can resume. Dose delay criteria also apply to the placebo version of each agent, given the blinded nature of this study.

Study drug (nivolumab, ipilimumab and placebo version of each agent) administration should be delayed for the following:

- Grade 2 non-skin, drug-related AE, with the exception of fatigue
- Grade 2 drug-related creatinine, AST, ALT and/or Total Bilirubin abnormalities
- Grade 3 skin, drug-related AE
- Grade 3 drug-related laboratory abnormality, with the following exceptions:
  - Grade 3 lymphopenia or asymptomatic amylase or lipase does not require dose delay
  - Grade ≥ 3 AST, ALT, Total Bilirubin will require dose discontinuation (see section 8)
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

A Data Monitoring Committee (DMC) will be established to provide oversight of safety and efficacy considerations in protocol CA209915. Additionally, the DMC will provide advice to the sponsor regarding actions the committee deems necessary for the continuing protection of participants enrolled in the study. The DMC will be charged with assessing such actions in light of an acceptable benefit/risk profile for nivolumab in combination with ipilimumab, nivolumab and ipilimumab. The DMC will act in an advisory capacity to BMS and will monitor subject safety and evaluate the available efficacy data for the study. The oncology therapeutic area of BMS has primary responsibility for design and conduct of the study.

Details of the DMC responsibilities and procedures will be specified in the DMC charter.

[redacted]

2 SCHEDULE OF ACTIVITIES

Participants originally assigned to Arm C (ipilimumab 10 mg/kg) who switch to nivolumab after the implementation of Amendment 6 after receiving ipilimumab 10 mg/kg and completing an 8 week washout should receive nivolumab 480 mg every 4 weeks, and procedures should be performed at the same visit when dosing occurs as follows:

- All Safety Assessments (Targeted Physical Examination, Vital Signs, Weight and Performance Status, Adverse Events Assessments, Review of Concomitant Medications, Laboratory Tests, Pregnancy Tests) except Immunogenicity should be performed
- [redacted]
- Tumor surveillance assessment schedule (Efficacy Assessments) is remaining unchanged, and the timing should continue to be done from the first dose of study treatment in the study.
- [redacted]
- IRT will dispense study treatment (open-label)
- [redacted]

Table 2-8 provides the schedule of activities for the participants originally assigned to Arm C (ipilimumab 10 mg/kg) who continue on ipilimumab.

Table 2-9 provides the schedule of activities described above for participants originally assigned to Arm C (ipilimumab 10 mg/kg) who switch to nivolumab 480 mg.

Table 2-1: Screening Procedural Outline (CA209915)

Procedure	Screening Visit (Before Day 1, prior to Randomization)	Notes
Eligibility Assessments		
Informed Consent	X	Must be obtained prior to performing any screening procedures. If re-enrolled, the participant must be re-consented and assigned a new participant number from IRT.
Inclusion/Exclusion Criteria	X	All inclusion/exclusion criteria should be assessed during screening and confirmed prior to randomization.
Medical History	X	
[redacted]	[redacted]	[redacted]
Review of pathology report	X	Stage III: The pathology report must be reviewed, signed and dated by the investigator prior to randomization. Stage IV: The pathology report confirming negative margins must be reviewed, dated, and signed by the investigator prior to randomization.
Tumor Tissue Samples	X	Sufficient tumor tissue from the resected site of the disease (a block or a minimum of 15 slides) must be available and sent to a central laboratory for biomarker analysis. PD-L1 status will be assessed prior to randomization (PD-L1 expression < 1% or indeterminate, 1%-<5%, ≥5% tumor cell surface expression) (see Section 9.8.1)
Safety Assessments		
Physical Examination	X	Including height and weight, within 14 days prior to randomization
Vital Signs	X	Including blood pressure (BP), heart rate (HR), temperature; obtain at the screening visit and within 72 hours prior to first dose
Performance Status (ECOG)	X	Within 14 days prior to randomization
Assessment of Signs and Symptoms	X	Within 14 days prior to randomization
Serious Adverse Events	X	Serious Adverse Events from time of consent. See Section 9.2.1.
Electrocardiogram (ECG)	X	Within 14 days prior to randomization

Table 2-1: Screening Procedural Outline (CA209915)

Procedure	Screening Visit (Before Day 1, prior to Randomization)	Notes
Laboratory Tests	X	Must be completed with 14 days prior to randomization • CBC w/ differential • Chemistry panel including AST, ALT, ALP, T. Bili, blood urea nitrogen (BUN) or serum urea level, creatinine, creatinine clearance (Screening only), phosphate, Ca, Na, K, CL, LDH, and glucose • Thyroid panel including TSH, free T4, free T3 • Hep B/C (HBVsAG, HCV antibody, or HCV RNA) • Albumin at screening and as clinically indicated after screening visit
Pregnancy Test	X	WOCBP only. Serum or urine to be done at screening visit and repeated within 24 hours prior to first dose of study therapy.
Efficacy assessment		
Tumor surveillance assessments	X	Performed within 28 days prior to randomization; see Section 9.1.4
Other		
Interactive Response Technology (IRT)	X	For participant number assignment at the time informed consent is obtained

Table 2-2: On-Treatment Assessments Week 1 - Week 9 (CA209915) (Participants on Arm A or Arm B)

Procedure	Day 1 Week 1	Day 1 Week 3	Day 1 Week 5	Day 1 Week 7	Day 1 Week 9	Notes
Safety Assessments						
Targeted Physical Examination	X	X	X	X	X	To be performed within 72 hours prior to dosing
Vital Signs	X	X	X	X	X	Including BP, HR, temperature
Weight and performance status	X	X	X	X	X	Within 72 hours prior to dosing
Adverse Events Assessment	Continuously					
Review of concomitant [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Laboratory Tests	X		X		X	Within 72 hrs. prior to dosing to include CBC w/differential, AST, ALT, ALP, T. Bili, BUN or serum urea level, creatinine, Ca, Phosphate, Mg, Na, K, Cl, LDH, Glucose, TSH (with reflexive Free T4 and Free T3 only if TSH is abnormal) Note: Week 1 Laboratory tests do not need to be repeated if performed within 14 days prior to first dose Albumin, ACTH, cortisol, amylase, and lipase as clinically indicated.
Pregnancy Test	X		X		X	Within 24 hours prior to the initial administration of study drug, then every 4 weeks ± 1 week. Serum or Urine
Immunogenicity blood sample	X		X		X	Details regarding specific sample timing are specified in Table 9.5.2-1
[redacted]						
[redacted]	[redacted]		[redacted]		[redacted]	[redacted]

Table 2-2: On-Treatment Assessments Week 1 - Week 9 (CA209915) (Participants on Arm A or Arm B)

Procedure	Day 1 Week 1	Day 1 Week 3	Day 1 Week 5	Day 1 Week 7	Day 1 Week 9	Notes
[redacted]						
[redacted]	[redacted]			[redacted]		[redacted]
[redacted]	[redacted]					[redacted]
[redacted]	[redacted]					[redacted]
[redacted]	[redacted]					[redacted]
[redacted]	[redacted]			[redacted]		[redacted]
[redacted]	[redacted]			[redacted]		[redacted]

Table 2-2: On-Treatment Assessments Week 1 - Week 9 (CA209915) (Participants on Arm A or Arm B)

Procedure	Day 1 Week 1	Day 1 Week 3	Day 1 Week 5	Day 1 Week 7	Day 1 Week 9	Notes
Biopsy of affected [redacted]	[redacted]					
[redacted]	[redacted]					
Efficacy Assessments						
Tumor Surveillance Assessments	Every 12 weeks (± 7 days) from first dose of study treatment through 12 months (until local, regional, or distant recurrence [whichever comes first] for stage IV participants and until distant recurrence for stage III participants)					See Section 9.1.4
Study Drug						
IRT Randomize	X					Tumor tissue submitted to central lab must be logged as received and PDL1 results must be documented by the central lab in IRT prior to randomization. Allow approximately 10 business days to be processed from the date of receipt.
IRT Dispense Study Treatment (Active drug or placebo - blinded)	X	X	X	X	X	First dose to be administered within 3 calendar days of randomization. Subsequent doses may be administered within 3 days before or after the scheduled date if necessary. Full details of the dosing schedule are provided in Table 7.1-1
[redacted]						
[redacted]	[redacted]		[redacted]		[redacted]	[redacted]
[redacted]	[redacted]		[redacted]		[redacted]	
[redacted]	[redacted]		[redacted]		[redacted]	

Table 2-2: On-Treatment Assessments Week 1 - Week 9 (CA209915) (Participants on Arm A or Arm B)

Procedure	Day 1 Week 1	Day 1 Week 3	Day 1 Week 5	Day 1 Week 7	Day 1 Week 9	Notes
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 2-3: On-Treatment Assessments Week 10 - Week 19 (CA209915) (Participants on Arm A or Arm B)

Procedure	Day 1 Week 11	Day 1 Week 13	Day 1 Week 15	Day 1 Week 17	Day 1 Week 19	Notes
Safety Assessments						
Targeted Physical Examination	X	X	X	X	X	Within 72 hours prior to dosing
Vital Signs	X	X	X	X	X	Including BP, HR, temperature
Weight and performance status	X	X	X	X	X	Within 72 hours prior to dosing
Adverse Events Assessment	Continuously					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Laboratory Tests		X		X		Within 72 hrs. prior to dosing to include CBC w/differential, AST, ALT, ALP, T. Bili, BUN or serum urea level, creatinine, Ca, Phosphate, Mg, Na, K, Cl, LDH, Glucose, TSH (with reflexive Free T4 and Free T3 if TSH is abnormal) Albumin, ACTH, cortisol, amylase, and lipase as clinically indicated
Pregnancy Test		X		X		Every 4 weeks ± 1 week. Serum or Urine
Immunogenicity blood sample			X			Details regarding specific sample timing are specified in Table 9.5.2-1

Table 2-3: On-Treatment Assessments Week 10 - Week 19 (CA209915) (Participants on Arm A or Arm B)

Procedure	Day 1 Week 11	Day 1 Week 13	Day 1 Week 15	Day 1 Week 17	Day 1 Week 19	Notes
[redacted]						
[redacted]			[redacted]			[redacted]
[redacted]						
[redacted]		[redacted]				[redacted]
[redacted]		[redacted]				[redacted]
[redacted]		[redacted]				[redacted]
[redacted]		[redacted]				[redacted]
[redacted]		[redacted]				[redacted]

Table 2-3: On-Treatment Assessments Week 10 - Week 19 (CA209915) (Participants on Arm A or Arm B)

Procedure	Day 1 Week 11	Day 1 Week 13	Day 1 Week 15	Day 1 Week 17	Day 1 Week 19	Notes
[redacted]						[redacted]
[redacted]	[redacted]					
Efficacy Assessments						
Tumor Surveillance Assessments	Every 12 weeks (± 7 days) from first dose of study treatment through 12 months (until local, regional, or distant recurrence [whichever comes first] for stage IV participants; until distant recurrence for stage III participants)					See Section 9.1.4
Study Drug						
IRT Dispense Study Treatment (Active drug or placebo - blinded)	X	X	X	X	X	Subsequent doses may be administered within 3 days before or after the scheduled date if necessary. Full details of dosing schedule are provided in Table 7.1-1
[redacted]						
[redacted]		[redacted]		[redacted]		[redacted]

Table 2-3: On-Treatment Assessments Week 10 - Week 19 (CA209915) (Participants on Arm A or Arm B)

Procedure	Day 1 Week 11	Day 1 Week 13	Day 1 Week 15	Day 1 Week 17	Day 1 Week 19	Notes
[redacted]		[redacted]		[redacted]		[redacted]
[redacted]		[redacted]		[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 2-4: On-Treatment Assessments Week 21 - Week 29 (CA209915) (Participants on Arm A or Arm B)

Procedure	Day 1 Week 21	Day 1 Week 23	Day 1 Week 25	Day 1 Week 27	Day 1 Week 29	Notes
Safety Assessments						
Targeted Physical Examination	X	X	X	X	X	Within 72 hours prior to dosing
Vital Signs	X	X	X	X	X	Including BP, HR, Temperature
Weight and performance status	X	X	X	X	X	Within 72 hours prior to dosing
Adverse Events Assessment	Continuously					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Laboratory Tests	X		X		X	Within 72 hrs. prior to dosing to include CBC w/differential, AST, ALT, ALP, T. Bili, BUN or serum urea level, creatinine, Ca, Phosphate, Mg, Na, K, Cl, LDH, Glucose, TSH (with reflexive Free T4 and Free T3 if TSH is abnormal) Albumin, ACTH, cortisol, amylase, and lipase as clinically indicated
Pregnancy Test	X		X		X	Every 4 weeks ± 1 week. Serum or Urine
Immunogenicity blood sample	X					Details regarding specific sample timing are specified in Table 9.5.2-1
[redacted]						
[redacted]	[redacted]					[redacted]
[redacted]						
[redacted]					[redacted]	[redacted]
[redacted]					[redacted]	[redacted]

Table 2-4: On-Treatment Assessments Week 21 - Week 29 (CA209915) (Participants on Arm A or Arm B)

Procedure	Day 1 Week 21	Day 1 Week 23	Day 1 Week 25	Day 1 Week 27	Day 1 Week 29	Notes
[redacted]						[redacted]
[redacted]					[redacted]	[redacted]
[redacted]					[redacted]	[redacted]
[redacted]					[redacted]	[redacted]
[redacted]	[redacted]					
[redacted]	[redacted]					
Efficacy Assessments						
Tumor Surveillance Assessments	Every 12 weeks (± 7 days) from first dose of study treatment through 12 months (until local, regional, or distant recurrence [whichever comes first] for stage IV participants and until distant recurrence for stage III participants)					See Section 9.1.4

Table 2-4: On-Treatment Assessments Week 21 - Week 29 (CA209915) (Participants on Arm A or Arm B)

