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Clinical Protocol CA017055

A Phase 3, Randomized, Double-blind Study of BMS-986205 Combined with Nivolumab versus Nivolumab in Participants with Metastatic or Unresectable Melanoma that is Previously Untreated

Revised Protocol 02
Incorporates Administrative Letters: 01 and 02

Study Director/Medical Monitor
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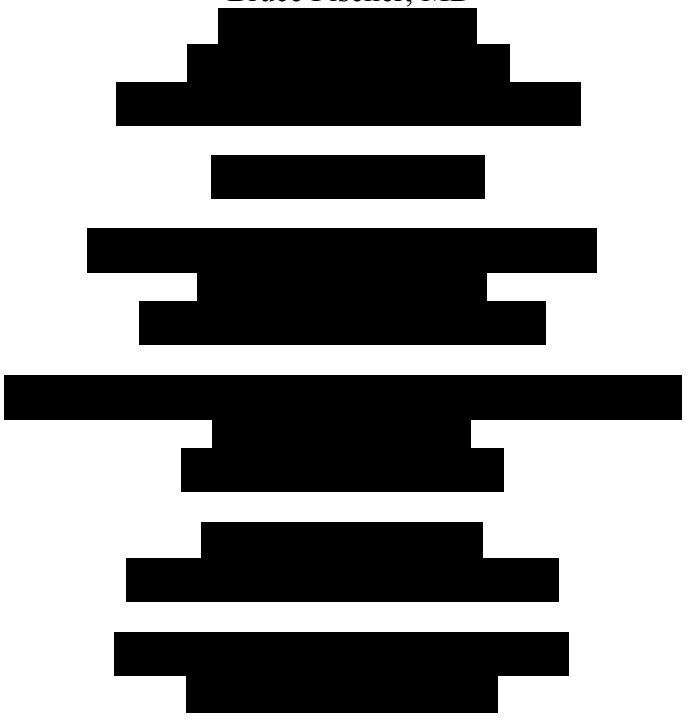

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Replace all previous version(s) of the protocol with this revised protocol and please provide a copy of this revised protocol to all study personnel under your supervision, and archive the previous versions.

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 02	25-Oct-2018	Revised Protocol incorporates the Administrative Letters 01 and 02, clarifies typographical errors in the Revised Protocol 01 and incorporates clarifications on prohibited treatments, Appendices 03 and 05 of the BMS Protocol Model Document
Administrative Letter 02	09-Aug-2018	The purpose of this administrative letter is to clarify some typographical errors that occurred during the formatting of the Revised Protocol 01.
Administrative Letter 01	03-Aug-2018	This letter serves to clarify the language in the contraceptive appendix. A vasectomized partner is considered a highly effective method of contraception for WOCBP participants in this study. An additional note is added to reinforce that, vasectomized males receiving BMS-986205 must still use a synthetic or latex condom to prevent exposure in partners who are WOCBP or pregnant.
Revised Protocol 01	13-Jun-2018	To close the enrollment into the study, and to remove collection of efficacy assessments. In addition, safety collections were updated.
Original Protocol	28-Aug-2017	Not applicable

OVERALL RATIONALE FOR REVISED PROTOCOL 02:

[redacted].

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Cover Page	Change of Medical Monitor.	N/A
Appendix **03** - Adverse events and serious adverse events: Definitions and procedures for recording, evaluating, follow up and reporting	The Restructured Protocol Model Document Appendix 3 was rolled out on March 28 included changes in order to clarify our policy relative to the collection of disease related events. Those Appendix 3 changes were made in error and are now clarified.	[redacted]
Appendix **04**-Women of Childbearing Potential; Contraceptive Guidance for Female Participants of Child Bearing Potential	An additional note is added to reinforce that, vasectomized males receiving BMS-986205 must still use a synthetic or latex condom to prevent exposure in partners who are WOCBP or pregnant.	[redacted]
Appendix **05** - [redacted]	[redacted]	[redacted]
Section 7 – Table 7-1	BMS-986205-04 50or100mg is Unblinded.	[redacted]
Section 7-1.2, Nivolumab Dosing	Total infusion volume is 160mL.	[redacted]
Section 7.7.1, Prohibited treatments	Any live / attenuated vaccine is prohibited during study treatment and within 100 days post last dose.	[redacted]

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1 SYNOPSIS

Protocol Title: A Phase 3, Randomized, Double-blind Study of BMS-986205 Combined with Nivolumab versus Nivolumab in Participants with Metastatic or Unresectable Melanoma that is Previously Untreated

Study Phase: 3

[redacted]

Study Population:

The study population consists of adult (≥ 18 years of age, or age of majority) participants with unresectable or metastatic melanoma that is previously untreated who have not received prior systemic therapy for their disease. Enrollment in this study was closed on 19-Apr-2018.

Key Inclusion Criteria:

- Histologically confirmed Stage III (unresectable) or Stage IV melanoma, per the American Joint Committee on Cancer (AJCC) Staging Manual (8th edition)
- Treatment-naïve participants (ie, no prior systemic anticancer therapy for unresectable or metastatic melanoma). Note that prior adjuvant or neoadjuvant melanoma therapy is permitted in the setting of completely resected disease if it was completed at least 6 months prior to randomization, and all related adverse events (AEs) have either returned to baseline or stabilized.
- At least one measurable lesion by computed tomography (CT) or magnetic resonance imagery (MRI) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria
- Tumor tissue (biopsy or surgical specimen, where applicable) from an unresectable or metastatic site of disease must be provided for biomarker analyses. In order to be randomized, a participant must be classified as PD-L1 positive (≥ 1% tumor cell membrane staining) vs

PD-L1 negative (< 1% tumor cell membrane staining)/PD-L1 indeterminate (tumor cell membrane scoring hampered by high cytoplasmic staining or melanin content). If an insufficient amount of tumor tissue from an unresectable or metastatic site is available prior to the start of the screening phase, then a fresh biopsy will be required during the screening phase for performance of biomarker analyses.

- Participants must have known BRAF V600 mutation status or consent to BRAF V600 mutation testing per local institutional standards during the Screening Period and have results of BRAF testing available prior to randomization. Participants with indeterminate BRAF status or with BRAF status not documented prior to randomization are not permitted to randomize to a treatment arm.
- Prior radiotherapy must have been completed at least 2 weeks prior to study treatment administration.
- Participants must be able to swallow pills intact.

Key Exclusion Criteria:

- Women who are pregnant or breastfeeding
- Active brain metastases or leptomeningeal metastases. Participants with brain metastases are eligible if these have been treated and there is no magnetic resonance imagery (MRI) evidence of progression for at least 8 weeks after treatment is complete and within 28 days prior to first dose of study treatment administration.
- Uveal or ocular melanoma
- Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of start of study treatment. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
- Participants with a personal or family (ie, in a first-degree relative) history of cytochrome b5 reductase deficiency (previously called methemoglobin reductase deficiency) or other diseases that put them at risk of methemoglobinemia. All participants will be screened for methemoglobin levels prior to randomization.
- Participants with a history of glucose 6-phosphate dehydrogenase (G6PD) deficiency or other congenital or autoimmune hemolytic disorders. All participants will be screened for G6PD levels prior to randomization.
- Prior treatment with an anti-PD-1 (except if given as adjuvant or neoadjuvant therapy for melanoma), anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody (except if given as adjuvant or neoadjuvant therapy for melanoma), or any other antibody or drug specifically targeting T-cell costimulation or immune checkpoint pathways
- Prior treatment with BMS-986205 or any other IDO1 inhibitors

Objectives and Endpoints:

As of 19-Apr-2018 enrollment in this study was closed and only safety assessments will be collected. No analyses of efficacy, quality of life/patient reported outcomes, pharmacokinetics, or

health resource utilization, are planned. Previously collected biomarker specimens may be analyzed, but no formal analyses are planned.

Overall Design:

This is a Phase 3, randomized, study of BMS-986205 in combination with nivolumab versus nivolumab monotherapy in adult and adolescent participants with unresectable or metastatic melanoma that is previously untreated. (This study was originally double blind with respect to BMS-986205 but was unblinded with Revised Protocol 01.)

- A pre-treatment tumor sample to determine PD-L1 status is required to be submitted from all participants prior to randomization. The sample must be obtained within 3 months prior to enrollment from a metastatic tumor lesion or from an unresectable primary tumor lesion; the tumor sample must be taken from a site of disease that has not been previously irradiated. In addition, no intervening treatment may have been administered between the time of biopsy/surgery and randomization.
- Participants must have a documented BRAF status prior to randomization.
- Depending on the treatment arm, the participant will receive BMS-986205 plus nivolumab or nivolumab monotherapy for up to 104 weeks (approximately 2 years) of study treatment. Under Revised Protocol 01, BMS-98205 Placebo will not be administered to Arm B participants, and investigators have the option of continuing on nivolumab monotherapy in participants assigned to Arm A (nivolumab + BMS986205).
- One cycle of treatment is defined as 4 weeks. Treatment will continue until investigator-assessed disease progression per RECIST v1.1 criteria, unacceptable toxicity, withdrawal of consent/assent, or completion of 104 weeks of treatment, whichever occurs first. Treatment beyond initial progression is permitted if the participant has investigator-assessed clinical benefit, is tolerating study treatment (see Sections 8.1.1 and 8.1.3.2 of the protocol), and has not yet completed 104 weeks of study treatment.
- On-study tumor assessments will follow the schedule of the local standard of care.

Number of Participants:

As of 19-April-2018 enrollment into this study was closed.

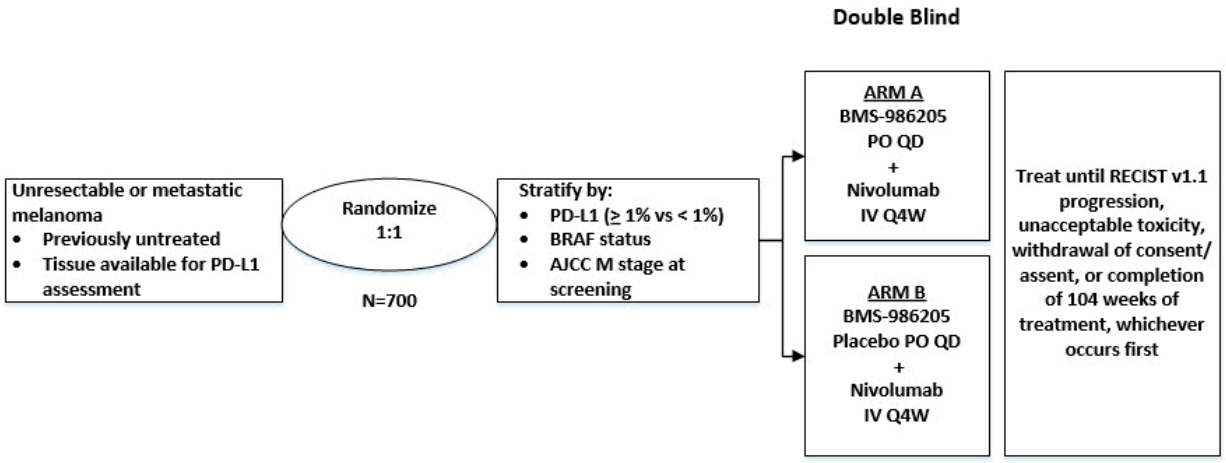
Treatment Arms and Duration:

Study treatment:

Study Drug for CA017055		
Medication	**Potency**	**IP/Non-IP**
BMS-936558-01 (Nivolumab) Solution for Injection	100 mg (10 mg/mL)	IP
BMS-986205-04	100 mg	IP
BMS-986205-04	50 mg	IP

The original study design schematic is presented in Figure 1-1. Under Revised Protocol 01 the study is closed to enrollment and is no longer double blind.

Figure 1-1: Study Schematic



Note: As of Revised Protocol 01, treatment will no longer be blinded, and participants in Arm B will no longer receive BMS-986205 Placebo. Participants in Arm A, have the option to discontinue BMS-986205, and continue nivolumab monotherapy, at investigator discretion.

During the treatment phase, participants will receive:

- In Arm A: BMS-986205 100 mg PO QD and Nivolumab 480 mg IV Q4W for a maximum of 104 weeks. Under Revised Protocol 01 investigators have the option of continuing participants on nivolumab monotherapy.
- In Arm B: BMS-986205 Placebo PO QD and Nivolumab 480 mg IV Q4W for a maximum of 104 weeks. Under Revised Protocol 01 BMS-986205 Placebo should not be administered.

Dose reductions are not permitted for nivolumab. One dose reduction is permitted for BMS-986205, from a 100 mg QD tablet to a 50 mg QD tablet. No re-escalation is permitted after dose reduction. BMS-986205 tablets must be taken by mouth, and swallowed whole and intact. Crushing, chewing, dissolving, and other alterations to the formulation or route of administration are not permitted.

Doses of BMS-986205 and nivolumab should be delayed due to treatment-related AEs described in Section 7.4.3 of the protocol. Treatment-related AEs resulting in permanent discontinuation of study treatment are described in Section 8 of the protocol. Treatment may be prematurely discontinued due to unacceptable toxicity, withdrawal of consent, disease progression, or completion of treatment cycles, whichever occurs first. A Data Monitoring Committee (DMC) will provide independent oversight of safety, study conduct and efficacy of the study treatments.

Duration:

As of 19-Apr-2018, enrollment in the study was closed. Participants currently enrolled in the study may continue to receive treatment until progression, unacceptable toxicity, withdrawal of consent, or 104 weeks from the first dose of nivolumab.

2 SCHEDULE OF ACTIVITIES

Table 2-1: Screening Procedural Outline (CA017055)

Per Revised Protocol 01 enrollment in the study is closed. Participants in screening who have not been randomized at the time of enrollment closure (19-Apr-2018) will not start study treatment and should be screen failed (see Section 3.1.1).		
Procedure[a]	**Screening Visit**	**Notes (All windows are based on calendar days)**
Eligibility Assessments		
Informed Consent	X	Register in Interactive Response system (IRT) to obtain participant number
Inclusion/Exclusion Criteria	X	Must be confirmed prior to randomization
Medical History	X	All medical history relevant to the disease under study. Include concomitant medications, prior cancer therapy, American Joint Committee on Cancer (AJCC) stage, and BRAF mutation status. Glucose-6-phosphate dehydrogenase (G6PD) deficiency history, and cytochrome b5 reductase deficiency history. For participants without BRAF mutation status documented at screening, they must consent to BRAF mutation testing at this time and BRAF mutation results must be available prior to randomization.
Tumor Tissue Samples	X	All participants must have tumor tissue available, either recent archival sample (obtained within 3 months prior to enrollment from a site not previously irradiated and with no intervening treatment between time of acquisition and enrollment) or a fresh pre-treatment biopsy obtained during the screening period. Tissue may be from a core biopsy, punch biopsy, excisional biopsy or surgical specimen; fine needle aspiration and other cytology samples are not acceptable. Sufficient quantities must be available: a block or, optimally, at least 20 slides is requested, with a minimum of 10 slides required. In order to be randomized, a participant must have quantifiable PD-L1 expression (≥ 1% [positive] or < 1% [negative] tumor cell membrane staining) or be classified as PD-L1 indeterminate. See Section 5.1. The analytical laboratory must provide IRT with confirmation of the related results prior to randomization. Please refer to Section 9.8.1 for additional information.
Body Imaging	X	Contrast enhanced computed tomography (CT) of the chest, contrast-enhanced CT (or magnetic resonance imagery [MRI] with and without contrast) of the

Table 2-1: Screening Procedural Outline (CA017055)

Per Revised Protocol 01 enrollment in the study is closed. Participants in screening who have not been randomized at the time of enrollment closure (19-Apr-2018) will not start study treatment and should be screen failed (see Section 3.1.1).		
Procedure[a]	**Screening Visit**	**Notes (All windows are based on calendar days)**
		abdomen, pelvis, and all known sites of disease within 28 days prior to randomization. See Section 9.1.
Brain Imaging	X	For participants with a history or clinical symptoms of brain metastasis an MRI brain with and without gadolinium is required at Screening within 28 days prior to randomization. See Section 9.1.
Other Imaging (eg, Bone Scan)	X	As clinically indicated. See Section 9.1.
Safety Assessments		
Targeted Physical Examination, Measurements, Vital Signs, and Performance Status	X	Height, weight, and ECOG Performance Status (See Appendix 6), blood pressure (BP), heart rate (HR), temperature. Must be collected within 14 days prior to randomization. Vital signs must be obtained at the screening visit and within 3 calendar days prior to first dose.
Oxygen saturation	X	Oxygen saturation by pulse oximetry at rest within 14 days prior to randomization.
Assessment of Signs and Symptoms	X	Within 14 days prior to randomization
[redacted]	[redacted]	[redacted]
Serious Adverse Events (SAEs) Assessment	X	SAEs collected from time of consent
ECG	X	At rest
Laboratory Tests		
Complete Blood Count (CBC) with differential, methemoglobin levels, G6PD levels, Chemistry, Endocrine, Viral, , C-reactive protein, Urinalysis	X	For all except viral testing: must be performed within 14 days prior to randomization. Methemoglobin levels to be assessed on arterial or venous blood sample or by co-oximetry (performed locally). For viral testing and C-reactive protein: must be performed within 28 days prior to randomization.