Procedure	Day 1 Week 21	Day 1 Week 23	Day 1 Week 25	Day 1 Week 27	Day 1 Week 29	Notes
Study Drug						
IRT Dispense Study Treatment (Active drug or placebo - blinded)	X	X	X	X	X	Subsequent doses may be administered within 3 days before or after the scheduled date if necessary Full details of dosing schedule are provided in Table 7.1-1
[redacted]						
[redacted]	[redacted]		[redacted]		[redacted]	[redacted]
[redacted]	[redacted]		[redacted]		[redacted]	
[redacted]	[redacted]		[redacted]		[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 2-5: On-Treatment Assessments Week 31 - Week 37 (CA209915) (Participants on Arm A or Arm B)

Procedure	Day 1 Week 31	Day 1 Week 33	Day 1 Week 35	Day 1 Week 37	Notes
Safety Assessments					
Targeted Physical Examination	X	X	X	X	Within 72 hours prior to dosing
Vital Signs	X	X	X	X	Including BP, HR, temperature
Weight and performance status	X	X	X	X	Within 72 hours prior to dosing
Adverse Events Assessment	Continuously				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Laboratory Tests		X		X	Within 72 hrs. prior to dosing to include CBC w/differential, AST, ALT, ALP, T. Bili, BUN or serum urea level, creatinine, Ca, Phosphate, Mg, Na, K, Cl, LDH, Glucose, TSH (with reflexive Free T4 and Free T3 if TSH is abnormal) Albumin, ACTH, cortisol, amylase, and lipase as clinically indicated
Pregnancy Test		X		X	Every 4 weeks ± 1 week. Serum or Urine
Immunogenicity blood sample				X	Details regarding specific sample timing are specified in Table 9.5.2-1
[redacted]					
[redacted]				[redacted]	[redacted]
[redacted]					
[redacted]					[redacted]

Table 2-5: On-Treatment Assessments Week 31 - Week 37 (CA209915) (Participants on Arm A or Arm B)

Procedure	Day 1 Week 31	Day 1 Week 33	Day 1 Week 35	Day 1 Week 37	Notes
[redacted]					[redacted]
[redacted]	[redacted]				
Efficacy Assessments					
Tumor Surveillance Assessments	Every 12 weeks (± 7 days) from first dose of study treatment through 12 months (until local, regional, or distant recurrence [whichever comes first] for stage IV participants and until distant recurrence for stage III participants)				See Section 9.1.4
Study Drug					
IRT Dispense Study Treatment (Active drug or placebo - blinded)	X	X	X	X	Subsequent doses may be administered within 3 days before or after the scheduled date if necessary
[redacted]					
[redacted]		[redacted]		[redacted]	[redacted]
[redacted]		[redacted]		[redacted]	
[redacted]		[redacted]		[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 2-6: On-Treatment Assessments Week 39 - Week 47 (CA209915) (Participants on Arm A or Arm B)

Procedure	Day 1 Week 39	Day 1 Week 41	Day 1 Week 43	Day 1 Week 45	Day 1 Week 47	Notes
Safety Assessments						
Targeted Physical Examination	X	X	X	X	X	Within 72 hours prior to dosing
Vital Signs	X	X	X	X	X	Including BP, HR, temperature
Weight and performance status	X	X	X	X	X	Within 72 hours prior to dosing
Adverse Events Assessment	Continuously					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Laboratory Tests		X		X		Within 72 hrs. prior to dosing to include CBC w/differential, AST, ALT, ALP, T. Bili, BUN or serum urea level, creatinine, Ca, Phosphate, Mg, Na, K, Cl, LDH, Glucose, TSH (with reflexive Free T4 and Free T3 if TSH is abnormal) Albumin, ACTH, cortisol, amylase, and lipase as clinically indicated
Pregnancy Test		X		X		Every 4 weeks ± 1 week. Serum or Urine
Immunogenicity blood sample						Details regarding specific sample timing are specified in Table 9.5.2-1
[redacted]						
[redacted]						[redacted]
[redacted]						
[redacted]				[redacted]		[redacted]

Table 2-6: On-Treatment Assessments Week 39 - Week 47 (CA209915) (Participants on Arm A or Arm B)

Procedure	Day 1 Week 39	Day 1 Week 41	Day 1 Week 43	Day 1 Week 45	Day 1 Week 47	Notes
[redacted]						[redacted]
[redacted]	[redacted]					
Efficacy Assessments						
Tumor Surveillance Assessments	Every 12 weeks (± 7 days) from first dose of study treatment through 12 months (until local, regional, or distant recurrence [whichever comes first] for stage IV participants and until distant recurrence for stage III participants)					See Section 9.1.4
Study Drug						
IRT Dispense Study Treatment (Active drug or placebo - blinded)	X	X	X	X	X	Subsequent doses may be administered within 3 days before or after the scheduled date if necessary
[redacted]						
[redacted]		[redacted]		[redacted]		[redacted]
[redacted]		[redacted]		[redacted]		
[redacted]		[redacted]		[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 2-7: On-Treatment Assessments Week 48 - Week 49 (CA209915) (Participants on Arm A or Arm B)

Procedure	Day 1 Week 49	Notes
Safety Assessments		
Targeted Physical Examination	X	Within 72 hours prior to dosing
Vital Signs	X	Including BP, HR, temperature
Weight and performance status	X	Within 72 hours prior to dosing
Adverse Events Assessment	Continuously	
[redacted]	[redacted]	
Laboratory Tests	X	Within 72 hrs. prior to dosing to include CBC w/differential, AST, ALT, ALP, T. Bili, BUN or serum urea level, creatinine, Ca, Phosphate, Mg, Na, K, Cl, LDH, Glucose, TSH (with reflexive Free T4 and Free T3 if TSH is abnormal) Albumin, ACTH, cortisol, amylase, and lipase as clinically indicated
Pregnancy Test	X	Every 4 weeks ± 1 week. Serum or Urine
Immunogenicity blood sample		Details regarding specific sample timing are specified in Table 9.5.2-1
[redacted]		
[redacted]		[redacted]
[redacted]		
[redacted]		[redacted]
[redacted]		[redacted]
[redacted]	[redacted]	

Table 2-7: On-Treatment Assessments Week 48 - Week 49 (CA209915) (Participants on Arm A or Arm B)

Procedure	Day 1 Week 49	Notes
Efficacy Assessments		
Tumor Surveillance Assessments	Every 12 weeks (± 7 days) from first dose of study treatment through 12 months (until local, regional, or distant recurrence [whichever comes first] for stage IV participants and until distant recurrence for stage III participants)	See Section 9.1.4
Study Drug		
IRT Dispense Study Treatment (Active drug or placebo - blinded)	X	Subsequent doses may be administered within 3 days before or after the scheduled date if necessary
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]

Table 2-8: Arm C Open Label for Participants who continue on Ipilimumab 10 mg/kg

Procedure	At Dosing Visit	Notes
Safety Assessments		
Targeted Physical Examination	X	To be performed within 72 hours prior to dosing
Vital Signs	X	Including BP, HR, temperature
Weight and performance status	X	Within 72 hours prior to dosing
Adverse Events Assessment	X	
[redacted]	[redacted]	
Laboratory Tests	X	Within 72 hrs. prior to dosing to include CBC w/differential, AST, ALT, ALP, T. Bili, BUN or serum urea level, creatinine, Ca, Phosphate, Mg, Na, K, Cl, LDH, Glucose, TSH (with reflexive Free T4 and Free T3 only if TSH is abnormal) Albumin, ACTH, cortisol, amylase, and lipase as clinically indicated.
Pregnancy Test	X	Serum or Urine. Pregnancy test not required at week 13.
Efficacy Assessments		
Tumor Surveillance Assessments	See comment	Every 12 weeks (± 7 days) from first dose of study treatment through 12 months (until local, regional, or distant recurrence [whichever comes first] for stage IV participants and until distant recurrence for stage III participants) See Section 9.1.4
Study Drug		
IRT Dispense Study Treatment	X	IRT will dispense study treatment (open-label) Doses may be administered within 3 days before or after the scheduled date if necessary

On treatment visits at week 1, 4, 7, 10, 13, 24, 36 and 48 should take place. (There is no dosing at Week 13, only safety assessments.) These participants will have these visits only.

These participants will also have laboratory tests and pregnancy test at each of these visits (pregnancy test is not required at Week 13 for these subjects as no study medication is administered at this visit).

Table 2-9: Arm C Open Label for Participants who switch to Nivolumab 480 mg Q4W

Procedure	At Dosing Visit (Q4W)	Notes
Safety Assessments		
Targeted Physical Examination	X	To be performed within 72 hours prior to dosing
Vital Signs	X	Including BP, HR, temperature
Weight and performance status	X	Within 72 hours prior to dosing
Adverse Events Assessment	X	
[redacted]	[redacted]	
Laboratory Tests	X	Within 72 hrs. prior to dosing to include CBC w/differential, AST, ALT, ALP, T. Bili, BUN or serum urea level, creatinine, Ca, Phosphate, Mg, Na, K, Cl, LDH, Glucose, TSH (with reflexive Free T4 and Free T3 only if TSH is abnormal) Albumin, ACTH, cortisol, amylase, and lipase as clinically indicated.
Pregnancy Test	X	Within 24 hours prior to the initial administration of study drug, then every 4 weeks ± 1 week. Serum or Urine
Immunogenicity blood sample	Not required	
[redacted]		
[redacted]	[redacted]	

Table 2-9: Arm C Open Label for Participants who switch to Nivolumab 480 mg Q4W

Procedure	At Dosing Visit (Q4W)	Notes
[redacted]		
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]	[redacted]	
Efficacy Assessments		
Tumor Surveillance Assessments	See comment	Every 12 weeks (± 7 days) from first dose of study treatment through 12 months (until local, regional, or distant recurrence [whichever comes first] for stage IV participants and until distant recurrence for stage III participants) See Section 9.1.4
Study Drug		
IRT Dispense Study Treatment	X	IRT will dispense study treatment (open-label) Doses may be administered within 3 days before or after the scheduled date if necessary

Table 2-9: Arm C Open Label for Participants who switch to Nivolumab 480 mg Q4W

Procedure	At Dosing Visit (Q4W)	Notes
[redacted]		
[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	

Table 2-10: Follow-Up Procedural Outline (CA209915)

Procedure	Follow-up, Visits 1 and 2[a]	Survival, Follow up Visits[b]	Notes
Safety Assessments			
Targeted Physical Examination	X		
Adverse Events Assessment	X	X	Record at each visit. Collect continuously throughout the treatment period and for a minimum of 100 days following discontinuation of dosing.
Laboratory Tests	X		CBC w/ differential, chemistry panel, thyroid test for Follow-up Visit 1 (repeat at Visit 2 if toxicities are present). Refer to Section 9.4.4 Clinical Safety Laboratory Assessments for list of laboratory test. Laboratory toxicities (eg, suspected drug induced liver enzyme elevations) will be monitored during the follow-up phase, based on results from on-site/local labs, until all study drug related toxicities resolve, return to baseline, or are deemed irreversible.
Pregnancy Test	X		Serum or urine
[redacted]	[redacted]		[redacted]
Immunogenicity blood sample	X[f]		Details regarding specific sample timing are specified in Table 9.5.2-1
[redacted]			
[redacted]	[redacted]		[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]
[redacted]	[redacted]		

Table 2-10: Follow-Up Procedural Outline (CA209915)

Procedure	Follow-up, Visits 1 and 2[a]	Survival, Follow up Visits[b]	Notes
Efficacy Assessments			
Tumor Surveillance Assessment	Every 12 weeks (± 7 days) < 12 month[d] Every 12 weeks (± 14 days) > 12 months through 36 months[d,] Every 6 months (± 4 weeks) > 36 months through and up to Year 5[d,] Until local, regional, or distant recurrence (whichever comes first) for stage IV participants and until distant recurrence for stage III participants. All time points are relative to the first dose of study treatment.		See Section 9.1.4 Note: If a participant starts systemic therapy for melanoma recurrence after study drug discontinuation, follow-up scans should be discontinued. If a participant starts systemic therapy for a new non-melanoma tumor after study drug discontinuation, follow-up scans can be done as per standard of care.
Survival Status			
Survival status	X	X	Every 3 months (± 14 days), maybe accomplished by visit or phone contact, to include subsequent anti-cancer therapy[e]
[redacted]			
[redacted]	[redacted]		[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		

Table 2-10: Follow-Up Procedural Outline (CA209915)

Procedure	Follow-up, Visits 1 and 2[a]	Survival, Follow up Visits[b]	Notes
[redacted]	[redacted]		
[redacted]	[redacted]		[redacted]

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

[b] First Survival Follow-up visit 3 months (± 14 days) after FU2; subsequent survival FU visits every 3 months (± 14 days)

[c] [redacted]

[d] Every 12 weeks (± 7 days) through 12 months for participants who discontinued early from treatment (relative to the first dose of study drug);
Every 12 weeks (± 14 days) if > 12 months through 36 months (relative to the first dose of study drug)
Every 6 months (± 4 weeks) if > 36 months through and up to Year 5 (relative to the first dose of study drug).