Table 2-1: Screening Procedural Outline (CA017055)

Per Revised Protocol 01 enrollment in the study is closed. Participants in screening who have not been randomized at the time of enrollment closure (19-Apr-2018) will not start study treatment and should be screen failed (see Section 3.1.1).		
Procedure[a]	**Screening Visit**	**Notes (All windows are based on calendar days)**
		For HIV: testing at sites where locally mandated; see Appendix 13. For full list of assessments, see Section 9.4.1.
Pregnancy Test (WOCBP only)	X	Serum or urine pregnancy test (minimum sensitivity equivalent units 25IU/L or equivalent units of HCG) to be done at screening visit and repeated within 24 hours prior to first dose of study treatment

[a] 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 treatment physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

Table 2-2: On-study Assessments (CA017055)

Procedure[a]	BMS-986205 PO once daily (QD) + Nivolumab 480 mg[b], IV (Arm A) every 4 weeks (Q4W) OR Nivolumab 480 mg IV(Arm B) Q4W (Per Revised Protocol 01, no BMS-986205 Placebo will be given)			Notes[c]
	Cycle 1 (Day 1)	Cycle 1 (Day 14 ± 3 days)	Cycle 2 and subsequent on-treatment visits (Day 1 ± 3 days) (1 Cycle = 4 Weeks) Treat until progression, unacceptable toxicity, or completion of 104 weeks of therapy	
Study Treatment				
Randomize	X			First dose to be administered within 3 calendar days following randomization.
IRT Drug Assignment	X		X	
Administer Study Treatment	X		X	First dose to be administered within 3 calendar days following randomization. Advise participants on dosing of BMS-986205 with a meal. After the first nivolumab infusion, subjects should be monitored per local/institutional guidelines. If no such guidelines exist, an observation period of 2 hours after the end of the nivolumab infusion is suggested.
Dispense BMS-986205 and Pill Diary	**On C1D7 ± 3 days:** contact by telephone to ensure compliance with BMS-986205		X	Review pill diary during each visit for compliance of daily administration of BMS-986205. Collect pill diary at the completion of each cycle for participants receiving BMS-986205.

Table 2-2: On-study Assessments (CA017055)

Procedure[a]	BMS-986205 PO once daily (QD) + Nivolumab 480 mg[b], IV (Arm A) every 4 weeks (Q4W) OR Nivolumab 480 mg IV(Arm B) Q4W (Per Revised Protocol 01, no BMS-986205 Placebo will be given)			Notes[c]
	Cycle 1 (Day 1)	Cycle 1 (Day 14 ± 3 days)	Cycle 2 and subsequent on-treatment visits (Day 1 ± 3 days) (1 Cycle = 4 Weeks) Treat until progression, unacceptable toxicity, or completion of 104 weeks of therapy	
	dosing requirements			
Safety Assessments				
Targeted Physical Examination, Measurements, Vital Signs, and Performance Status	X	X	See note	Weight, BP, HR, temperature, and ECOG status prior to each dose. Targeted physical examination to be performed only as clinically indicated within 3 calendar days prior to dosing.
Oxygen Saturation	X	X	X	Oxygen saturation by pulse oximetry or co-oximetry at rest prior to dosing.
Adverse Events (AEs) Assessments (including SAEs)	Continuously			Record at each visit
ECG	X	X	See note	At rest. C1D1 and C1D14: Pre-dose for all participants, and 4 hours post dose for participants receiving BMS-986205. For Cycle 2 and beyond: Pre-dose, as clinically indicated, including if concomitant medications which may prolong the QTc interval are added.

Table 2-2: On-study Assessments (CA017055)

Procedure[a]	BMS-986205 PO once daily (QD) + Nivolumab 480 mg[b], IV (Arm A) every 4 weeks (Q4W) OR Nivolumab 480 mg IV(Arm B) Q4W (Per Revised Protocol 01, no BMS-986205 Placebo will be given)			Notes[c]
	Cycle 1 (Day 1)	Cycle 1 (Day 14 ± 3 days)	Cycle 2 and subsequent on-treatment visits (Day 1 ± 3 days) (1 Cycle = 4 Weeks) Treat until progression, unacceptable toxicity, or completion of 104 weeks of therapy	
[redacted]	[redacted]			[redacted]
Laboratory Tests				
CBC with differential, Chemistry panel, Thyroid testing Methemoglobin (only for participants receiving BMS-986205)	X	CBC only	X	For full list of laboratory assessments to be performed within 3 calendar days prior to dosing, assessments, see Section 9.4.1. For participants receiving BMS-986205: Methemoglobin should be assessed **locally** on arterial or venous blood sample or by co-oximetry once each treatment cycle, and as clinically indicated based on symptoms (all participants) (See Section 7.7.4) Also measure TSH starting at C2D1, and every 8 weeks/2 cycles thereafter. If TSH abnormal, reflex to free T3, and T4 at those measurement time points.
Pregnancy Test (WOCBP only)	X		X	A negative pregnancy test should be documented within 24 hours prior to start of each dose of nivolumab.

Table 2-2: On-study Assessments (CA017055)

Procedure[a]	BMS-986205 PO once daily (QD) + Nivolumab 480 mg[b], IV (Arm A) every 4 weeks (Q4W) OR Nivolumab 480 mg IV(Arm B) Q4W (Per Revised Protocol 01, no BMS-986205 Placebo will be given)			Notes[c]
	Cycle 1 (Day 1)	Cycle 1 (Day 14 ± 3 days)	Cycle 2 and subsequent on-treatment visits (Day 1 ± 3 days) (1 Cycle = 4 Weeks) Treat until progression, unacceptable toxicity, or completion of 104 weeks of therapy	
[redacted]				
[redacted]				
[redacted]				
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Table 2-2: On-study Assessments (CA017055)

Procedure[a]	BMS-986205 PO once daily (QD) + Nivolumab 480 mg[b], IV (Arm A) every 4 weeks (Q4W) OR Nivolumab 480 mg IV(Arm B) Q4W (Per Revised Protocol 01, no BMS-986205 Placebo will be given)			Notes[c]
	Cycle 1 (Day 1)	Cycle 1 (Day 14 ± 3 days)	Cycle 2 and subsequent on-treatment visits (Day 1 ± 3 days) (1 Cycle = 4 Weeks) Treat until progression, unacceptable toxicity, or completion of 104 weeks of therapy	
[redacted]				
[redacted]			[redacted]	
[redacted]				
[redacted]			[redacted]	
[redacted]			[redacted]	

[a] If a dose is delayed, the procedures scheduled for that same time point (except tumor assessments) should also be delayed to coincide with when that time point's dosing actually occurs.

[b] Per Revised Protocol-01, investigators have the option of discontinuing participants in Arm A from BMS-986205 treatment and continuing nivolumab treatment.

[c] 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.

Table 2-3: Follow-up Procedural Outline (CA017055)

Procedure	Follow-Up[a] Visits 1 and 2	Survival Follow-Up Visits (not applicable per Revised Protocol 01)	Notes[b]
Safety Assessments			
Targeted Physical Examination, Measurements, Vital Signs, and Performance Status	X		Weight, BP, HR, temperature, and ECOG status. Targeted physical examination to be performed only as clinically indicated.
AEs Assessment (including SAEs)	Continuously		Record at each visit
[redacted]	[redacted]		[redacted]
Pregnancy Test (WOCBP only)	X		Serum or urine pregnancy test must be performed (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG)
Laboratory Tests			
CBC with differential, Chemistry panel, Thyroid testing	X01-yes X02 - if toxicities are present		For full list of assessments, see Section 9.4.1.
[redacted]			
[redacted]	[redacted]		
[redacted]			
[redacted]			
[redacted]	[redacted]		

Table 2-3: Follow-up Procedural Outline (CA017055)

Procedure	Follow-Up[a] Visits 1 and 2	Survival Follow-Up Visits (not applicable per Revised Protocol 01)	Notes[b]
[redacted]			
[redacted]	[redacted]		
[redacted]	[redacted]		[redacted]

[a] Participants must be followed for at least 100 days after last dose of study treatment. Follow-up visit #1 should occur 30 days from the last dose (± 7 days) or can be performed on the date of discontinuation if that date is greater than 42 days from the last dose. Follow-up visit #2 occurs approximately 100 days (± 7 days) from last dose of study treatment. Both follow-up visits should be conducted in person. No follow-up visit is required for participants who screen fail.

[b] 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.

4 OBJECTIVES AND ENDPOINTS

Not applicable per Revised Protocol 01. Only safety assessments will be conducted. No analyses of efficacy, quality of life/patient reported outcomes, pharmacokinetics, or health resource utilization, are planned. Previously collected biomarker samples may be analyzed, but no further collections are planned with this revised protocol.

5 STUDY DESIGN

See Section 3.1.1for updates on Study Design as per Revised Protocol 01.