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

[f] [redacted]

[redacted]

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Primary	
• To compare the efficacy, as measured by recurrence-free survival (RFS), provided by nivolumab plus ipilimumab versus nivolumab monotherapy in participants with completely resected stage IIIb/c/d or stage IV no evidence of disease (NED) melanoma (in all randomized participants with PD-L1 expression level < 1%. and all randomized participants)	• Recurrence-free survival, RFS
Secondary	
• To compare the overall survival provided by nivolumab plus ipilimumab versus nivolumab monotherapy in participants with completely resected stage IIIb/c/d or stage IV NED melanoma (in all randomized participants with PD-L1 expression level < 1%. and all randomized participants)	• Overall survival (OS)
• To evaluate the association between PD-L1 expression and RFS	• PD-L1 expression • Objective response rates (if applicable)

Table 4-1: Objectives and Endpoints

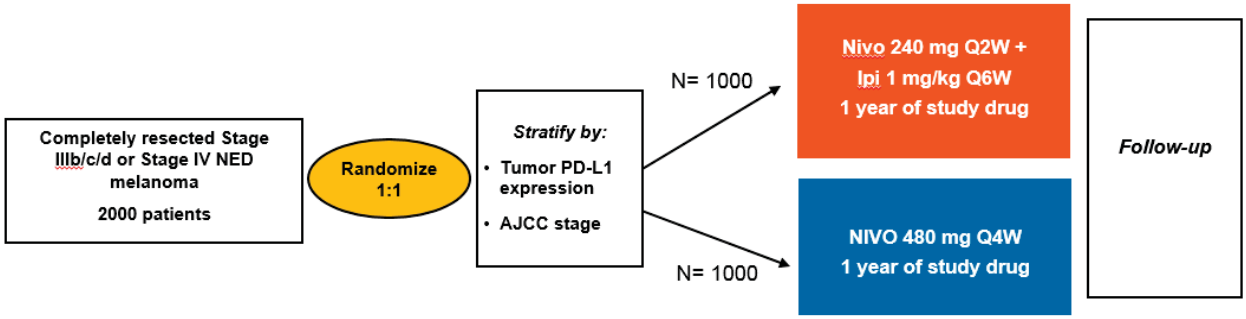
Objectives	Endpoints
• To evaluate investigator-assessed outcomes on next-line therapies	• Duration of treatment on next-line therapies • PFS2 defined as time from randomization to second recurrence/objective disease progression, or death from any cause, whichever occurs first. • End-of-next-line-treatment: To be used for situations where PFS2 cannot be reliably determined. Event defined as end or discontinuation of next-line treatment, second objective disease progression, or death from any cause, whichever occurs first.
[redacted]b	[redacted]

5 STUDY DESIGN

5.1 Overall Design

The study design schematic is presented in Figure 5.1-1.

Figure 5.1-1: Study Design Schematic



This is a Phase 3, randomized, double-blind study of nivolumab plus ipilimumab vs nivolumab monotherapy in participants (≥ 12 years) with completely resected stage IIIb/c/d or stage IV no evidence of disease (NED) melanoma.

Participants will be treated with one of the following:

- Arm A: nivolumab 240 mg IV Q2 weeks plus ipilimumab 1 mg/kg IV Q6 weeks (for 1 year of study drug treatment)
- Arm B: nivolumab 480 mg IV Q4 weeks (for 1 year of study drug treatment) with nivolumab placebo on Weeks 3, 7, 11, 15, 19, 23, 27, 31, 35, 39, 43, & 47 and ipilimumab placebo on Weeks 1, 7, 13, 19, 25, 31, 37, 43, & 49
  - The original study design included an ipilimumab monotherapy arm (Arm C). Randomization into Arm C was discontinued upon implementation of Amendment 06. Sites who have randomized patients to the ipilimumab arm will be unblinded to that information and the patients will be allowed to continue as open-label on either ipilimumab 10 mg/kg IV Q3 weeks for 4 doses, then Q12 weeks starting at Week 24 or switch to the nivolumab 480 mg IV Q4 weeks in 8 weeks after the last dose of ipilimumab. The change will be implemented upon IRT modification.
  - For adolescents between 12 to < 18 years of age the dosing of nivolumab is body weight based dosing as follows: Q2 week dosing - 3 mg/kg IV Q2 weeks up to a maximum of 240 mg; Q4 week dosing - 6 mg/kg Q4 weeks up to a maximum of 480 mg. This will be applicable for participants enrolled after IRB approval of Revised Protocol 02 and will be implemented upon IRT modification.

Approximately 2000 participants will be randomized in a 1:1 ratio to nivolumab plus ipilimumab versus nivolumab monotherpy and stratified by PD-L1 status (PD-L1 expression < 1% or indeterminate, 1% - < 5%, ≥ 5% tumor cell surface expression) and American Joint Committee on Cancer (AJCC) stage IIIb vs stage IIIc/d vs stage IV (Appendix 1). Accrual will be stopped when

approximately 600 participants with PD-L1 expression level < 1% will be randomized in a 1:1 ratio to nivolumab plus ipilimumab and nivolumab respectively. The prevalence of participants with PD-L1 expression level < 1% is expected to be around 30% of all randomized participants. Therefore, it is estimated that approximately 2000 participants will be randomized in a 1:1 ratio to nivolumab plus ipilimumab and nivolumab respectively. No more than 1400 participants with PD-L1 expression level ≥ 1% will be randomized to nivolumab plus ipilimumab and nivolumab respectively. In addition, there will be a number of participants that were already randomized to the ipilimumab arm under the original protocol.

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

This study will consist of three phases: screening, treatment, and follow-up. For a complete list of study required procedures, please refer to Section 9.

Screening Phase:

- Begins by establishing the participant's initial eligibility and signing of the informed consent form (ICF)
- Participant is enrolled using the IRT
- Participant is assessed for complete study eligibility within the required timeframe found in Table 2-1
- A pregnancy test for WOCBP should be documented within 24 hours prior to the start of the first dose of study medication
- Tumor tissue must be received at the Central Laboratory for PD-L1 IHC testing in order for the participant to be randomized. PD-L1 status will be used as a stratification factor
- If stage III, the pathology reports of clinically detectable node(s) confirming malignancy must be reviewed, dated, and signed by the investigator prior to randomization
- If stage IV, the pathology report confirming negative margins must be reviewed, dated, and signed by the investigator prior to randomization

Treatment Phase:

- Following confirmation of the participant's eligibility, the randomization call to the IRT can be made. The participant is randomly assigned to receive either nivolumab plus ipilimumab, nivolumab monotherapy.
- Within 3 calendar days from randomization the participant must receive the first dose of study medication (Day 1 of Week 1)
- On-study laboratory assessments should be drawn within 72 hours prior to dosing
- Adverse event assessments should be documented at each clinic visit and WOCBP must have a pregnancy test every four weeks ± 1 week
- [redacted]

- Treated participants will be evaluated for recurrence every 12 weeks ± 7 days. No central imaging assessments are planned. Scans will be submitted to central vendor for collect and hold, once the participant has been randomized and throughout the study period.
- [redacted]
- This phase ends when the participant is discontinued early from study therapy or at a maximum of 1 year of treatment. For a complete list of reasons for treatment discontinuation, see Section 8.1.

Follow-up Phase:

- Begins after 1 year of treatment or when the decision is made to discontinue a participant from study therapy
- [redacted]
- After completion of the first two follow -up visits, participants will be followed every 3 months for survival
- Participants who discontinue treatment for reasons other than recurrence will continue to have surveillance assessments (until local, regional, or distant recurrence (whichever comes first) recurrence for stage IV participants and until distant recurrence for stage III participants)
- Tumor surveillance assessments should occur every 12 weeks ± 7 days during the first year after randomization, every 12 weeks ±14 days from 12 months to 36 months after randomization. From 36 months until Year 5 after the first dose of study treatment, assessments should be performed every 6 months (± 4 weeks). No central imaging assessments are planned. Scans will be submitted to central vendor for collect and hold, once the participant has been randomized and throughout the study period.
- Participants will be followed for drug-related toxicities according to the Section 9. All toxicities will be documented for a minimum of 100 days after the last dose of study medication
- [redacted]

5.1.1 Data Monitoring Committee and Other External Committees

A Data Monitoring Committee (DMC) will be established to provide oversight of safety and efficacy considerations in protocol CA209915. Additionally, the DMC will provide advice to the sponsor regarding actions the committee deems necessary for the continuing protection of participants enrolled in the study. The DMC will be charged with assessing such actions in light of an acceptable benefit/risk profile for nivolumab in combination with ipilimumab, nivolumab and ipilimumab. The DMC will act in an advisory capacity to BMS and will monitor participant 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.

Details of the DMC responsibilities and procedures will be specified in the DMC charter.

5.2 Number of Participants

Approximately 2000 participants will be randomized in a 1:1 ratio to nivolumab plus ipilimumab versus nivolumab monotherapy (1000 vs 1000 participants) and stratified by PD-L1 status (PD-L1 expression < 1% or indeterminate, 1% - < 5%, ≥ 5% tumor cell surface expression) and American Joint Committee on Cancer (AJCC) stage IIIb vs stage IIIc/d vs stage IV. In addition, there are a number of participants who have already been randomized to the ipilimumab arm under the original protocol. Accrual will be stopped when approximately 600 participants with PD-L1 expression level < 1% will be randomized in a 1:1 ratio to nivolumab plus ipilimumab and nivolumab respectively. The prevalence of participants with PD-L1 expression level < 1% is expected to be around 30% of all randomized participants. Therefore, it is estimated that approximately 2000 participants will be randomized in a 1:1 ratio to nivolumab plus ipilimumab and nivolumab respectively. No more than 1400 participants with PD-L1 expression level ≥ 1% will be randomized to nivolumab plus ipilimumab and nivolumab respectively.

5.3 End of Study Definition

The start of the trial is defined as the first visit for the first participant entered. End of trial is defined as the last visit or scheduled procedure shown in the Schedule of Activities for the last participant. Study completion is defined as the final date on which data for the primary endpoint was or is expected to be collected, if this is not the same.

The total duration of the study from start of randomization to final analysis of OS is expected to be approximately 5 years. The study will end once survival follow-up has concluded.

[redacted]

[redacted]

6 STUDY POPULATION

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

6.1 Inclusion Criteria

1) Signed Written Informed Consent

a) Participants 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 participant care

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

2) Type of Participant and Target Disease Characteristics

a) All participants must be either stage IIIb/c/d or stage IV AJCC (AJCC Cancer Staging, 8th edition; see also Appendix 1) and have histologically confirmed melanoma that is completely surgically resected in order to be eligible. All melanomas, except ocular/uveal melanoma, regardless of primary site of disease will be allowed; mucosal melanomas are eligible. Participants must have been surgically rendered free of disease with negative margins on resected specimens.

When T is....	And N is.....	And M is....	The pathological stage is...
T0	N1b, N1c	M0	IIIB
T0	N2b, N2c, N3b, N3c	M0	IIIC
T1a/b-T2a	N1b/c or N2b	M0	IIIB
T2b/T3a	N1a-N2b	M0	IIIB
T1a-T3a	N2c or N3a/b/c	M0	IIIC
T3b/T4a	Any N ≥N1	M0	IIIC
T4b	N1a-N2c	M0	IIIC
T4b	N3a/b/c	M0	IIID
Ant T, Tis	Any N	M1	IV

i) If stage III melanoma (whether stage IIIb or IIIc or IIId) the participants should have clinical or radiographic evidence of regional metastases, either in the regional lymph nodes or locoregional metastases manifesting as satellite or in-transit metastases, or microsatellites discovered at the time of microscopic evaluation of the primary tumor diagnostic biopsy. Participants must have pathological evidence of regional metastases, regional lymph node and/or microsatellite/satellite/in-transit metastases, and no distant metastasis. The pathology report for stage IIIb, IIIc, and IIId must be reviewed, signed and dated by the investigator; this process will be confirmed during the IRT randomization call.

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

iii) For CNS lesion(s), documentation indicating that there has been complete resection of CNS lesion(s) will suffice as confirmation of negative margins

b) Complete resection of stage III disease that is documented on the surgical and pathology reports or complete resection of stage IV disease with margins negative for disease that is documented on the pathology report

c) Complete resection must be performed within 12 weeks prior to randomization

d) All participants must have disease-free status documented by a complete physical examination and imaging studies within 4 weeks prior to randomization. Imaging studies must include CT or MRI scans of the chest, abdomen, pelvis, and all known sites of

resected disease, and brain magnetic resonance (MRI) or CT (brain CT allowable if MRI is contraindicated or if there is no known history of resected brain lesions). Participants with equivocal lymph nodes ≥ 10 mm and < 15 mm in a short axis may be eligible if confirmation with histology/cytology is available. If risk of biopsy is too high or biopsy is not feasible, two sequential CT or MRI scans should be available and showing no progressive and measureable disease or PET/CT demonstrating no FDG uptake. The second scan should occur at least 4 weeks after the initial scan. Lymph nodes ≥ 15 mm in a short axis are defined as pathological.

e) The complete set of baseline images must be available before randomization

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

g) Tumor tissue from the resected site of disease must be provided for biomarker analyses (preferably collected within 12 weeks of assessment time). In order to be randomized, a participant must have quantifiable PD-L1 expression (< 1% or 1% - < 5% or ≥ 5% tumor cell membrane staining) or be classified as PD-L1 indeterminate. If insufficient tumor tissue content is provided for analysis, acquisition of additional tumor tissue (block and/or slides) for the biomarker analysis is required.

h) Participants must not have received anti-cancer therapy (for example but not limited to systemic, local, radiation, radiopharmaceuticals) for their melanoma except:

   i) Surgery for the melanoma lesion(s)

   ii) Adjuvant radiation therapy (RT) after neurosurgical resection for central nervous system (CNS) lesions

   iii) Prior adjuvant interferon if completed ≥ 6 months prior to randomization

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

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

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

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

3) Age and Reproductive Status

a) Males and Females, at least 12 years of age, except where local regulations and/or institutional policies do not allow for participants < 18 years of age (pediatric population) to participate. For those sites, the eligible participant population is ≥ 18 years of age.

b) Women of childbearing potential (WOCBP, Appendix 3) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study treatment

c) Women must not be breastfeeding

d) Women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception for the duration of study drug treatment and 5 months after the last dose of study treatment (ie, 30 days [duration of ovulatory cycle] plus the time required for the study drug to undergo approximately five half-lives).

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of study treatment and 7 months after the last dose of study treatment {ie, 90 days (duration of sperm turnover) plus the time required for study drug to undergo approximately five half-lives}

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

Investigators shall counsel WOCBP, and male participants who are sexually active with WOCBP, on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise on the use of highly effective methods of contraception (Appendix 3) which have a failure rate of < 1% when used consistently and correctly.

6.2 Exclusion Criteria

1) Medical Conditions

a) History of ocular/uveal melanoma

b) Weight ≤ 40 kg *"Not applicable as per amendment 07"*

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

d) 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.

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

f) Pregnant or nursing women

2) Prior/Concomitant Therapy

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

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

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

c) Treatment with botanical preparations (eg herbal supplements or traditional Chinese medicines) intended for general health support or to treat the disease under study within 2 weeks prior to randomization/treatment. Refer to Section 7.7.1 for prohibited therapies.