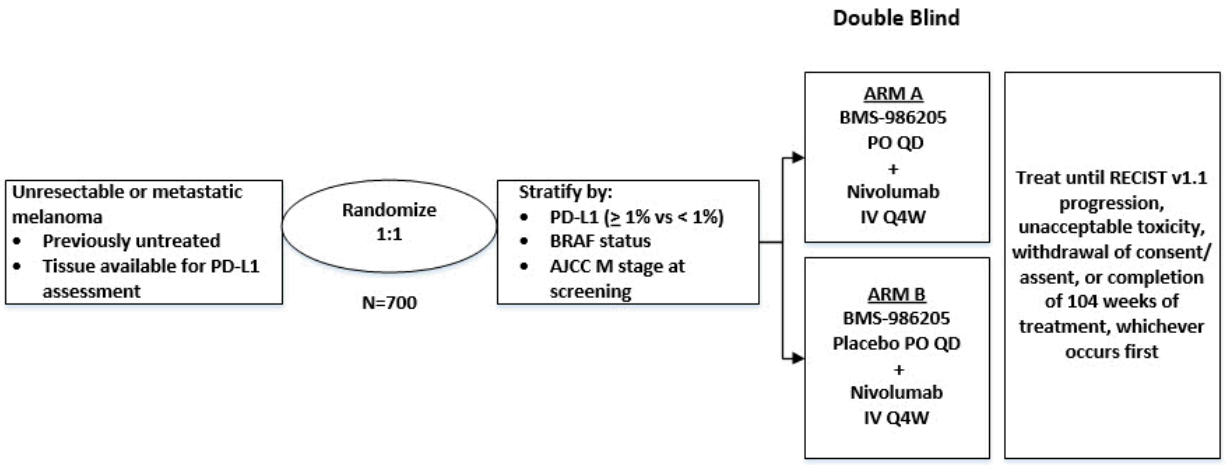
5.1 Overall Design

The original design was a Phase 3, randomized, double-blind study of BMS-986205 in combination with nivolumab versus nivolumab monotherapy in adult (18 years of age and older, or age of majority) participants with unresectable or metastatic melanoma that is previously untreated. As of 19-Apr-2018, enrollment in the study was closed (see Section 3.1.1).

Participants must have unresectable Stage III or Stage IV melanoma, per the 8th edition of the American Joint Committee on Cancer (AJCC) Staging Manual[30] (See Appendix 7), and must not have received prior systemic therapy for the treatment of unresectable or metastatic melanoma. Prior adjuvant or neoadjuvant therapy in participants with previously completely resected disease that has now recurred is permitted if this therapy was completed at least 6 months prior to randomization.

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

Figure 5.1-1: Study Design Schematic



Note: As of Revised Protocol 01, treatment will no longer be blinded, and participants in Arm B will no longer receive BMS-986205 Placebo. Participants in Arm A, have the option to discontinue BMS-986205, and continue nivolumab monotherapy, at investigator discretion.

A pre-treatment tumor sample to determine PD-L1 status is required to be submitted from all participants prior to randomization. The sample must be obtained within 3 months prior to enrollment from a metastatic tumor lesion or from an unresectable primary tumor lesion. The tumor sample must be taken from a site of disease which has not been previously irradiated. In

addition, no intervening treatment may have been administered between the time of biopsy/surgery and randomization. Pre-treatment tumor tissue biopsy specimens in the form of a paraffin-embedded block or, optimally, at least 20 unstained slides, will be requested; a minimum of 10 slides is required. The pre-treatment tumor sample must be a core biopsy, punch biopsy, excisional biopsy, or surgical specimen; fine needle aspiration samples and cytology samples are not acceptable. If sufficient tissue is not available from within 3 months prior to enrollment, then a fresh biopsy will be required during the screening period. Samples will be submitted to the analytical laboratory for PD-L1 testing. The analytical laboratory must provide IRT with confirmation of the related results prior to randomization.

Participants must have a documented BRAF status prior to randomization. Those participants enrolling in this study without documented results must have testing performed locally and results (wild type or mutant) be available prior to randomization. Participants with indeterminate or unknown BRAF status results will not be permitted to randomize to a treatment arm.

During the treatment phase, adult participants will receive:

- Arm A: BMS-986205 100 mg PO QD and Nivolumab 480 mg IV Q4W for up to 104 weeks (approximately 2 years). Under Revised Protocol 01 investigators have the option of continuing participants on nivolumab monotherapy.
- Arm B: Nivolumab 480 mg IV Q4W for up to 104 weeks (approximately 2 years). Under Revised Protocol 01 BMS-986205 Placebo should not be administered.

One cycle of treatment is defined as 4 weeks.

Dose reductions will be not be allowed for nivolumab; dose reductions will be permitted for BMS-986205 if the participant is an adult or an adolescent receiving 100 mg tablets. See Section 7.4.2 for more information.

Per Revised Protocol 01 tumor assessments should be conducted per the timing of the local standard of care.

Treatment beyond initial investigator-assessed Response Evaluation Criteria in Solid Tumors (RECIST) v1.1-defined progression (see Appendix 12) is permitted if the participant has investigator-assessed clinical benefit, is tolerating study treatment, and has not yet completed 104 weeks of study treatment (Section 8.1.1 and Section 8.1.3).

5.1.1 Data Monitoring Committee and Other External Committees

Not Applicable per Revised Protocol 01.

5.2 Number of Participants

As of 19-April-2018 enrollment into this study was closed (see Section 3.1.1).

5.3 End of Study Definition

The start of the trial is defined as the first visit for the first participant screened. As of Revised Protocol 01, study completion is defined as the final date on which data is collected for this study. The total duration of the study will be determined by the last follow-up visit for the last subject to stop treatment.

6 STUDY POPULATION

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

6.1 Inclusion Criteria

Per Revised Protocol 01, enrollment in the current study has been stopped as of 19-Apr-2018. Male participants continuing treatment should follow the updated contraceptive guidance below (and in Appendix 4).

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 patient care.

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

c) For adolescent participants unable to give their written consent, in accordance with local regulations, one or both parents, a guardian, or a legally acceptable representative must be informed of the study procedures and must document permission by signing the informed consent form approved for the study prior to clinical study participation. Each participant must be informed about the nature of the study to the extent compatible with his or her understanding. Should a participant become capable or reach the age of majority, his or her consent should be obtained as soon as possible. The explicit wish of a participant who is a minor or 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. Minors who are judged to be of an age of reason as determined by local requirements should also give their assent. The assent should be documented based on local requirements. Continued assent should be documented when important new information becomes available that is relevant to the participant's assent.

2) Type of Participant and Target Disease Characteristics

a) Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 1 (see Appendix 6)

b) Histologically confirmed Stage III (unresectable) or Stage IV melanoma, per the American Joint Committee on Cancer (AJCC) Staging Manual (8th edition) (see Appendix 7)

c) Treatment-naïve participants (ie, no prior systemic anticancer therapy for unresectable or metastatic melanoma). Note that prior adjuvant or neoadjuvant melanoma therapy is permitted in the setting of completely resected disease if it was completed at least 6 months prior to randomization, and all related AEs have either returned to baseline or stabilized.

d) At least one measurable lesion by computed tomography (CT) or magnetic resonance imagery (MRI) per RECIST v1.1 criteria (see Appendix 12)

e) Tumor tissue (biopsy or surgical specimen, where applicable) from an unresectable primary tumor or from a metastatic site of disease must be provided for biomarker analyses. The tumor sample must be obtained from a site of disease that has not been previously irradiated. In order to be randomized, a participant must be classified as PD-L1 positive (≥ 1% tumor cell membrane staining) vs PD-L1 negative (< 1% tumor cell membrane staining)/PD-L1 indeterminate (tumor cell membrane scoring hampered by high cytoplasmic staining or melanin content). If an insufficient amount of tumor tissue from an unresectable or metastatic site is available from prior to the start of the screening phase, then a fresh biopsy will be required during the screening phase for performance of biomarker analyses. PD-L1 expression will be determined using the Dako PD-L1 IHC 28-8 pharmDx assay

i) Either a recent archival sample obtained within 3 months prior to enrollment (with no intervening treatment between time of acquisition and enrollment) or a fresh

pre-treatment biopsy is to be submitted as a formalin-fixed, paraffin-embedded (FFPE) tissue block or unstained tumor tissue sections (optimally at least 20 slides, but a minimum of 10 slides required), with an associated pathology report, to the analytical laboratory for inclusion. The analytical laboratory must provide IRT with confirmation of receipt of the related results prior to randomization. Biopsy should be excisional, incisional, or core needle. Fine needle aspiration or cytology specimens are not acceptable for submission.

f) Participants must have known BRAF V600 mutation status prior to enrollment or consent to BRAF V600 mutation testing per local institutional standards during the Screening Period and have results of BRAF testing available prior to randomization. Participants with indeterminate or BRAF status not reported prior to randomization are not permitted to randomize to a treatment arm.

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

h) Participants must be able to swallow pills intact.

i) Participant Re-enrollment: This study permits the re-enrollment of a participant who has discontinued the study as a pre-treatment failure (ie, participant has not been randomized) after obtaining agreement from the Medical Monitor/designee prior to re enrolling a participant. If re-enrolled, the participant must be re-consented.

3) Age and Reproductive Status

a) Males and females, ages 12 years or older, 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, or age majority.

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

c) Women must not be breastfeeding

d) Women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception (see Appendix 4) for the duration of treatment with study treatment plus 5 months after the last dose of study treatment (ie, 30 days [duration of ovulatory cycle] plus the time required for nivolumab to undergo approximately 5 half-lives).

e) Males who are receiving BMS-986205, and are sexually active with WOCBP, must agree to use a male synthetic or latex condom during sexual activity for the duration of treatment with study treatment plus 7 months after the last dose of the study treatment (ie, 90 days [duration of sperm turnover] plus the time required for nivolumab to undergo approximately 5 half-lives). Males receiving nivolumab monotherapy must agree to use contraception (see Appendix 4) for the duration of treatment with study treatment plus 7 months after the last dose of the study treatment (ie, 90 days [duration of sperm turnover] plus the time required for nivolumab to undergo approximately 5 half-lives). These critera apply to azoospermic males as well. In addition, male participants must be willing to refrain from sperm donation during this time.

f) 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 4) which have a failure rate of < 1% when used consistently and correctly. **Hormonal contraceptives are not highly effective methods of contraception for participants in this study who are WOCBP receiving BMS-986205.**

6.2 Exclusion Criteria

Per Revised Protocol 01, enrollment in the current study was closed on 19-Apr-2018.