3) Physical and Laboratory Test Findings

a) WBC < 2000/μL

b) Neutrophils < 1500/μL

c) Platelets < $100*10^3$/μL

d) Hemoglobin < 9.0g/dL

e) Serum creatinine > 1.5 × ULN, unless creatinine clearance ≥ 40 mL/min (measured or calculated using Cockcroft-Gault formula)

f) AST/ALT > 3.0 × ULN

g) Total bilirubin > 1.5 × ULN (except participants with Gilbert Syndrome who must have a total bilirubin level of < 3.0 × ULN)

h) Any positive test result for hepatitis B virus or hepatitis C virus indicating presence of virus, eg, Hepatitis B surface antigen (HBsAg, Australia antigen) positive, or Hepatitis C antibody (anti-HCV) positive (except if HCV-RNA negative)

i) Known history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). Note: Testing for HIV must be performed at sites where mandated locally.

4) Allergies and Adverse Drug Reaction

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

b) History of allergy or hypersensitivity to study drug components

c) As per Amendment 06, this criteria has been moved under “Medical Conditions” as 1d.

d) Excluding participants with serious or uncontrolled medical disorders

5) Other Exclusion Criteria

a) Prisoners or participants who are involuntarily incarcerated. (Note: under certain specific circumstances a person who has been imprisoned may be included as a participant. Strict conditions apply and Bristol-Myers Squibb approval is required).

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

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

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

6.3 Lifestyle Restrictions

Not applicable; no lifestyle restrictions are required.

6.3.1 Meals and Dietary Restrictions

Not applicable

6.3.2 Caffeine, Alcohol and Tobacco

Not applicable

6.3.3 Activity

Not applicable

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and to respond to queries from regulatory authorities. Minimal information includes date of consent, demography, screen failure details, eligibility criteria, and any serious AEs.

6.4.1 Retesting During Screening or Lead-In Period

Participant re-enrollment: this study permits the re-enrollment of a participant who has discontinued the study as a screen failure (ie, participant has not been randomized/has not been treated). If re-enrolled, the participant must be re-consented.

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

The most current result prior to Randomization is the value by which study inclusion will be assessed, as it represents the participant's most current, clinical state.

Laboratory parameters and/or assessments that are included in Table 2-1, Screening Procedural Outline may be repeated in an effort to find all possible well-qualified participants. Consultation with the Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

7 TREATMENT

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo or medical device intended to be administered to a study participant according to the study randomization or treatment allocation.

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

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

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, investigational products are nivolumab and ipilimumab (Table 7-1).

Table 7-1: Study treatments for CA209915

Product Description/ Class / Dosage Form	Potency	IP/Non-IMP	Packaging / Appearance	Storage Conditions
BMS-936558 Nivolumab Solution for Injection	100 mg (10 mg/mL) or 40 mg (10 mg/mL)	IP	10 mL per vial (5 or 10 vials per carton) or 4 mL/vial (240 mg kits: 2-100 mg vials and 1-40 mg vial)	Store at 2° - 8° C Protect from light and freezing
Ipilimumab Solution for Injection	200 mg (5 mg/mL)	IP	40 mL/vial (4 vials/carton)	Store at 2° - 8° C Protect from light and freezing
Placebo	Placebo for Nivolumab or Ipilimumab will be considered as drug diluent alone, either Normal Saline or Dextrose 5%. Preparation of placebo, blinding and labeling will be outlined in the CA209915 pharmacy manual.			

7.1 Treatments Administered

Arm A (Nivolumab + Ipilimumab) Dosing:

Participants randomized to Arm A will receive treatment with nivolumab at a dose of 240 mg as a 30-minute infusion on Day 1 every 2 weeks plus ipilimumab 1 mg/kg as a 30-minute infusion every 6 weeks until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first with a maximum of 1 year total duration of study medication. For adolescents between 12 to < 18 years of age, use the body weight-based dosing for nivolumab of 3 mg/kg Q2W up to a maximum of 240 mg. This will be applicable for participants enrolled after IRB approval of Revised Protocol 02 and will be implemented upon IRT modification. Participants should begin study treatment within 3 calendar days of randomization.

When study drugs (nivolumab and ipilimumab) are to be administered on the same day, nivolumab is to be administered first. Nivolumab infusion must be promptly followed by a saline flush to clear the line of nivolumab before starting the ipilimumab infusion. The second infusion will always be the ipilimumab study drug and will start after the infusion line has been flushed, filters changed and participant has been observed to ensure no infusion reaction has occurred. The time in between infusions is expected to be approximately 30-minutes but may be more or less depending on the situation.

Participants may be dosed with nivolumab no less than 12 days from the previous dose. There are no premedications recommended.

Participants should be carefully monitored for infusion reactions. If an acute infusion reaction is noted, participant should be managed according to Section 7.4.2.

Doses of nivolumab and/or ipilimumab may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment. For more details, see Sections 7.4 (dose modification) and Section 8 (discontinuations).

Please refer to the current version of the Investigator Brochure and/or pharmacy manual for complete preparation, storage, and handling information for nivolumab and ipilimumab.

Arm B (Nivolumab) Dosing:

Participants should receive nivolumab at a dose of 480 mg as a 30 minute infusion on Day 1 of each treatment cycle every 4 weeks until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first with a maximum of 1-year total duration of study medication. For adolescents between 12 to < 18 years of age, use the body weight-based dosing for nivolumab 6 mg/kg Q4W up to a maximum of 480 mg. This will be applicable for participants enrolled after IRB approval of Revised Protocol 02 and will be implemented upon IRT modification. Participants should begin study treatment within 3 calendar days of randomization.

In order to maintain the blind, nivolumab placebo will be administered on D1WK3, D1WK7, D1WK11, D1WK15, D1WK19, D1WK23, D1WK27, D1WK31, D1WK35, D1WK39, D1WK43 and D1WK47. Ipilimumab placebo will be administered on D1WK1, D1WK7, D1WK13, D1WK19, D1WK25, D1WK31, D1WK37, D1WK43, and D1WK49. (See Table 7.1-1)

For participants who have been randomized to Arm C: (Ipilimumab) before the implementation of Amendment 06:

Sites that have randomized participants to the ipilimumab arm will be unblinded to that information and the participants will be allowed to continue as open-label on either ipilimumab 10 mg/kg or switch to nivolumab 480 mg. The change will be implemented upon IRT modification

For participants who continue on Ipilimumab 10 mg/kg:

Open label

Participants should continue receiving ipilimumab at a dose of 10 mg/kg as a 90-minute IV infusion, on Day 1 of each treatment cycle every 3 weeks for 4 doses, then every 12 weeks beginning at Week 24, until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first with a maximum of 1-year total duration of study medication. Participants should begin study treatment within 3 calendar days of randomization. (See Table 2-8)

For Participants who switch to Nivolumab 480 mg.

Open-label.

The first dose of nivolumab 480 mg should occur 8 weeks +/- 3 days after the last dose of ipilimumab 10 mg/kg. Participants should receive nivolumab at a dose of 480 mg as a 30 minute IV infusion in each treatment cycle every 4 weeks until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first, with a maximum of 1-year total duration of study medication starting from first dose of ipilimumab 10 mg/kg. (See Table 2-9) For adolescents between 12 to < 18 years of age, use the body weight-based dosing for nivolumab 6 mg/kg Q4W up to a maximum of 480 mg. The change will be implemented upon IRT modification.

Dosing calculations should be based on the body weight assessed at baseline. It is not necessary to re-calculate subsequent doses if the participant weight is within 10% of the weight used to calculate the previous dose. All doses should be rounded up or to the nearest milligram per institutional standard.

Table 7.1-1 outlines the dosing schedule for Arms A and B in this study.

Table 7.1-1: Dosing Schedule for Study CA209915[a,b]

	D1, W1	D1, W3	D1, W5	D1, W7	D1, W9
Arm A[c]	Nivo 240 mg Ipi 1 mg/kg	Nivo 240 mg	Nivo 240 mg	Nivo 240 mg Ipi 1 mg/kg	Nivo 240 mg
Arm B[d]	Nivo 480 mg Placebo- ipi	Placebo - nivo	Nivo 480 mg	Placebo - nivo Placebo - ipi	Nivo 480 mg
	D1, W11	**D1, W13**	**D1, W15**	**D1, W17**	**D1, W19**
Arm A	Nivo 240 mg	Nivo 240 mg Ipi 1 mg/kg	Nivo 240 mg	Nivo 240 mg	Nivo 240 mg Ipi 1 mg/kg
Arm B	Placebo - nivo	Nivo 480 mg Placebo - ipi	Placebo - nivo	Nivo 480 mg	Placebo - nivo Placebo - ipi
	D1, W21	**D1, W23**	**D1, W25**	**D1, W27**	**D1, W29**
Arm A	Nivo 240 mg	Nivo 240 mg	Nivo 240 mg Ipi 1 mg/kg	Nivo 240 mg	Nivo 240 mg
Arm B	Nivo 480 mg	Placebo - nivo	Nivo 480 mg Placebo - ipi	Placebo - nivo	Nivo 480 mg
	D1, W31	**D1, W33**	**D1, W35**	**D1, W37**	**D1, W39**
Arm A	Nivo 240 mg Ipi 1 mg/kg	Nivo 240 mg	Nivo 240 mg	Nivo 240 mg Ipi 1 mg/kg	Nivo 240 mg
Arm B	Placebo - nivo Placebo - ipi	Nivo 480 mg	Placebo - nivo	Nivo 480 mg Placebo - ipi	Placebo - nivo
	D1, W41	**D1, W43**	**D1, W45**	**D1, W47**	**D1, W49**
Arm A	Nivo 240 mg	Nivo 240 mg Ipi 1 mg/kg	Nivo 240 mg	Nivo 240 mg	Nivo 240 mg Ipi 1 mg/kg
Arm B	Nivo 480 mg	Placebo - nivo Placebo - ipi	Nivo 480 mg	Placebo - nivo	Nivo 480 mg Placebo - ipi

[a] Nivo = nivolumab, Ipi = ipilimumab

[b] For adolescents between 12 to < 18 years of age the dosing of nivolumab is body weight based dosing as follows Q2 week dosing - 3 mg/kg IV Q2 weeks up to a maximum of 240 mg; Q4 week dosing - 6 mg/kg Q4 weeks up to a maximum of 480 mg. This will be applicable for participants enrolled after IRB approval of Revised Protocol 02 and will be implemented upon IRT modification.

[c] Arm A: Nivo 240 mg Q2W + Ipi 1 mg/kg Q6W

[d] Arm B: Nivo 480 mg Q4W (nivo placebo on Weeks 3, 7, 11, 15, 19, 23, 27, 31, 35, 39, 43, & 47 and ipilimumab placebo Weeks 1, 7, 13, 19, 25, 31, 37, 43, & 49)

7.2 Method of Treatment Assignment

After the participant's initial eligibility is established and informed consent has been obtained, the participant must be enrolled into the study through IRT web to obtain the participant number. Every participant that signs the informed consent form must be assigned a participant number in

IRT. Specific instructions for using IRT will be provided to the investigational site in a separate document. The investigator or designee will register the participant for enrollment by following the enrollment procedures established by BMS. The following information is required for enrollment:

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

Once enrolled in IRT, enrolled participants that have met all eligibility criteria (including the required tumor tissue being received and processed and PD-L1 expression levels logged into the IRT by the central laboratory as well as the pathology report being approved by the investigator) will be ready to be randomized through the IRT. The randomization call will be performed by the unblinded pharmacy site staff. The following information is required for participant randomization:

- Participant number
- Date of birth
- Participants will be stratified by:
  - PD-L1 evaluable status (PD-L1 expression < 1% or indeterminate, 1% - <5%, ≥ 5% tumor cell surface expression) is entered by the central laboratory into the IRT system and both the site and the BMS study team remain blinded to the result. The statistician may be unblinded to the participant's PD-L1 status results in order to track the overall number of events in the primary population (subjects with PD-L1 < 1%).
  - AJCC Stage, 8th edition
    - stage IIIb
    - stage IIIc/d
    - stage IV

Participants will be treated with one of the following:

- Arm A: nivolumab 240 mg IV Q2 weeks plus ipilimumab 1 mg/kg IV Q6 weeks (for 1 year of treatment)
- Arm B: nivolumab 480 mg IV Q4 weeks (for 1 year of treatment) with nivo placebo on Weeks 3, 7, 11, 15, 19, 23, 27, 31, 35, 39, 43, & 47 and ipilimumab placebo Weeks 1, 7, 13, 19, 25, 31, 37, 43, & 49

The original study design included an ipilimumab monotherapy arm (Arm C). Randomization into Arm C was discontinued upon implementation of Amendment 06. Sites that have randomized participants to the ipilimumab arm will be unblinded to that information and the participants will be allowed to continue as open-label on either ipilimumab 10 mg/kg IV Q3W for 4 doses, then

Q12W starting at Week 24 or switch to nivolumab 480 mg IV Q4W after 8 weeks +/- 3 days washout after the last dose of ipilimumab. The change will be implemented upon IRT modification. See Table 2-8 and Table 2-9 for additional information.

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

7.3 Blinding

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 participant in which knowledge of the investigational product is critical to the participant's management, the blind for that participant may be broken by the investigator. The participant's safety takes priority over any other considerations in determining if a treatment assignment should be unblinded.

Before breaking the blind of an individual participant's treatment, the investigator should determine that the unblinded information is necessary, ie, that it will alter the participant'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 participant 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. The actual task of unblinding can be delegated by the investigator to a designee assigned the task on the Delegation of Authority. The Principal Investigator should only call in for emergency unblinding AFTER the decision to discontinue the participant has been made.

For this study, the method of unblinding for emergency purposes is IRT.

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

Any request to unblind a participant for non-emergency purposes must be discussed with the Medical Monitor.

In case of an emergency, the investigator(s) has unrestricted access to randomization information via the Interactive Response Technology system (IRT) and is capable of breaking the blind through the IRT system without prior approval from sponsor. Following the unblinding the Investigator shall notify the medical monitor and/or study director.

Designated staff of BMS 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 BMS 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. The unblinded data will not impact the data integrity of the study. The pharmacist at the site and/or designate will be unblinded to the randomized treatment assignments in order to dispense treatment from bulk supplies, as needed. Except as noted above, other members of BMS Research and Development will remain blinded.

To further minimize bias, the sponsor central study team and the investigative clinical site staff are blinded to results from PD-L1 analysis. Designated staff (ie, statistician) may be unblinded to the participant's PD-L1 status results in order to track the overall number of events in the primary population (subjects with PD-L1 < 1%). The unblinded data will not impact the data integrity of the study.

7.4 Dose Modification

Dose reductions or dose escalations are not permitted. All dose modification rules apply to all arms given the blinded nature of this study.

7.4.1 Dose Delay Criteria

Dose delay criteria apply for all drug-related adverse events regardless of whether or not the event is attributed to nivolumab, ipilimumab, or both. All study drugs must be delayed until treatment can resume (Section 7.4.3).

Dose delay criteria also apply to the placebo version of each agent, given the blinded nature of this study. Study drug administration should be delayed for the following:

- Grade 2 non-skin, drug-related AE, with the exception of fatigue
- Grade 2 drug-related creatinine, AST, ALT and/or Total Bilirubin abnormalities
- Grade 3 skin, drug-related AE
- Grade 3 drug-related laboratory abnormality, with the following exceptions:
  - Grade 3 lymphopenia or asymptomatic amylase or lipase does not require dose delay
  - Grade ≥ 3 AST, ALT, Total Bilirubin will require dose discontinuation (see Section 8)
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

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

7.4.2 Treatment of Nivolumab or Ipilimumab Related Infusion Reactions

Since nivolumab and ipilimumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritis, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the BMS Medical Monitor and reported as an SAE if criteria are met. Infusion reactions should be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE (version 4.0)) guidelines.

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

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

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

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

Stop the nivolumab or ipilimumab infusion, begin an IV infusion of normal saline, and treat the participant with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor participant 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 participant closely. If symptoms recur then no further nivolumab or ipilimumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the participant until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF). The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional nivolumab or ipilimumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

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

Immediately discontinue infusion of nivolumab or ipilimumab. Begin an IV infusion of normal saline, and treat the participant 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. Participant should be monitored until the investigator is comfortable that the symptoms will not recur. Nivolumab or ipilimumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor participant until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritis within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids).

7.4.3 Criteria to Resume Treatment

Participants may resume treatment with study treatment when the drug-related AE(s) resolve to Grade ≤ 1 or baseline value, with the following exceptions:

- Participants may resume treatment in the presence of Grade 2 fatigue
- Participants who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- For participants with Grade 2 AST, ALT and/or Total Bilirubin Abnormalities, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete.
- Drug-related pulmonary toxicity, diarrhea or colitis must have resolved to baseline before treatment is resumed. Participants with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by BMS Medical Monitor (or designee).

Participants with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the BMS Medical Monitor (or designee). Adrenal insufficiency ≥ Grade 3 requires discontinuation regardless of control with hormone replacement.

If the criteria to resume treatment are met, the participant should restart treatment at the next scheduled time point per protocol. However, if the treatment is withheld past the window period of the next scheduled time point per protocol to ensure adequate recovery from the adverse event or tapering of immunosuppression, the next scheduled time point will be delayed until dosing resumes.

If treatment is withheld > 6 weeks from the last dose, the participant must be permanently discontinued from study therapy, except as specified in Section 8.

7.5 Preparation/Handling/Storage/Accountability

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 Participants. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

The product storage manager should ensure that the study treatment 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 treatment arise, the study treatment should not be dispensed and contact BMS immediately.

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

Investigational product documentation (whether supplied by BMS or not) must be maintained that includes all processes required to ensure drug is accurately administered. This includes

documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

Storage facilities for controlled substances must be securely locked and substantially constructed, with restricted access to prevent theft or diversion, as applicable by local regulations.

Further guidance and information for final disposition of unused study treatment are provided in Appendix 4.

Please refer to the current version of the Investigator Brochure and/or pharmacy manual for complete preparation, storage, and handling information for nivolumab and ipilimumab.

7.5.1 Retained Samples for Bioavailability/Bioequivalence

Not applicable.

7.6 Treatment Compliance

Study treatment compliance will be periodically monitored by drug accountability.

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

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 participants.

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 participant: (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 participants 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 participants prior to enrollment.

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

[redacted]

7.8 Treatment After the End of the Study

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

BMS reserves the right to terminate access to BMS supplied study treatment if any of the following occur: a) the study is terminated due to safety concerns; b) the development of nivolumab is terminated for other reasons, including but not limited to lack of efficacy and/or not meeting the study objectives; c) the participant can obtain medication from a government sponsored or private health program. In all cases BMS will follow local regulations.

8 DISCONTINUATION CRITERIA

8.1 Discontinuation from Study Treatment

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

- Participant's request to stop study treatment. Participants 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 participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information
- 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 participant
- 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. (Note: Under specific circumstances, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply and BMS approval is required.)

In the case of pregnancy, the investigator must immediately notify the Sponsor or designee of this event. In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). Please contact the Sponsor or designee within 24 hours of awareness of the pregnancy. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug, a discussion between the investigator and the Sponsor or designee must occur.

All participants who discontinue study treatment should comply with protocol specified follow-up procedures as outlined in Section 2. The only exception to this requirement is when a participant withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

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

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

Treatment should be permanently discontinued for the following:

- Any Grade 2 drug-related uveitis, 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 AE lasting > 7 days, or recurs with the following exceptions for laboratory abnormalities, diarrhea, colitis, neurologic toxicity, drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, infusion reactions, and endocrinopathies:
  - Grade 3 drug-related diarrhea, colitis, neurologic toxicity, uveitis, pneumonitis, bronchospasm, myocarditis, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
  - Grade 3 drug-related endocrinopathies, adequately controlled with only physiologic hormone replacement do not require discontinuation. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
    - Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
      - Grade ≥ 3 drug-related AST, ALT or Total Bilirubin requires discontinuation*
      - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2x ULN

*In most cases of Grade 3 AST or ALT elevation, study drug(s) will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug(s), a discussion between the investigator and the BMS Medical Monitor/designee must occur.

- Any Grade 3 non-hormonal immune-mediated adverse reaction that recurs on reintroduction of nivolumab or ipilimumab, or a requirement for 10 mg per day or greater of prednisone or prednisone equivalent for more than 12 weeks
  - Persistent Grade 2 or 3 immune-mediated adverse drug reactions that last 12 weeks or longer with exception for Grade 2 endocrinopathies.
- Any Grade 4 drug-related adverse event or laboratory abnormality (including but not limited to creatinine, AST, ALT, or Total Bilirubin), except for the following events which do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia or leukopenia or asymptomatic amylase or lipase

  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
  - Grade 4 drug-related endocrinopathy adverse events, such as, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS Medical Monitor.
- Any event that leads to delay in dosing lasting >6 weeks from the previous dose requires discontinuation, with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events are allowed.
  - Dosing delays lasting > 6 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS medical monitor.

Prior to re-initiating treatment in a participant with a dosing delay lasting >6 weeks, the BMS Medical Monitor (or designee) must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.

Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the participant with continued study drug dosing.

Refer to the Schedule of Activities for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that can be completed.

8.1.1 Rechallenge

See Section 7.4.3.

8.1.2 Post Study Treatment Study Follow-up

In this study, recurrence-free survival and OS are key endpoints of the study. Post study follow-up is of critical importance and is essential to preserving participant safety and the integrity of the study. Participants who discontinue study treatment must continue to be followed for collection of tumor surveillance assessments and survival follow-up data as required and in line with Section 5 until death or the conclusion of the study.

BMS may request that survival data be collected on all treated/randomized participants outside of the protocol defined window (see Table 2-10). At the time of this request, each participant will be contacted to determine their survival status unless the participant has withdrawn consent for all contacts or is lost to follow-up.

8.2 Discontinuation from the Study

Participants 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

participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information.

- Participants 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 treatment 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 participant 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.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

8.3 Lost to Follow-Up

- All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant.
- Lost to follow-up is defined by the inability to reach the participant after a minimum of **three** documented phone calls, faxes, or emails as well as lack of response by participant to one registered mail letter. All attempts should be documented in the participant's medical records.
- If it is determined that the participant has died, the site will use permissible local methods to obtain 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 participant's informed consent, then the investigator may use a Sponsor retained third-party representative to assist site staff with obtaining participant's contact information or other public vital status data necessary to complete the follow-up portion of the study.
- The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information.
- If after all attempts, the participant remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the participant's medical records.

9 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and timing are summarized in the Schedule of Activities, Section 2.

- Protocol waivers or exemptions are not allowed.
- All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.

- Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Schedule of Activities.
- Additional measures, including non-study required laboratory tests, should be performed as clinically indicated or to comply with local regulations. Laboratory toxicities (eg, suspected drug induced liver enzyme evaluations) 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.
- If a participant shows pulmonary-related signs (hypoxia, fever) or symptoms (eg, dyspnea, cough, and fever) consistent with possible pulmonary adverse events, the participant should be immediately evaluated to rule out pulmonary toxicity, according to the suspected pulmonary toxicity management algorithm in the BMS-936558 (nivolumab) Investigator Brochure.
- Some of the assessments referred to in this section may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

9.1 Efficacy Assessments

Study evaluations will take place in accordance with the flow charts in Section 2. Baseline disease assessments should be performed within 28 days prior to randomization utilizing CT or MRI. This includes a CT or MRI scans of chest, abdomen, pelvis, and all known sites of resected disease in the setting of stage IIIb/c/d and stage IV, and brain MRI (brain CT allowable if MRI is contraindicated or if there is no known history of resected brain lesions). Participants will be evaluated for presence or continued lack of tumor until local, regional, or distant recurrence (whichever comes first) for stage IV participants and until distant recurrence for stage III participants beginning 12 weeks (± 7 days) relative to the first dose of study treatment, and will continue to have surveillance assessment every 12 weeks (± 7 days) for the first 12 months. From > 12 months to 36 months after randomization, efficacy assessments should be every 12 weeks (± 14 days). From > 36 months until Year 5 after first dose of study treatment, efficacy assessments should be performed every 6 months (± 4 weeks).

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

9.1.1 Definitions

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

Local Cutaneous Recurrence:

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

Regional Lymphatic and Nodal Recurrences:

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

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

Patterns of Metastases:

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

9.1.2 Methods of measurements

- Cross-sectional imaging
  - CT and MRI are an important part of the work-up to establish recurrence. Contrast enhanced CT and MRI are the preferred imaging modalities. See Section 9.1.4 for details.
  - PET alone will not be considered for the disease assessment. Complementary CT and/or MRI or biopsy must be performed in such cases.
- Cytology and/or histology are mandatory to confirm recurrence in solitary or in doubtful lesions, cutaneous, subcutaneous or lymph node lesions. Histological or cytological evidence of recurrence should be attempted in all cases except for brain metastases when safe and

clinically feasible. An example when obtaining a biopsy to confirm recurrence may not be safe and clinically feasible is brain metastases.

- Clinically detected new lesions:
  - Superficial cutaneous lesions: the neoplastic nature must be confirmed by cytology/histology.
  - Deep subcutaneous lesions and lymph node lesions should be documented by ultrasound and histological/cytological evidence should be attempted. In absence of pathology report, lesion recurrence will be documented with a CT scan/MRI.
- Tumor markers or auto-antibodies alone cannot be used to assess recurrence.

9.1.3 Date of Recurrence

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

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

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

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

9.1.4 Imaging Assessment for the Study

Contrast enhanced CT or MRI scans of the chest, abdomen and pelvis and all other known/suspected sites of disease should be performed at all timepoints.

- Should a participant have contraindication for CT intravenous contrast, a non-contrast CT of the chest and a contrast-enhanced MRI of the abdomen, pelvis, and other known/suspected sites of disease should be obtained.
- Should a participant have contraindication for both MRI and CT intravenous contrasts, a non-contrast CT or non-contrast MRI of the chest, abdomen, pelvis, and other known/suspected sites of disease should be obtained.
- Should a participant have contraindication for MRI (eg, incompatible pacemaker) in addition to contraindication to CT intravenous contrast, a non-contrast CT of the chest, abdomen, pelvis, and other known/suspected sites of disease is acceptable.

At Screening, MRI (brain CT allowable if MRI is contraindicated) of the brain without and with contrast is required in participants with known history of brain metastases; Participants without known history of brain metastases should have head CT or MRI without and with contrast. On

treatment and follow-up, participants with a history of brain metastasis should have surveillance MRI approximately every 12 weeks, or sooner if clinically indicated; Participants without history of brain metastases should have MRI or CT if clinically indicated.

The same method of assessment used at Screening should be used for on-study timepoints. CT and MRI scans should be acquired with slice thickness of 5 mm or less with no intervening gap (contiguous). Every attempt should be made to image each participant using an identical acquisition protocol on the same scanner for all imaging timepoints.

All participants must have disease-free status defined as no clinical or radiographic evidence of recurrence of disease documented by a complete physical examination and imaging studies within 4 weeks prior to randomization. Participants with equivocal nodes ≥ 10 mm and < 15 mm in a short axis may be eligible after if confirmation with histology/cytology is available. If risk of biopsy is too high or biopsy is not feasible, two sequential CT or MRI scans should be available and showing no signs of progressive and measurable disease or PET/CT demonstrating no FDG uptake. The second scan should occur at least 4 weeks after the initial scan. Lymph nodes ≥ 15 mm in a short axis are defined as pathological.

If recurrence is unequivocal (eg, multiple measurable lesions), confirmation with histology/cytology should be attempted but is not required.

If recurrence is equivocal, lymph node only, solitary lesion, confirmation with histology/cytology must be attempted. If risk of biopsy is too high or biopsy not feasible, either a follow-up CT or MRI scan showing progressive and measurable disease or PET/CT demonstrating unequivocal FDG uptake must confirm recurrence. Follow-up (confirmatory) scan should occur in 4-12 weeks after the initial scan. The date of initial scan showing recurrence will count as recurrence.