1) Medical Conditions

a) Women who are pregnant or breastfeeding

b) Active brain metastases or leptomeningeal metastases. Participants with brain metastases are eligible if these have been treated and there is no magnetic resonance imagery (MRI) evidence of progression for at least 8 weeks after treatment is complete and within 28 days prior to first dose of study treatment administration.

c) Uveal or ocular melanoma

d) 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.

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

f) Participants with a personal or family (ie, in a first-degree relative) history of cytochrome b5 reductase deficiency (previously called methemoglobin reductase deficiency) or other diseases that put them at risk of methemoglobinemia. All participants will be screened for methemoglobin levels prior to randomization.

g) Participants with a history of G6PD deficiency or other congenital or autoimmune hemolytic disorders. All participants will be screened for G6PD deficiency prior to randomization using quantitative or qualitative levels per local standard of care. Interpretation of G6PD assay results to ensure no deficiency is present should also be per local standard of care, including with consultation of appropriate medical subspecialists, as needed..

h) Participants with serious or uncontrolled medical disorders

i) 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

2) Prior/Concomitant Therapy

a) Prior treatment with an anti-PD-1 (except if given as adjuvant or neoadjuvant therapy for melanoma), anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody (except if given as adjuvant or neoadjuvant therapy for melanoma), or any other antibody or drug specifically targeting T-cell costimulation or immune checkpoint pathways

b) Prior treatment with BMS-986205 or any other IDO1 inhibitors

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.

3) Physical and Laboratory Test Findings

a) WBC < 2000/μL

b) Neutrophils < 1500/μL

c) Platelets < 100x 10^3/μL

d) Hemoglobin < 9.0 g/dL (transfusion to achieve this level is not permitted within 2 weeks of this laboratory assessment)

e) Serum creatinine > 1.5x ULN or calculated creatinine clearance (CLcr) < 40 mL/min (using the Cockcroft-Gault formula):

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

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

f) AST or ALT > 3.0x ULN

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

j) Quantitative or qualitative G6PD assay results suggesting underlying G6PD deficiency

k) Blood methemoglobin > ULN, assessed in an arterial or venous blood sample or by co-oximetry

l) Positive pregnancy test at enrollment or prior to administration of study medication

4) Allergies and Adverse Drug Reaction

a) History or presence of hypersensitivity or idiosyncratic reaction to methylene blue

b) History of allergy or hypersensitivity to any study treatment components

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 or permitted to continue as a participant. Strict conditions apply and BMS approval is required.

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

Eligibility criteria for this study have been carefully considered to ensure the safety of the study 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 restrictions are required.

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, as applicable, and to respond to queries from regulatory authorities. Minimal information includes date of consent, demography, screen failure details, eligibility criteria, and any SAEs.

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 pre-treatment failure (ie, participant has not been randomized). If re-enrolled, the participant must be re-consented.

Retesting of laboratory parameters and/or other assessments within the 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/designee 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.

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

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.

Investigational products (IP) used in this trial are provided in Table 7-1. There are no non-investigational products in this study.

Table 7-1: Study treatments for Study CA017055

Product Description / Class and Dosage Form	Potency	IP/Non-IP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
BMS-936558-01 (Nivolumab) Solution for Injection[a]	100 mg (10 mg/mL)	IP	Open Label	Vial	Refer to the label on container and/or pharmacy manual
BMS-986205-04	100 mg	IP	Unblinded[b]	Tablet	Refer to the label on container and/or pharmacy manual
BMS-986205-04	50 mg	IP	Unblinded[b]	Tablet	Refer to the label on container and/or pharmacy manual

[a] May be labeled as "Nivolumab" or "BMS-936558-01 Solution for Injection"

[b] Per Revised Protocol 01, treatment assignment will be unblinded and participants in Arm B will be discontinued from BMS-986205 Placebo. Participants in Arm A, may at the discretion of the investigator, discontinue BMS-986205, and continue on nivolumab monotherapy.

Abbreviations: NA = not applicable; IP = investigational product

7.1 Treatments Administered

The selection and timing of dose for each participant is presented in Table 7.1-1.

Study treatments will be dispensed at the study visits as listed in Schedule of Activities (Section 2).

Table 7.1-1: Selection and Timing of Dose

Per Revised Protocol 01, treatment assignment will be unblinded and participants in Arm B will be discontinued from BMS-986205 Placebo. Participants in Arm A, may at the discretion of the investigator, discontinue BMS-986205, and continue on nivolumab monotherapy.

Study Treatment	Unit dose strength(s)/Dosage level(s)	Dosage formulation Frequency of Administration	Route of Administration
Nivolumab	480 mg	Solution for injection/ every 4 weeks	IV
BMS-986205	100 mg	Tablet/once daily	PO

Abbreviations: NA=not applicable; PO=by mouth; IV=intravenous

7.1.1 BMS-986205 Dosing

Per Revised Protocol 01, treatment assignment will be unblinded and participants in Arm B will be discontinued from BMS-986205 Placebo. Participants in Arm A, may at the discretion of the investigator, discontinue BMS-986205, and continue on nivolumab monotherapy.

For participants in Arm A that continue on BMS-986205, a bottle of BMS-986205 should be dispensed at each Day 1 visit within a cycle. Participants should be instructed that BMS-986205 should be administered once a day (approximately 24 hours apart) following a meal. The tablet must administered by mouth, swallowed whole, and not be crushed, chewed, dissolved or altered in any way.

Participants in Arm A that continue taking BMS-986205 should be provided with pill diaries at each visit and instructed to record intake of BMS-986205 in the diary after each daily administration.

BMS-986205 will be administered on an out-patient basis. Additional information on study drug preparation, handling and administration can be found in the Pharmacy Manual.

Participants should receive BMS-986205 until progression, unacceptable toxicity, withdrawal of consent by the participant, or completion of 104 weeks of treatment, whichever occurs first. Participants should begin study treatment within 3 calendar days of randomization.

Doses of BMS-986205 may be modified, interrupted or discontinued depending on how well the participant tolerates the treatment (See Section 7.4.2 [modification], Section 7.4.3 [delay], and Section 8.1.1 [discontinuation]). If the dose of BMS-986205 is reduced, escalation will not be permitted. Skipped doses during interruptions should not be administered within the same cycle.

If nivolumab dosing is delayed for reasons other than study drug toxicity (eg, administrative issues, holidays, etc), BMS-986205 dosing should continue uninterrupted.

For details on prepared drug storage, preparation, and administration, please refer to the BMS-986205 IB and/or pharmacy binder. The selection and timing of dose for each participant is provided in Table 7.1-1.

7.1.2 Nivolumab Dosing

Participants 18 years of age and older, or age of majority, should receive nivolumab at a dose of 480 mg as a 30-minute infusion on Day 1 of each treatment cycle until progression, unacceptable toxicity, withdrawal of consent/assent, or completion of 104 weeks of treatment, whichever occurs first.

Participants should begin study treatment within 3 calendar days of randomization

The dose of BMS-986205 (for participants in Arm A that continue receiving BMS-986205) should be given before the dose of nivolumab, but specific timing is not required. Participants should begin study treatment within 3 calendar days of randomization.

There will be no dose escalations or reductions of nivolumab allowed. For Q4W dosing cycles, participants may be dosed within a ± 3 day window. For this dosing cycle, participants may be dosed no less than 25 days and no more than 31 days between doses. In extenuating circumstances in which the participant cannot make the dosing schedule within the 3-day window, the BMS Medical Monitor/designee should be contacted.

Premedication is not recommended for the first dose of nivolumab.

Participants should be carefully monitored for infusion reactions during nivolumab administration. After the first nivolumab infusion, subjects should be monitored per local/institutional guidelines. If no such guidelines exist, an observation period of 2 hours after the end of the nivolumab infusion is suggested.

If an acute infusion reaction is noted, participants should be managed according to Section 7.7.5.

Doses of nivolumab may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment. Dosing visits are not skipped, only delayed.

Nivolumab Injection, 100 mg/10 mL (10 mg/mL) is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding in-line filter at the protocol-specified doses. It is not to be administered as an IV push or bolus injection. When the dose is based on participant's weight (ie, mg/kg), nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to protein concentrations as low as 0.35 mg/mL. When the dose is fixed (eg, 480 mg flat dose), nivolumab injection can be infused undiluted or diluted so as not to exceed a total infusion volume of 160 mL. Nivolumab infusion must be promptly followed by a saline flush to clear the line. Instructions for dilution and infusion of nivolumab injection will be provided in the pharmacy binder. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

Nivolumab infusions are compatible with polyvinyl chloride (PVC) or polyolefin containers and infusion sets, and glass bottles.