Imaging assessments will be submitted to a third party radiology vendor on an ongoing basis; participant management is not dependent on third-party review of tumor assessments.

9.2 Adverse Events

The definitions of an AE or serious adverse event (SAE) can be found in Appendix 5.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue before completing the study.

Contacts for SAE reporting are specified in Appendix 5

Immune-mediated adverse events are AEs consistent with an immune-mediated mechanism or immune-mediated component for which non-inflammatory etiologies (eg, infection or tumor progression) have been ruled out. IMAEs can include events with an alternate etiology which were exacerbated by the induction of autoimmunity.

Immune-mediated adverse reactions are specific events occurring within 100 days of the last dose [which includes pneumonitis, diarrhea/colitis, hepatitis, nephritis/renal dysfunction, rash, and endocrine abnormalities (adrenal insufficiency, hypothyroidism/thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis)], regardless of causality, for which subjects received immunosuppressive medication for treatment of the event. The exception to the immunosuppressive medication criteria for IMARs is endocrine events (hypothyroidism/thyroiditis, hyperthyroidism, hypophysitis, diabetes mellitus, adrenal insufficiency), which are included regardless of treatment since these events are often managed without immunosuppression. In order to prospectively identify immune-mediated adverse reactions and to assist with the optimal management of such patients, please refer to the current version of the Investigator Brochure and the Adverse Event Management Algorithms for Immuno-Oncology Agents (Appendix 6 to this protocol).

Information supporting the assessment will be collected on the participant's case report form.

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

The collection of nonserious AE information should begin at initiation of study treatment until the timepoints specified in the Schedule of Activities (Section 2). 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 participants.

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

All SAEs must be collected that occur during the screening period and within 100 days of the last dose of study treatment. For participants randomized to treatment and never treated with study drug, SAEs should be collected for 30 days from the date of randomization. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

The investigator must report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure, (eg, a follow-up skin biopsy).

- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the appropriate section of the eCRF section.
- All SAEs will be recorded and reported to Sponsor or designee within 24 hours, as indicated in Appendix 5.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of this being available.

Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant

has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.

The method of evaluating, and assessing causality of AEs and SAEs and the procedures for completing and reporting/transmitting SAE reports are provided in Appendix 5.

9.2.2 Method of Detecting AEs and SAEs

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a participant. Care should be taken not to introduce bias when collecting AE and/or SAEs. Inquiry about specific AEs should be guided by clinical judgement in the context of known adverse events, when appropriate for the program or protocol. Every adverse event must be assessed by the investigator with regard to whether it is considered immune-mediated. For events which are potentially immune-mediated, additional information will be collected on the participant's case report form.

9.2.3 Follow-up of AEs and SAEs

- Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Appendix 5).
- Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study treatment 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.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 9.2 will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up (as defined in Section 8.3).

Further information on follow-up procedures is given in Appendix 5.

9.2.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of SAEs is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a product under clinical investigation are met.
- An investigator who receives an investigator safety report describing SAEs or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

All SAEs must be collected that occur during the screening period and within 100 days of the last dose of study treatment. For participants randomized/assigned to treatment and never treated with study drug, SAEs should be collected for 30 days from the date of randomization.

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

9.2.5 Pregnancy

If, following initiation of the study treatment, it is subsequently discovered that a participant is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half-lives after product administration, the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Appendix 5

In most cases, the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). Please call the BMS Medical Monitor within 24 hours of awareness of the pregnancy.

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 Sponsor or designee. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

9.2.6 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form electronic, as appropriate. Paper forms are only intended as a back-up option when the electronic system is not functioning.

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

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

9.2.7 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 Appendix 5 for reporting details).

Potential drug induced liver injury is defined as:

1. AT (ALT or AST) elevation > 3 times 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.

9.2.8 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.

9.3 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 Appendix 5, Safety).

9.4 Safety

Planned time points for all safety assessments are listed in the Schedule of Activities, Section 2.

Participants will be evaluated for safety if they have received any study drug. Toxicity assessments will be continuous during the treatment phase. During the safety follow-up phase (Table 2-10), toxicity assessments should be done in person. Once participants reach the survival follow-up phase either in person or documented telephone calls (telephone calls are only allowed during times where no surveillance assessments are to be done) to assess the participant's status are acceptable.

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

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

9.4.1 Physical Examinations

Refer to Schedule of Activities.

9.4.2 Vital signs

Refer to Schedule of Activities.

9.4.3 Electrocardiograms

Refer to Schedule of Activities.

9.4.4 Clinical Safety Laboratory Assessments

Investigators must document their review of each laboratory safety report. See the Schedule of Activities for specific assessments and time points.

Hematology	
Hemoglobin	
Hematocrit	
Total leukocyte count, including differential	
Platelet count	
Serum Chemistry	
Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Total bilirubin Alkaline phosphatase Lactate dehydrogenase (LDH) Creatinine Blood Urea Nitrogen (BUN) Glucose Amylase as clinically indicated Lipase as clinically indicated	Albumin at screening and as clinically indicated Thyroid Sodium Potassium Chloride Calcium Phosphate Magnesium Creatinine clearance (CLcr) - screening only ACTH as clinically indicated Cortisol as clinically indicated
Serology	
a) Serum for hepatitis C antibody, hepatitis B surface antigen, HIV-1 and -2 antibody (screening only) Note: Testing for HIV must be performed at sites where mandated locally.	
Other Analyses	
Pregnancy test (WOCBP only: as it is indicated on Section 2. Tables 2-1 to 2-8).	
Follicle stimulating hormone (FSH) (screening only for women only)	

9.4.5 Suicidal Risk Monitoring

Not applicable

9.4.6 Imaging Safety Assessment

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.

[redacted]

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

The sample size of the study is based on a comparison of the RFS distribution between participants randomized to nivolumab plus ipilimumab and participants randomized to nivolumab. RFS will be evaluated for treatment effect using the following testing strategy: RFS will be compared first in the all randomized participants with PD-L1 expression level < 1% subgroup with an alpha allocation of 0.03 (two-sided); and if significant, the alpha allocated to this subgroup will be recycled to the treatment comparison in the overall population (all randomized participants). Thus RFS will be compared in all randomized participants with an alpha allocation of 0.05 (two-sided). If the treatment comparison in all randomized participants with PD-L1 expression level < 1% is not significant, RFS will be compared in all randomized participants with an alpha allocation based on the method published by Spiessens and Debois[53]. This method takes into account the correlation between the test statistics for the overall and the subgroup analysis, and is essentially the same as the method used when dealing with interim analyses, ie, group sequential method. The alpha allocated to the overall analysis will be calculated based on the fraction of information in the subgroup, relative to the overall population, which is determined by the ratio of events observed in the two groups. For example, if 257 events are observed in the PD-L1 expression level < 1% subgroup, and 651 events are observed in the overall population (ie, about 40% of all events in the PD-L1<1% subgroup), the alpha allocated to the overall analysis is 0.0265.

Simulation models incorporating aspects of immunotherapy like delayed separation (observed as late separation of survival curves between the experimental and SOC arms) and long term survival benefits (observed as a long-lasting plateau towards the tail of the survival curve) were developed for sample size estimation. Sample size calculations for this study design were done using EAST 6 (v 6.3.1) and R.

The sample size is driven by the comparison of RFS between all randomized participants with PD-L1 expression level < 1% randomized to receive nivolumab plus ipilimumab vs nivolumab. Approximately 600 participants with PD-L1 expression level < 1% will be randomized in a 1:1 ratio to nivolumab plus ipilimumab and nivolumab respectively. Approximately 257 RFS events in all randomized participants with PD-L1 expression level < 1% will provide approximately 90% power to detect an average hazard ratio (HR) of 0.65 with an alpha level of 0.03 (two-sided). In case the 257 RFS events would be reached at a timepoint earlier than 13 months of minimum follow-up (from the randomization of the last participant), analysis of RFS will be conducted when there would be a minimum follow up of 13 months (ie, at the time when approximately 257 events are reached or a minimum follow-up of 13 months, whatever occurs later).

Accrual will be stopped when approximately 600 participants with PD-L1 expression level < 1% will be randomized in a 1:1 ratio to nivolumab plus ipilimumab and nivolumab respectively. The prevalence of participants with PD-L1 expression level < 1% is expected to be around 30% of all randomized participants. Therefore, it is estimated that approximately 2000 participants will be randomized in a 1:1 ratio to nivolumab plus ipilimumab and nivolumab respectively. No more than 1400 participants with PD-L1 expression level ≥ 1% will be randomized to nivolumab plus ipilimumab and nivolumab respectively. Approximately 700 participants with PD-L1 expression level < 1% were randomized in a 1:1 ratio to nivolumab plus ipilimumab and nivolumab respectively.

Approximately 651 RFS events in all randomized participants will provide approximately 90% power to detect an average hazard ratio (HR) of 0.76 with an alpha level of 0.0265 (two-sided).

The analysis of RFS in the all randomized participants with PD-L1 expression level < 1% subgroup will be performed at the time when approximately 257 RFS events are observed in this subgroup or a minimum follow-up of 13 months is reached, whatever occurs later.

If the treatment comparison in the all randomized participants with PD-L1 expression level < 1% subgroup is significant, RFS will be compared in all randomized participants with an alpha allocation of 0.05. In this case, two analyses, an interim and a final, will be conducted in all randomized participants. The interim analysis will take place at the same time as the RFS analysis for the PD-L1 expression level < 1% subgroup. The final analysis will take place when approximately 560 RFS events are observed in the overall population. The stopping boundaries at the interim and final analyses will be derived based on the exact number of RFS events using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries.

If the treatment comparison in all randomized participants with PD-L1 expression level < 1% subgroup is not significant, RFS will be compared in the overall population with an alpha

allocation based on the method published by Spiessens and Debois.[53] In this case, no interim analysis is planned. The final RFS analysis for the overall population will be conducted when approximately 651 RFS events are observed (assuming allocated alpha is 0.0265). In case the events come slower than projected, final analysis of RFS for the overall population will be conducted when the minimum follow up from randomization of the last participant reaches 30 months.

Given actual accrual rates so far and estimated accrual rates of 157 participants per month for the coming months, it is estimated that accrual of 2000 participants (ie, 1000 participants in a 1:1 ratio in the nivolumab plus ipilimumab and nivolumab arms each) and the participants in the ipilimumab arm that has already taken place, will take approximately 17 months. Given actual accrual rates, accrual took approximately 13.5 months.

Additional details on monitoring of events will be provided in the DMC charter.

10.1.1 RFS

The primary objective of the study is to compare RFS of nivolumab plus ipilimumab to nivolumab monotherapy in participants with completely resected stage IIIb/c/d or stage IV no evidence of disease (NED) melanoma. The number of events and power were calculated assuming a non-proportional hazards model with a 3-month delayed treatment effect and a cure rate in each of the treatment arms.

10.1.1.1 RFS in All Randomized Participants with PD-L1 Expression Level < 1%

For this comparison of RFS between nivolumab plus ipilimumab and nivolumab in all randomized participants with PD-L1 expression level < 1%, at least 257 RFS events would be required with PD-L1 expression level < 1% in the two respective treatment arms for a two-sided experiment-wise alpha = 0.03 log-rank test, to show a statistically significant difference in RFS between the treatment arms with at least 90.0% power when the average hazard ratio (HR) of the nivolumab plus ipilimumab arm to the nivolumab arm is 0.65. A cure rate of 0.42 is assumed in the nivolumab treatment arm. Under the assumptions for accrual and RFS distribution as per CA209238, Section 7.3 of the Clinical Study Report, nivolumab estimates and assumed HR as stated above, it would take approximately 29 months from the randomization of the first participant to observe the required number of RFS events. It is projected that an observed HR of 0.76 or less would result in a statistically significant improvement at the final analysis of RFS.

10.1.1.2 RFS in All Randomized Participants

For this comparison of RFS between nivolumab plus ipilimumab and nivolumab in all randomized participants, at least 651 RFS events would be required in the two respective treatment arms for a two-sided alpha = 0.0265 log-rank test, to show a statistically significant difference in RFS between the treatment arms with approximately 90% power when the average hazard ratio (HR) of the nivolumab plus ipilimumab arm to the nivolumab arm is 0.76. A cure rate of 0.49 is assumed in the nivolumab treatment arm. Under the assumptions for accrual and RFS distribution as per CA209238, Section 7.3 of the Clinical Study Report, nivolumab estimates and assumed HR as stated above, it would take approximately 44 months from the randomization of the first participant

to observe the required number of RFS events. It is projected that an observed HR of 0.84 or less would result in a statistically significant improvement at the final analysis of RFS.

For this comparison of RFS between nivolumab plus ipilimumab and nivolumab in all randomized participants, at least 560 RFS events would be required in the two respective treatment arms for a two-sided alpha = 0.05 log-rank test, to show a statistically significant difference in RFS between the treatment arms with approximately 90% power when the average hazard ratio (HR) of the nivolumab plus ipilimumab arm to the nivolumab arm is 0.76. A cure rate of 0.49 is assumed in the nivolumab treatment arm. Under the assumptions for accrual and RFS distribution as per CA209238, Section 7.3 of the Clinical Study Report, nivolumab estimates and assumed HR as stated above, it would take approximately 30 months from the randomization of the first participant to observe the required number of RFS events. It is projected that an observed HR of 0.85 or less would result in a statistically significant improvement at the final analysis of RFS.

10.1.2 Overall Survival

The secondary objective of the study is to compare OS of nivolumab plus ipilimumab to nivolumab monotherapy in participants with completely resected stage IIIb/c/d or stage IV no evidence of disease (NED) melanoma. The number of events and power were calculated assuming a non-proportional hazards model with a cure rate in each of the treatment arms.

10.1.2.1 OS in All Randomized Participants with PD-L1 Expression Level < 1%

For this comparison of OS between nivolumab plus ipilimumab and nivolumab in all randomized participants with PD-L1 expression level <1%, at least 250 deaths would be required in the two respective treatment arms for a two-sided experiment-wise alpha = 0.05 adjusted log-rank test, to show a statistically significant difference in OS between the treatment arms with at least 80% power when the average hazard ratio (HR) of the nivolumab plus ipilimumab arm to the nivolumab arm is 0.70. It is projected that an observed HR of 0.78 or less would result in a statistically significant improvement at the final analysis of OS.

10.1.2.2 OS in All Randomized Participants

For this comparison of OS between nivolumab plus ipilimumab and nivolumab in all randomized participants, at least 630 deaths would be required in the two respective treatment arms for a two-sided experiment-wise alpha = 0.05 adjusted log-rank test, to show a statistically significant difference in OS between the treatment arms with at least 80% power when the average hazard ratio (HR) of the nivolumab plus ipilimumab arm to the nivolumab arm is 0.80. It is projected that an observed HR of 0.85 or less would result in a statistically significant improvement at the final analysis of OS.

For this comparison of OS between nivolumab plus ipilimumab and nivolumab in all randomized participants, at least 753 deaths would be required in the two respective treatment arms for a two-sided experiment-wise alpha = 0.0265 adjusted log-rank test, to show a statistically significant difference in OS between the treatment arms with at least 80% power when the average hazard ratio (HR) of the nivolumab plus ipilimumab arm to the nivolumab arm is 0.80. It is projected that

an observed HR of 0.85 or less would result in a statistically significant improvement at the final analysis of OS.

10.2 Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
All enrolled participants	All participants who signed an informed consent form and were registered into the IVRS.
All randomized participants	All participants who were randomized to any treatment arm in the study.
All randomized participants with PD-L1 expression level < 1%	All randomized participants with baseline tumor sample testing per IHC result < 1% membranous staining in tumor cell.
All treated participants	All participants who received at least one dose of study drug.
All treated participants with PD-L1 expression level < 1%	All participants with baseline tumor sample testing per IHC result < 1% membranous staining in tumor cell who received at least one dose of study drug.
[redacted]	[redacted]
Immunogenicity evaluable participants: -Nivolumab ADA evaluable participants -Ipilimumab ADA evaluable participants	 -All treated participants with baseline and at least 1 post baseline pre-infusion nivolumab immunogenicity assessment -All treated participants with baseline and at least 1 post baseline pre-infusion ipilimumab immunogenicity assessment
[redacted]	[redacted]

10.3 Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock and will describe the selection of participants to be included in the analyses, and procedures for accounting for missing and unused data. Below is a summary of planned statistical analyses of the primary and secondary endpoints. For participants in the ipilimumab arm, their data will be presented separately.

A description of the participant population will be included in the statistical output reported, including subgroup of age, gender, and race.

10.3.1 Efficacy Analyses

10.3.1.1 Primary Endpoint Analysis

The primary endpoint is RFS. The primary endpoint of RFS will be programmatically determined based on the disease recurrence date provided by the investigator and is defined as the time between the date of randomization and the date of first recurrence (local, regional or distant metastasis), new primary melanoma (including melanoma in situ), or death (whatever the cause), whichever occurs first. (Note: a participant who dies without reported recurrence will be considered to have recurred on the date of death.) For participants who remain alive and whose disease has not recurred, RFS will be censored on the date of last evaluable disease assessment. For those participants who remained alive and had no recorded post-randomization tumor assessment, RFS will be censored on the day of randomization. Censoring rules for the primary analysis of RFS are presented in Table 10.3.1.1-1.

Table 10.3.1.1-1: Censoring Scheme for Primary Definition of RFS

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

RFS distributions will be compared between treatment groups (nivolumab plus ipilimumab vs nivolumab) using a two-sided log-rank test stratified by AJCC stage at screening at a significance level of 3% (two-sided) in all randomized participants with PD-L1 expression level <1%.

RFS distributions will be compared, as described in Sections 10.1 and 10.3.4, between treatment groups (nivolumab plus ipilimumab vs nivolumab) using a two-sided log-rank test stratified by PD-L1 status and AJCC stage at screening in all randomized participants.

The hazard ratio and corresponding 100x (1-adjusted α)% confidence intervals (CIs) will be estimated using a Cox proportional hazards model, with treatment group as a single covariate, stratified by the above factors.

RFS curves will be estimated using Kaplan-Meier (KM) product-limit methodology. Median RFS with two-sided 95% CIs using the log-log transformation will be computed. In addition, RFS rates at 6, 12, 24 and 36 months (and yearly after depending on follow-up) with two-sided 95% CIs using the log-log transformation will be computed.

The proportional hazards assumption will be assessed at the time of analysis and appropriate methods will be employed in case of non-proportional hazards.

10.3.1.2 Secondary Endpoint Analyses

Overall Survival

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

OS distributions will be compared in hierarchical testing order (order defined in Section 10.3.4) between treatment groups (nivolumab plus ipilimumab vs nivolumab) using a two-sided log-rank test stratified by AJCC stage at screening at the overall significance level of 5% (two-sided) in all randomized participants with PD-L1 expression level < 1%.

OS distributions will be compared in hierarchical testing order (order defined in Section 10.3.4) between treatment groups (nivolumab plus ipilimumab vs nivolumab) using a two-sided log-rank test stratified by PD-L1 status and AJCC stage at screening at the overall significance level of 5% (two-sided) in all randomized participants.

The hazard ratio and corresponding two-sided 100x (1-adjusted α)% CIs will be estimated using a Cox proportional hazards model, with treatment group as a single covariate, stratified by the above factors.

OS curves will be estimated using Kaplan-Meier (KM) product-limit methodology. Median OS with two-sided 95% CIs using the log-log transformation will be computed. In addition, OS rates at 6, 12, 24 and 36 months (and yearly after depending on follow-up) with two-sided 95% CIs using the log-log transformation will be computed.

Association between PD-L1 expression and RFS

The secondary objective (to evaluate the association between PD-L1 expression and RFS) will be measured by the endpoint RFS based on PD-L1 expression level.

Analyses of PD-L1 expression will include;

- Examination of the distribution of PD-L1 expression using descriptive statistics and, cumulative distribution plots.

- Assessment of the potential association between PD-L1 expression using >= 1% expression level and RFS: forest plots of unstratified hazard ratios with 95% CIs for treatment effect on RFS by PD-L1 expression.
- Assessment of the potential association between PD-L1 expression using >= 5% expression level and RFS: forest plots of unstratified hazard ratios with 95% CIs for treatment effect on RFS by PD-L1 expression.

Investigator-Assessed Outcomes on Next-Line Therapies

PFS2 is defined as the time from randomization to second recurrence/objective disease progression, or death from any cause, whichever occurs first.

In case PFS2 cannot be reliably determined, we will analyze the time from randomization to end or discontinuation of next-line treatment, second objective disease progression, or death from any cause, whichever occurs first.

These endpoints will be analyzed using a two-sided log-rank test at the overall significance level of 5% (two-sided) in all randomized participants. The hazard ratio and corresponding 95% confidence intervals (CIs) will be estimated using a Cox proportional hazards model, with treatment group as a single covariate. No multiplicity adjustment will be applied.

Objective response rates and duration of treatment on next-line therapies will be summarized.

10.3.2 Safety Analyses

Safety and tolerability of nivolumab combined with ipilimumab and nivolumab monotherapy will be measured by the incidence of adverse events, serious adverse events, deaths, and laboratory abnormalities.

Safety analyses will be performed in all treated participants with PD-L1 expression level <1% as well as in all treated participants. Descriptive statistics of safety will be presented using NCI CTCAE version 4.0 by treatment group (for the nivolumab combined with ipilimumab and nivolumab monotherapy arms). All on-study AEs, treatment-related AEs, SAEs, and treatment-related SAEs will be tabulated using worst grade per NCI CTCAE v 4.0 criteria by system organ class and preferred term. On-study lab parameters including hematology, chemistry, liver function, and renal function will be summarized using worst grade NCI CTCAE v 4.0 criteria.

[redacted]

[redacted]

[redacted]

10.3.4 Interim Analyses and Hierarchical Testing

RFS will be evaluated for treatment effect using the following testing strategy: RFS will be compared first in the all randomized participants with PD-L1 expression level < 1% subgroup with an alpha allocation of 0.03 (two-sided); and if significant, the alpha allocated to this subgroup will be recycled to the treatment comparison in the overall population (all randomized participants). Thus RFS will be compared in all randomized participants with an alpha allocation of 0.05 (two-sided). If the treatment comparison in all randomized participants with PD-L1 expression level < 1% is not significant, RFS will be compared in all randomized participants with an alpha allocation

based on the method published by Spiessens and Debois.[53] This method takes into account the correlation between the test statistics for the overall and the subgroup analysis, and is essentially the same as the method used when dealing with interim analyses, ie, group sequential method. The alpha allocated to the overall analysis will be calculated based on the fraction of information in the subgroup, relative to the overall population, which is determined by the ratio of events observed in the two groups. For example, if 257 events are observed in the PD-L1 expression level < 1% subgroup, and 651 events are observed in the overall population (ie, about 40% of all events in the PD-L1<1% subgroup), the alpha allocated to the overall analysis is 0.0265.

If the treatment comparison in the all randomized participants with PD-L1 expression level < 1% subgroup is significant, RFS will be compared in all randomized participants with an alpha allocation of 0.05. In this case, two analyses, an interim and a final, will be conducted in all randomized participants. The interim analysis will take place at the same time as the RFS analysis for the PD-L1 expression level < 1% subgroup. The final analysis will take place when approximately 560 RFS events are observed in the overall population. The stopping boundaries at the interim and final analyses will be derived based on the exact number of RFS events using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries.

If the treatment comparison in the all randomized participants with PD-L1 expression level < 1% subgroup is not significant, RFS will be compared in the overall population with an alpha allocation based on the method published by Spiessens and Debois[53]. In this case, no interim analysis is planned. The final RFS analysis for the overall population will be conducted when approximately 651 RFS events are observed. (assuming allocated alpha is 0.0265). In case the events come slower than projected, final analysis for the overall population will be conducted when the minimum follow up from randomization of the last participant reaches 30 months.

If both hypotheses for the RFS endpoint (for the PD-L1 < 1% subgroup and the overall population) are rejected, OS will be compared in all randomized participants with PD-L1 expression level < 1% with an alpha allocation of 0.05 (two-sided); and if significant, then OS will be compared in all randomized participants with an alpha allocation of 0.05 (two-sided). One formal OS interim analysis will be conducted at the time that approximately 162 deaths (65% information fraction) have been reached among all randomized participants with PD-L1 expression level < 1%. This formal comparison of OS will allow for early stopping for superiority. The stopping boundaries at the interim and final analyses will be derived based on the exact number of deaths using Lan DeMets alpha spending function with O'Brien-Fleming boundaries.

If the treatment comparison of RFS in the all randomized participants with PD-L1 expression level < 1% subgroup is not significant, but the treatment comparison of RFS in the all randomized participants population is significant (at alpha of 0.0265 or calculated), OS will be compared in all randomized participants at an alpha allocation of 0.0265 or calculated (two-sided).

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.

12 APPENDICES

APPENDIX 1 AJCC MELANOMA STAGING

[From AJCC Cancer Staging Manual, 8th Edition (pages 577 & 578)]

Definition of Primary Tumor (T)

T Category	Thickness	Ulceration Status
TX: primary tumor thickness cannot be assessed (e.g., diagnosis by curettage)	Not applicable	Not applicable
T0: no evidence of primary tumor (e.g., unknown primary or completely regressed melanoma)	Not applicable	Not applicable
Tis (melanoma *in situ*)	Not applicable	Not applicable
T1	≤1.0 mm	Unknown or unspecified
T1a	<0.8 mm	Without ulceration
T1b	<0.8 mm 0.8-1.0 mm	With ulceration With or without ulceration
T2	>1.0-2.0 mm	Unknown or unspecified
T2a	>1.0-2.0 mm	Without ulceration
T2b	>1.0-2.0 mm	With ulceration
T3	>2.0-4.0 mm	Unknown or unspecified
T3a	>2.0-4.0 mm	Without ulceration
T3b	>2.0-4.0 mm	With ulceration
T4	>4.0 mm	Unknown or unspecified
T4a	>4.0 mm	Without ulceration
T4b	>4.0 mm	With ulceration

Definition of Distant Metastasis (M)

M Category	Anatomic site	LDH level
M0	No evidence of distant metastasis	Not applicable
M1	Evidence of distant metastasis	See below
M1a	Distant metastasis to skin, soft tissue including muscle, and/or non-regional lymph node	Not recorded or unspecified
M1a(0)		Not elevated
M1a(1)		Elevated
M1b	Distant metastasis to lung with or without M1a sites of disease	Not recorded or unspecified
M1b(0)		Not elevated
M1b(1)		Elevated
M1c	Distant metastasis to non-CNS visceral sites with or without M1a or M1b sites of disease	Not recorded or unspecified
M1c(0)		Not elevated
M1c(1)		Elevated
M1d	Distant metastasis to CNS with or without M1a, M1b, or M1c sites of disease	Not recorded or unspecified
M1d(0)		Not elevated
M1d(1)		Elevated
Suffixes for M category: (0) LDH not elevated; (1) LDH elevated. No suffix is used if LDH is not recorded or is unspecified.		

Definition of Regional Lymph Node (N)

N Category	Number of tumor-involved regional lymph nodes	Presence of in-transit, satellite, or microsatellite metastases
NX	Regional nodes not assessed (e.g., SLN biopsy not performed, regional nodes previously removed for another reason) **Exception**: pathological N category is not required for T1 melanomas, use cN	No
N0	No regional metastases detected	No
N1	One tumor-involved node or in-transit, satellite, and/or microsatellite metastases with no tumor-involved nodes	
N1a	One clinically occult (i.e., detected by SLN biopsy)	No
N1b	One clinically detected	No
N1c	No regional lymph node disease	Yes
N2	Two or three tumor-involved nodes or in-transit, satellite, and/or microsatellite metastases with one tumor-involved node	
N2a	Two or three clinically occult (i.e., detected by SLN biopsy)	No
N2b	Two or three, at least one of which was clinically detected	No
N2c	One clinically occult or clinically detected	Yes
N3	Four or more tumor-involved nodes or in-transit, satellite, or microsatellite metastases with two or more tumor-involved nodes, or any number of matted nodes with or without in-transit, satellite, and/or microsatellite metastases	
N3a	Four or more clinically occult (i.e., detected by SLN biopsy)	No
N3b	Four or more, at least one of which was clinically detected, or presence any number of matted nodes	No
N3c	Two or more clinically occult or clinically detected, and/or presence any number of matted nodes	Yes

AJCC Prognostic Stage Groups

Clinical (cTNM)

Clinical stage includes microstaging of the primary melanoma and clinical/radiologic/biopsy evaluation for metastases. By convention, clinical staging should be used after biopsy of the primary melanoma, with clinical assessment for regional and distant metastases. Note that pathological assessment of the primary melanoma is used for both clinical and pathological classification. Diagnostic biopsies to evaluate possible regional and/or distant metastasis also are included. Note there is only one stage group for clinical Stage III melanoma.