Additional information on study drug preparation, handling and administration can be found in the Pharmacy Manual.

The selection and timing of dose for each participant is provided in Table 7.1-1.

7.2 Method of Treatment Assignment

As of 19-Apr-2018, enrollment in the study has been closed.

All participants will be centrally randomized using an Interactive Response Technology (IRT). Before the study is initiated, each user will receive log-in information and directions on how to access the IRT. After the participant's initial eligibility is established and informed consent has been obtained, the participant must be enrolled into the study by calling an IRT to obtain the participant number. Every participant who signs the informed consent form must be assigned a participant number in IRT. 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
- Year of birth
- Gender at birth

Once enrolled in IRT, enrolled participants who have met all eligibility criteria will be ready to be randomized through the IRT. The following information is required for participant randomization:

- Participant number
- Year of birth
- PD-L1 status (PD-L1 positive vs PD-L1 negative/indeterminate) entered by vendor ; PD-L1 expression will be determined using the Dako PD-L1 IHC 28-8 pharmDx assay.
- BRAF V600 mutational status
- M Stage at screening (see Appendix 7)

Participants meeting all eligibility criteria will be randomized in a 1:1 ratio and stratified by PD-L1 status, BRAF status, and AJCC M stage as described below:

- PD-L1 status
  - PD-L1 positive (≥ 1% tumor cell membrane staining in a minimum of 100 evaluable tumor cells) vs
  - PD-L1 negative (< 1% tumor cell membrane staining in a minimum of 100 evaluable tumor cells)/indeterminate (tumor cell membrane scoring hampered by high cytoplasmic staining or melanin content)

- BRAF status
  - BRAF V600 mutation positive vs
  - BRAF V600 wild type
- AJCC M stage at screening (See Appendix 7)
  - M0/M1any(0) vs
  - M1any(1)

Note: participants whose PD-L1 status is indeterminate/not evaluable will be classified with participant where PD-L1 expression is < 1%.

The randomization procedures will be carried out via permuted blocks within each stratum, defined by combination of PD-L1 status (positive, ≥ 1%, negative/indeterminate), BRAF V600 mutational status (BRAF mutation positive, BRAF wild type), and M Stage (M0/M1any[0], M1any[1]). The exact procedures for using the IRT will be detailed in the IRT manual.

7.3 Blinding

Per Revised Protocol 01, the study will be unblinded (see Section 3.1.1).

7.4 Dosage Modification

7.4.1 Nivolumab Dose Modifications

No dose modifications for nivolumab are permitted.

7.4.2 BMS-986205 Dose Modifications

A dose reduction of BMS-986205 is defined as a change from a 100 mg QD tablet to a 50 mg QD tablet.

Doses of BMS-986205 should be reduced for the following AEs attributable to study therapy that do not otherwise meet criteria for discontinuation:

- Grade 3 fatigue, nausea, vomiting, or anemia related to study treatment
- Methemoglobin ≥15%
- Clinically significant elevations in methemoglobin (generally 10%, with a normal hemoglobin level[51]) with any associated Grade 3 AE (hypoxia, dyspnea, confusion, etc.) attributable to sustained elevations of methemoglobin and not attributable to another etiology
- QTcF > 500 msec confirmed by at least 1 repeat ECG and at least 60 msec above baseline (See Appendix 9)

Dose modification and interruption of BMS-986205 may occur in the setting of lower grade AEs and/or be more conservative than indicated above based on the clinical judgment of the investigator and in consultation with the BMS Medical Monitor/designee. For an AE requiring dose modification, BMS-986205 should be delayed to allow improvement of the AE, even if the AE does not otherwise meet criteria for dose delay (Section 7.4.3).

Re-escalation of BMS-986205 will not be permitted once the dose of BMS-986205 has been reduced for a participant.

Only one dose reduction is permitted. The participant must discontinue study treatments if a subsequent dose reduction of BMS-986205 is required (see Section 8.1.1).

7.4.3 Dose Delay (BMS-986205 and Nivolumab)

BMS-986205 and nivolumab administration should be delayed for the following:

- Grade 2 non-skin, drug-related AE, with the exception of fatigue, nausea, vomiting and anemia
- Grade 2 drug-related creatinine, AST, ALT and/or Total Bilirubin abnormalities
- Grade 3 skin, drug-related AE
- Grade 3 drug-related fatigue, nausea, vomiting, and anemia
- Grade 3 drug-related laboratory abnormality, with the following exceptions:
  - Grade 3 lymphopenia or asymptomatic amylase or lipase elevations do not require dose delay
  - Grade ≥ 3 AST, ALT, Total Bilirubin will require dose discontinuation (see Section 8.1.1)
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication

In addition, **only BMS-986205** should be delayed for the following:

- Methemoglobin ≥ 15%
- Clinically significant elevations in methemoglobin (generally 10% with a normal hemoglobin level[51]) with any associated Grade 3 AE (hypoxia, dyspnea, confusion, etc.) attributable to sustained elevations of methemoglobin and not attributable to another etiology
- QTcF > 500 msec confirmed by at least 1 repeat ECG and at least 60 msec above baseline (See Appendix 9)

Appendix 14 presents the above criteria in tabular format.

If nivolumab dosing is delayed for reasons other than study drug toxicity (eg, administrative issues, holidays, etc), BMS-986205 dosing should continue uninterrupted.

Participants may continue to receive nivolumab during dose delays of BMS-986205for elevations of methemoglobin and associated events, as well as QTcF prolongations.

For participants with methemoglobin elevations with associated Grade 3 AEs, if contribution of nivolumab to the associated AE cannot be ruled out (eg, a participant with dyspnea in whom pneumonitis has not yet been ruled out), nivolumab dosing should be delayed as well. See Section 7.7.4 for management of methemoglobinemia.

If BMS-986205 dosing is delayed, dose reduction may be necessary. See Section 7.4.2.

If dosing is resumed after a delay, BMS-986205 may be resumed as soon as the criteria to resume treatment are met (see Section 7.4.4). Nivolumab should be resumed as soon as possible after criteria to resume treatment are met, but may be resumed later than BMS-986205 given the differences in each drug's administration.

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

7.4.4 Criteria to Resume Treatment (BMS-986205 and Nivolumab)

Participants may resume treatment with study treatments 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.
- Participants with combined AST/ALT AND total bilirubin values meeting discontinuation parameters (Section 8.1.1) should have treatment permanently discontinued.
- 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/designee.

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

For participants who have BMS-986205 held for elevations of methemoglobin, dosing may resume when the methemoglobin levels have decreased to below the institutional ULN and any associated AEs have resolved to Grade ≤ 1 or baseline value. Dose modification of BMS-986205 should be considered when resuming after a delay (see Section 7.4.2).

[redacted]

[redacted]

[redacted]

7.4.6 Detection of Methemoglobinemia

BMS-986205 may produce a p-chloroaniline metabolite. P-chloroaniline has been associated with the production of methemoglobin. Symptoms of methemoglobinemia are related to the lack of oxygen delivery to tissues and are proportional to the fraction of methemoglobin, as described below for participants with normal hemoglobin levels.

Symptoms associated with elevations of methemoglobin are as follows:

- 0% to 10% - Usually asymptomatic
- 10% to 20% - Cyanosis without other symptoms
- 20% to 50% - Headache, dyspnea, lightheadedness (possibly syncope), weakness, confusion, palpitations, chest pain
- 50% to 70% - Coma, seizures, arrhythmias; acidosis
- > 70% - Usually death

Note that participants with anemia may experience symptoms at lower methemoglobin percentages than listed above, depending on the degree of anemia.

Increasing levels of methemoglobin may confound the results of standard pulse oximeters, with values of around 85% reported consistently as methemoglobin levels increase, regardless of the true oxygen saturation.

When methemoglobinemia is suspected, part of the diagnostic work-up includes evaluation for other disorders that can present with a similar clinical picture, including cardiac and pulmonary disease. A fresh peripheral blood sample (either venous or arterial) should be sent for evaluation of methemoglobin levels; methemoglobin levels may vary with storage of blood.

In this study methemoglobin testing will be performed at screening, at each cycle (for BMS-986205 treated participants only), and as clinically indicated. For management of methemoglobinemia, see Section 7.7.4.

7.5 Preparation/Handling/Storage/Accountability

For nivolumab, refer to the current version of the IB and/or Pharmacy Manual for complete storage, handling, dispensing, and infusion information.

Similarly, for BMS-986205, refer to the current version of the IB and/or Pharmacy Manual for complete storage, handling, and dispensing information.

The investigational products should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational products are only dispensed to

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

The product storage manager should ensure that the study treatments are 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 treatments arise, do not dispense the study treatment 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).

Further guidance and information for final disposition of unused study treatments are provided in Appendix 2.

7.5.1 Retained Samples for Bioavailability / Bioequivalence

Not applicable.

7.6 Treatment Compliance

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

Treatment compliance of BMS-986205 will be monitored by drug accountability, as well as by recording BMS-986205 administration in the participant pill diary (as applicable), medical record, and eCRF. Participants should bring all drug containers to each study visit for drug reconciliation. The pill diary should be reviewed at each clinic visit and submitted at the end of each cycle, as applicable.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7.8 Treatment After the End of the Study

At the conclusion of the study, participants who continue to demonstrate clinical benefit will be eligible to receive BMS-supplied study treatment for the maximum treatment duration specified in Section 7.1. Study treatment will be provided via an extension of the study, a rollover study requiring approval by responsible health authority and ethics committee, or through another mechanism at the discretion of BMS. See Section 5.4.2 for more information.

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 BMS-986205 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. Withdrawal of consent/assent may be requested by participants, parents, guardians, or legally acceptable representatives, in accordance with

local regulations. The wishes of minor participants to withdraw their assent should also be respected. 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 the participant to provide this information.

- Any clinical 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 BMS
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Additional protocol-specified reasons for discontinuation (Section 8.1.1)
- Documented investigator-assessed progression as defined by RECIST v1.1 (see Appendix 12) unless participant meets criteria for treatment beyond progression

In the case of pregnancy, the investigator must immediately notify the Sponsor or designee of this event. In most cases, the study treatment 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 treatment, a discussion between the investigator and the Sponsor or designee must occur.

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.

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).

The assessment for discontinuation of nivolumab should be made separately from the assessment made for discontinuation of BMS-986205. Although there is overlap among the discontinuation criteria, if discontinuation criteria are met for BMS-986205 but not for nivolumab, treatment with nivolumab may continue if BMS-986205 is discontinued. If a participant discontinues nivolumab, they must also discontinue BMS-986205.

If a participant receiving nivolumab/BMS-986205 combination meets criteria for discontinuation and investigator is unable to determine whether the event is related to both or one study drug, the participant should discontinue both nivolumab and BMS-986205 and be taken off the treatment phase of the study.

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 eCRF page.

8.1.1 BMS-986205 and Nivolumab Dose Discontinuation

BMS-986205 and nivolumab treatment should be permanently discontinued for the following:

- Any occurrence of serotonin syndrome
- 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 time frame permitted for dose delays OR requires systemic treatment
- Any event requiring more than 1 dose reduction of BMS-986205 (see Section 7.4.2), except for those related to methemoglobinemia or QTc prolongations, which require only discontinuation of BMS-986205 alone; subjects may continue to receive nivolumab in these situations (see also Section 8.1.2)
- Any drug-related event requiring 10 mg per day or greater prednisone or equivalent for more than 12 weeks, except for adrenal replacement steroid dose >10mg.
- Immune-mediated encephalitis of any grade
- 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 treatment(s) will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment(s), a discussion between the investigator and the BMS Medical Monitor/designee must occur.
- Any Grade 4 drug-related AE 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 3 calendar days of their onset
  - Grade 4 drug-related endocrinopathy AEs, 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/designee.
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the participant with continued BMS-986205 and nivolumab dosing
- Any event that leads to delay in dosing of nivolumab lasting > 10 weeks from the previous dose requires discontinuation, with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related AEs are allowed.
  - Dosing delays lasting > 10 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS Medical Monitor/designee.
- Any event requiring 10 mg per day or greater prednisone or equivalent for more than 12 weeks except for adrenal replacement steroid dose >10mg

Prior to re-initiating treatment in a participant with a dosing delay lasting > 10 weeks, the BMS Medical Monitor/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 4 weeks or more frequently if clinically indicated during such dosing delays.

Participants who are discontinued from nivolumab, must also discontinue BMS-986205.

8.1.2 BMS-986205 Dose Discontinuation

The following events require discontinuation of BMS-986205 only; nivolumab may continue to be administered unless other events occur that would require delay or discontinuation of nivolumab as described in Sections 7.4.3 and 8.1.1.

- Any event requiring more than 1 dose reduction of BMS-986205
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the participant with continued BMS-986205 dosing
- For participants who delay BMS-986205 but continue nivolumab (see Section 7.4.3), any dose delay of BMS-986205 lasting > 10 weeks will result in the discontinuation of both BMS-986205 only.
- Per Revised Protocol 01, participants are permitted to discontinue BMS-986205, and continue nivolumab at investigator discretion (see Section 3.1.1)
- Any occurrence of serotonin syndrome

8.1.3 Treatment Beyond Progression

[redacted]

8.1.3.2 Criteria Required for Treatment Beyond Progression

Participants will be permitted to continue study treatment beyond initial RECIST v1.1-defined PD (see Appendix 12), assessed by the investigator, as long as they meet the following criteria:

- Investigator-assessed clinical benefit
- Tolerance of study treatment
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases).
- Participant provides written informed consent prior to receiving additional study treatment. All other elements of the main consent including description of reasonably foreseeable risks or discomforts, or other alternative treatment options will still apply.

A radiographic assessment/ scan should be performed within 8 weeks of initial investigator-assessed progression to determine whether there has been a decrease in the tumor size or continued PD. The assessment of clinical benefit should be balanced by clinical judgment as to whether the participant is clinically deteriorating and unlikely to receive any benefit from continued study treatment.

If the investigator feels that the participant continues to achieve clinical benefit by continuing treatment, the participant should remain on the trial and continue to receive monitoring according to the Schedule of Activities (Section 2).

For the participants who continue study therapy beyond progression, further progression is defined as an additional 10% increase in tumor burden with a minimum 5 mm absolute increase from time of initial PD. This includes an increase in the sum of diameters of all target lesions and/ or the

diameters of new measurable lesions compared to the time of initial PD. All study treatment should be discontinued permanently upon documentation of further progression.

New lesions are considered measurable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). Any new lesion considered non-measurable at the time of initial progression may become measurable and therefore included in the tumor burden if the longest diameter increases to at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). In situations where the relative increase in total tumor burden by 10% is solely due to inclusion of new lesions which become measurable, these new lesions must demonstrate an absolute increase of at least 5 mm.

8.1.4 Post-Study Treatment Study Follow-up

Per Revised Protocol 01, overall survival follow up is not required.

In this study, overall survival is a key endpoint 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 outcome and/or survival follow-up data as required and in line with Section 2 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 (Table 2-3). 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/assent 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/assent.

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 treatment-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 AEs, the participant should be immediately evaluated to rule out pulmonary toxicity, according to the suspected pulmonary toxicity management algorithm in the BMS-936558 (Nivolumab) IB. In addition, blood methemoglobin levels should be evaluated to rule out methemoglobinemia (see Section 7.4.6) and CBC measured to rule out anemia in participants with dyspnea.

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.

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

Screening Phase:

- Begins by establishing the participant's initial eligibility and signing of the informed consent form (ICF).

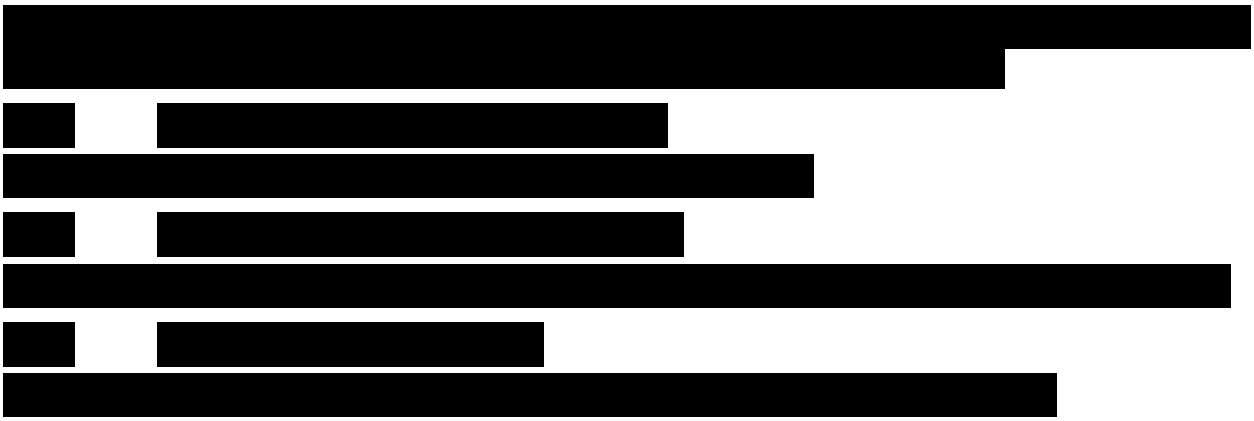
Treatment Phase:

- Begins with the randomization request to the IRT. The participant is randomly assigned to either the BMS-986205 + nivolumab arm or the BMS-986205 Placebo + nivolumab arm. (Per Revised Protocol 01, BMS-986205 Placebo will not be administered in this study. Participants in Arm B, may discontinue BMS-986205 and continue treatment with nivolumab monotherapy).
- Ends when the participant is discontinued from study therapy or completes 104 weeks of study therapy. For a complete list of reasons for treatment discontinuation, see Section 8.1.

Follow-Up Phase

- Begins when the decision to discontinue a participant from study therapy is made (no further treatment with study therapy) or when 104 weeks of study therapy has been completed, and ends when follow-up data have been collected for all participants (Section 8.1.4).

[redacted]



9.2 Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

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.