When T is....	And N is.....	And M is....	The clinical stage is...
Tis	N0	M0	0
T1a	N0	M0	IA
T1b	N0	M0	IB
T2a	N0	M0	IB
T2b	N0	M0	IIA
T3a	N0	M0	IIA
T3b	N0	M0	IIB
T4a	N0	M0	IIB
T4b	N0	M0	IIC
Any T, Tis	≥N1	M0	III
Any T	Any N	M1	IV

PATHOLOGICAL (PTNM)

Pathological staging includes microstaging of the primary melanoma, including any additional staging information from the wide excision (surgical) specimen that constitutes primary tumor surgical treatment and pathological information about the regional lymph nodes after SLN biopsy or therapeutic lymph node dissection for clinically evident regional lymph node disease.

When T is....	And N is.....	And M is....	The pathological stage is...
Tis	N0	M0	0
T1a	N0	M0	IA
T1b	N0	M0	IA
T2a	N0	M0	IB
T2b	N0	M0	IIA
T3a	N0	M0	IIA
T3b	N0	M0	IIB
T4a	N0	M0	IIB
T4b	N0	M0	IIC
T0	N1b, N1c	M0	IIIB
T0	N2b, N2c, N3b or N3c	M0	IIIC
T1a/b-T2a	N1a-N2a	M0	IIIA
T1a/b-T2a	N1b/c or N2b	M0	IIIB
T2b/T3a	N1a-N2b	M0	IIIB
T1a-T3a	N2c or N3a/b/c	M0	IIIC
T3b/T4a	Any N $\geq$N1	M0	IIIC
T4b	N1a-N2c	M0	IIIC
T4b	N3a/b/c	M0	IIID
Ant T, Tis	Any N	M1	IV
Pathological Stage 0 (melanoma *in situ*) and T1 do not require pathological evaluation of lymph nodes to complete pathological staging; use cN information to assign their pathological stage.			

APPENDIX 2 PERFORMANCE STATUS SCALES

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

APPENDIX 3 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40 mIU/mL to confirm menopause.

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

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

Local laws and regulations may require use of alternative and/or additional contraception methods.

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal

• Progestogen-only hormonal contraception associated with inhibition of ovulation[b] – oral – injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation [b] • Hormonal methods of contraception including oral contraceptive pills containing a combination of estrogen and progesterone, vaginal ring, injectables, implants and intrauterine hormone-releasing system (IUS)[c] • Intrauterine device (IUD)[c] • Bilateral tubal occlusion
• Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.* • It is not necessary to use any other method of contraception when complete abstinence is elected. • WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2. • Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence
NOTES: [a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. [b] Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized. [c] Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness

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

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

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

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Male participants are required to use a condom for study duration and until the end of relevant systemic exposure defined as 7 months after the end of treatment in the male participant.
- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 7 months after the end of treatment in the male participant.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 7 months after the end of treatment.
- Refrain from donating sperm for the duration of the study treatment and until 7 months after the end of treatment.

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 9.2.5 and the Appendix for Adverse Events and Serious Adverse Events Definitions and procedures for Evaluating, Follow-up and Reporting

APPENDIX 4 STUDY GOVERNANCE CONSIDERATIONS

The term 'Participant' is used in the protocol to refer to a person who has consented to participate in the clinical research study. The term 'Subject' used in the eCRF is intended to refer to a person (Participant) who has consented to participate in the clinical research study.

REGULATORY AND ETHICAL CONSIDERATIONS

GOOD CLINICAL PRACTICE

This study will be conducted in accordance with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines Good Clinical Practice (GCP),
- as defined by the International Council on Harmonisation (ICH)
- in accordance with the ethical principles underlying European Union Directive 2001/20/EC
- United States Code of Federal Regulations, Title 21, Part 50 (21CFR50)
- applicable local requirements.

The study will be conducted in compliance with the protocol. The protocol and any amendments and the participant informed consent will receive approval/favorable opinion by Institutional Review Board/Independent Ethics Committee (IRB/IEC), and regulatory authorities according to applicable local regulations prior to initiation of the study.

All potential serious breaches must be reported to Sponsor or designee immediately. A breach of the conditions and principles of Good Clinical Practice (GCP) (occurring in any country) in connection with that trial or the protocol related to the trial which is likely to affect to a significant degree the safety or physical or mental integrity of 1 or more subjects of the trial or the scientific value of the trial.

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 (e.g., loss of medical licensure, debarment).

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, participant recruitment materials (e.g., 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, Sponsor or designee should provide the IRB/IEC with reports, updates and other information (e.g., expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion of an amendment from the IRB/IEC (and if applicable, also by local health authority) 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 relevant approval/favorable opinion(s) the deviation or change will be submitted, as soon as possible to:

- IRB/IEC
- Regulatory Authority(ies), if applicable by local regulations (per national requirements)

Documentation of approval/favorable opinion signed by the chairperson or designee of the IRB(s)/IEC(s) and if applicable, also by local health authority must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the participant: (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).

FINANCIAL DISCLOSURE

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

INFORMED CONSENT PROCESS

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 by subjects, their legally acceptable representatives (as per country guidelines) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the participant volunteers to participate.

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

Investigators must:

- Provide a copy of the consent form and written information about the study in the language in which the participant is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
- Allow time necessary for participant or participant's legally acceptable representative to inquire about the details of the study.
- Obtain an informed consent signed and personally dated by the participant or the participant's legally acceptable representative and by the person who conducted the informed consent discussion.
- Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.

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

Revise the informed consent whenever important new information becomes available that is relevant to the participant's consent. The investigator, or a person designated by the investigator, should fully inform the participant or the participant's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the participant'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 participant records.

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

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

Subjects unable to give their written consent (e.g., stroke or subjects with or severe dementia) may only be enrolled in the study with the consent of a legally acceptable representative. The participant must also be informed about the nature of the study to the extent compatible with his or her understanding, and should this participant become capable, he or she should personally sign and date the consent form as soon as possible. The explicit wish of a participant 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.

SOURCE DOCUMENTS

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

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

STUDY TREATMENT RECORDS

Records for study treatments (whether supplied by BMS, its vendors, or the site) must substantiate study treatment integrity and traceability from receipt, preparation, administration, and through destruction or return. Records must be made available for review at the request of BMS/designee or a Health Authority.

If	Then
Supplied by BMS (or its vendors):	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 participant, including unique participant identifiers • amount transferred to another area/site for dispensing or storage • nonstudy disposition (e.g., 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.
Sourced by site, and not supplied by BMS or its vendors (examples include IP sourced from the sites stock or commercial supply, or a specialty pharmacy)	The investigator or designee accepts responsibility for documenting traceability and study treatment integrity in accordance with requirements applicable under law and the SOPs/standards of the sourcing pharmacy.

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

CASE REPORT FORMS

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

For sites using the Sponsor or designee 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 electronic SAE form and Pregnancy Surveillance form, respectively. If electronic SAE form is not available, a paper SAE form can be used. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by Sponsor or designee.

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, 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. Subinvestigators in Japan may not be delegated the CRF approval task 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 Sponsor or designee training requirements and must only access the BMS electronic data capture tool using the unique user account provided by Sponsor or designee. User accounts are not to be shared or reassigned to other individuals

MONITORING

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

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

In addition, the study may be evaluated by Sponsor or designee 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 Sponsor or designee.

RECORDS RETENTION

The investigator (or head of the study site in Japan) 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 or designee, whichever is longer. The investigator (or head of the study site in Japan) must contact BMS prior to destroying any records associated with the study.

BMS or designee will notify the investigator (or head of the study site in Japan) when the study records are no longer needed.

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

RETURN OF STUDY TREATMENT

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

If..	Then
Study treatments supplied by BMS (including its vendors	Any unused study treatments supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless study treatments containers must be immediately destroyed as required for safety, or to meet local regulations (e.g., cytotoxics or biologics). If study treatments will be returned, the return will be arranged by the responsible Study Monitor.
Study treatments sourced by site, not supplied by BMS (or its vendors) (examples include study treatments sourced from the sites stock or commercial supply, or a specialty pharmacy)	It is the investigator's or designee's responsibility to dispose of all containers according to the institutional guidelines and procedures.

It is the investigator's or designee's responsibility to arrange for disposal, 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. The following minimal standards must be 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.

It is the investigator's or designee's responsibility to arrange for disposal of all empty containers.

If conditions for destruction cannot be met the responsible Study Monitor will make arrangements for return of study treatments provided by BMS (or its vendors). Destruction of non- study treatments sourced by the site, not supplied by BMS, is solely the responsibility of the investigator or designee.

CLINICAL STUDY REPORT AND PUBLICATIONS

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

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

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

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

APPENDIX 5 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW UP AND REPORTING

ADVERSE EVENTS

Adverse Event Definition:
An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study treatment and that does not necessarily have a causal relationship with this treatment.
An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not considered related to the study treatment.
Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or results from other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Note that abnormal lab tests or other safety assessments should only be reported as AEs if the final diagnosis is not available. Once the final diagnosis is known, the reported term should be updated to be the diagnosis. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose, as a verbatim term (as reported by the investigator), should not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae and should specify "intentional overdose" as the verbatim term
Events NOT Meeting the AE Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

DEFINITION OF SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

SERIOUS ADVERSE EVENTS

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening (defined as an event in which the participant 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) 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 (e.g., 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 (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason) • admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)
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 participant or may require intervention [e.g., 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 9.2.7 for the definition of potential DILI.)

Pregnancy and potential drug induced liver injury (DILI) must follow the same transmission timing and processes to BMS as used for SAEs (see section 9.2.5 for reporting pregnancies).

EVALUATING AES AND SAES

Assessment of Causality
• The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. • A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated. • The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment. • For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. • There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Sponsor. • The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.

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

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

All SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

- SAEs, whether related or not related to study treatment, and pregnancies must be reported to BMS (or designee) immediately within 24 hours of awareness of the event.
- SAEs must be recorded on the SAE Report Form.
  - The required method for SAE data reporting is through the eCRF.
  - The paper SAE Report Form is only intended as a back-up option when the electronic data capture (EDC) system is unavailable/not functioning for transmission of the eCRF to BMS (or designee).
    - In this case, the paper form is transmitted via email or confirmed facsimile (fax) transmission
    - When paper forms are used, the original paper forms are to remain on site
- Pregnancies must be recorded on a paper Pregnancy Surveillance Form and transmitted via email or confirmed facsimile (fax) transmission

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

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

APPENDIX 7 ABBREVIATIONS AND TRADEMARKS

Term	Definition
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AT	aminotransaminases
AUC	area under the concentration-time curve
AUC(INF)	area under the concentration-time curve from time zero extrapolated to infinite time
AUC(0-T)	area under the concentration-time curve from time zero to the time of the last quantifiable concentration
AUC(TAU)	area under the concentration-time curve in one dosing interval
β-HCG	beta-human chorionic gonadotrophin
BLQ	below limit of quantification
BMS	Bristol-Myers Squibb
BP	blood pressure
BUN	blood urea nitrogen
C	Celsius
Ca^{++}	calcium
Cavg	average concentration
CBC	complete blood count
Cexpected-tau	expected concentration in a dosing interval
CFR	Code of Federal Regulations
CI	confidence interval
$C1^{-}$	chloride
CLcr	creatinine clearance
cm	centimeter
Cmax, CMAX	maximum observed concentration
Cmin, CMIN	minimum observed concentration
CNS	Central nervous system

Term	Definition
CRC	Clinical Research Center
CRF	Case Report Form, paper or electronic
Ctrough	Trough observed plasma concentration
CV	coefficient of variation
CYP	cytochrome p-450
D/C	discontinue
dL	deciliter
DMC	Data monitoring committee
ECG	electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eg	exempli gratia (for example)
ESR	Expedited Safety Report
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GFR	glomerular filtration rate
h	hour
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCO_3^-	bicarbonate
HIV	Human Immunodeficiency Virus
HR	heart rate
HRT	hormone replacement therapy
ICH	International Conference on Harmonisation
ie	id est (that is)

Term	Definition
IEC	Independent Ethics Committee
IMP	investigational medicinal products
IND	Investigational New Drug Exemption
IRB	Institutional Review Board
IRT	Interactive Response Technology
IU	International Unit
IV	intravenous
K	slope of the terminal phase of the log concentration-time curve
K_3EDTA	potassium ethylenediaminetetraacetic acid
K^+	potassium
kg	kilogram
L	liter
LDH	lactate dehydrogenase
ln	natural logarithm
mg	milligram
Mg^{++}	magnesium
min	minute
mL	milliliter
mmHg	millimeters of mercury
MMIS	malignant melanoma in situ
MMR	measles, mumps, rubella
µg	microgram
N	number of subjects or observations
Na^+	sodium
N/A	not applicable
ng	nanogram
NIMP	non-investigational medicinal products
NSAID	nonsteroidal anti-inflammatory drug
PD	pharmacodynamics
PK	pharmacokinetics

Term	Definition
QC	quality control
R^2	coefficient of determination
RBC	red blood cell
SAE	serious adverse event
SD	standard deviation
SOP	Standard Operating Procedures
t	temperature
T	time
T-HALF	Half life
TID, tid	ter in die, three times a day
Tmax, TMAX	time of maximum observed concentration
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential
WNOCBP	women **not** of childbearing potential