Immune-mediated adverse events (IMAEs) 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. Information supporting the assessment will be collected on the participant's case report form.

Contacts for SAE are reporting specified in Appendix 3.

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

The collection of non-serious AE information should begin at initiation of study treatment at the time points specified in the Schedule of Activities (Section 2). Non-serious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the participants.

Section 5.6 in the IBs for BMS-986205 and nivolumab represents the Reference Safety Information to determine expectedness of SAEs for expedited reporting. Following the participant's written consent/assent to participate in the study, all SAEs, whether related or not related to study treatment, 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, except in cases where a study participant has started a new anti-neoplastic therapy. However, any SAE occurring after the start of a new treatment that is suspected to be related to study treatment by the investigator will be reported.

For participants assigned to treatment and never treated with study treatment, SAEs should be collected for 30 days from the date of randomization.

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

- 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 3.
- 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 3.

9.2.2 Method of Detecting AEs and SAEs

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

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.

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

9.2.3 Follow-up of AEs and SAEs

- Non-serious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Appendix 3).
- Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study treatment and for those present at the end of study treatment as appropriate.
- All identified non-serious AEs must be recorded and described on the non-serious 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 9.2.5 and Appendix 15) 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 3.

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.

Sponsor or designee will be reporting AEs to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/EC and FDA Title 21 Code of Federal Regulations (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 Adverse Events of Special Interest

Adverse events of special interest (AEOSI) have been defined for this protocol which require expedited reporting by the investigator of these adverse events to BMS. These are:

- Hemophagocytic lymphohistiocytosis (HLH; also known as histiocytosis haematophagic)
- Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome

These AEOSI, whether related or not related to study drug, must be reported to BMS or designee within 24 hours of awareness of the event. These AEOSI are medically important events and are therefore considered SAEs. The reporting system for SAEs should be used (see Section 9.2.4 and Appendix 3).

As both HLH and DRESS syndrome may both pose diagnostic challenges due to varying clinical manifestations and signs and symptoms that may overlap with other clinical events. To assist investigators in identifying constellations of clinical symptoms that may be consistent with one of these diagnoses, standardized scoring criteria are provided in Appendix 15. Formal evaluation and documentation of diagnostic scores based on these systems is not required; investigators should use their best clinical judgement as informed by these provided criteria to determine if a subject has experienced one of these AEOSI.

9.2.6 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 3.

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/designee 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.

9.2.7 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the non-serious 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 delayed/ 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).

9.2.8 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 9.2 and Appendix 3 for reporting details).

Potential drug induced liver injury is defined as:

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

AND

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

AND

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

9.2.9 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, ECG, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a non-serious 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. Overdoses meeting the regulatory definition of SAE must be reported as an SAE (see Section 9.2.4 for reporting details).

In the event of an overdose the investigator/treating physician should:

1) Contact the Medical Monitor/designee immediately
2) Closely monitor the participant for AEs/SAEs and laboratory abnormalities
3) Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor/designee based on the clinical evaluation of the participant.

9.4 Safety

Planned time points for all safety assessments are listed in the Schedule of Activities. Safety assessments include AEs, physical examinations, vital signs, performance status, oxygen saturation, ECGs, assessment of signs and symptoms, laboratory tests, and pregnancy tests as outlined in the Schedule of Activities.

9.4.1 Clinical Safety Laboratory Assessments

Laboratory assessments are listed in Table 9.4.1-1.

- Investigators must document their review of each laboratory safety report.
- All clinical safety laboratory assessments will be performed locally per the Schedule of Activities (Section 2).

Table 9.4.1-1: Laboratory Assessment Panels

Hematology	
Hemoglobin	
Hematocrit	
Total leukocyte count, including differential	
Platelet count	
Methemoglobin **- screening for all participants, each treatment cycle for BMS-986205-treated participants, and then as clinically indicated for all participants**	
G6PD levels - **screening only**	
Serum Chemistry	
Aspartate aminotransferase (AST)	Sodium
Alanine aminotransferase (ALT)	Potassium
Total bilirubin	Chloride
Alkaline phosphatase (ALP)	Calcium
Gamma-glutamyl transferase (only when alkaline phosphatase is ≥Grade 2)	Phosphate
	Magnesium
Albumin	Creatinine
Lactate dehydrogenase (LDH)	Creatinine clearance (CLcr) - **screening only**
Uric acid	Blood Urea Nitrogen (BUN) or Serum Urea Level
TSH (reflex to free T3 and T4 if abnormal)	Glucose
Urinalysis (at screening)	
Protein	
Glucose	
Blood	
Leukocyte esterase	
Specific gravity	
pH	
Serology (at screening)	
Serum for hepatitis C antibody (if Hepatitis C antibody is positive reflex to hepatitis C RNA) or hepatitis C RNA, hepatitis B surface antigen, HIV-1 and HIV-2 antibodies. (Testing for HIV-1 and HIV-2 must be performed at sites where mandated by local requirements)	
Other Analyses	
Pregnancy test (women of child-bearing potential [WOCBP] only, Section 2).	
Follicle stimulating hormone (FSH) screening -only required to confirm menopause in women < age 55 (if	

Table 9.4.1-1: Laboratory Assessment Panels

needed to document postmenopausal status as defined in Appendix 4)

9.4.2 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 per standard medical/clinical judgment.

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

[redacted]

10 STATISTICAL CONSIDERATIONS

Per Revised Protocol 01, efficacy analysis will not be conducted (see Section 3.1.1 and the updated Schedule of Activities in Section 2).

10.1 Sample Size Determination

Per Revised Protocol 01 this section is not applicable.

The sample size is calculated in order to compare PFS between participants randomized to receive BMS-986205 with nivolumab vs nivolumab monotherapy. The number of events required is simulated based on results from Study CA209067; this simulation resulted in a median PFS of 6.9 months for nivolumab monotherapy and 11.8 months for BMS-986205 with nivolumab therapy, incorporating 35% of participants with durable response in the combined groups, and a non-proportional hazard resulting in an effective hazard ratio (HR) of approximately 0.73.

Based on these assumptions, the study requires at least 365 PFS events to ensure approximately 85% power to detect an HR of 0.73 with an overall type I error of 0.05 (two-sided). Approximately 700 participants will be randomized to the 2 treatment arms in a 1:1 ratio. While follow-up for the primary PFS endpoint is planned to occur when 365 participants have had a PFS event, the follow-up for the primary PFS endpoint can also be terminated 9 months after the randomization of the last participant if the 365th event has not occurred (e.g. slow arrival of events close to but less than 365 that suggest a higher than expected long-term response rate). Predictions for enrollment and follow-up are based on an estimation of approximately 12 months for enrollment and 7 months of follow-up after the end of enrollment. Various patterns of enrollment were assessed from uniform enrollment to enrollment of 25% of participants in the first half of enrollment and 75% in the second half of enrollment.

Follow-up for the overall survival (OS) endpoint is planned to occur when 330 participants have had an OS event. If the 330th event has not occurred at 24 months after randomization of the last participant, then the follow-up time can be terminated 24 months after the randomization of the last participant. A total of 330 OS events would provide approximately 90% power to detect an overall HR of approximate 0.70 with a type I error of 0.05 (two-sided).

10.2 Populations for Analyses

Per Revised Protocol 01, efficacy analysis will not be conducted (see Section 3.1.1 and the updated Schedule of Activities in Section 2).

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled Participants	All participants who sign informed consent and were registered into IRT
Randomized	All participants who are randomized to any treatment group.
Treated	All participants who received at least one dose of any study medication.
Safety	All randomized participants who take at least 1 dose of double-blind study treatment. Data in this data set will be analyzed based on randomized treatment, except in the following case:

Population	Description
	• If a participant received the same incorrect treatment throughout the study, then the participant will be analyzed based on the treatment received.
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

10.3 Statistical Analyses

A description of the participant population will be included in a statistical output report, including subgroups of age, gender and race.

Per Revised Protocol 01, efficacy analysis will not be conducted (see Section 3.1.1 and the updated Schedule of Activities in Section 2).

[redacted]

10.3.2 Safety Analyses

All safety analyses will be performed on the Safety Population.

Endpoint	Statistical Analysis Methods
Primary	Safety analyses will be performed in all treated participants. Descriptive statistics of safety will be presented using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 by treatment group. All on-study AEs, treatment-related AEs, SAEs, and treatment-related SAEs will be tabulated using worst grade per NCI CTCAE v 4.03 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 4.03 criteria.
Exploratory	Additional safety analyses will be described in the SAP finalized before database lock.

[redacted]

10.3.4 Interim Analyses

No interim analyses are planned.

12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
ADA	anti-drug antibody
ADME	absorption-distribution-metabolism-excretion
AE	adverse event
AIDS	acquired immunodeficiency syndrome
AJCC	American Joint Committee on Cancer
ALT	alanine aminotransferase
ALP	alkaline phosphatase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BICR	Blinded Independent Central Review
BMS	Bristol-Myers Squibb
BOR	best overall response
BP	blood pressure
BUN	blood urea nitrogen
Ca^{++}	calcium
Cavgss	average concentration at steady state
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
$C1^{-}$	chloride
CL	clearance
CLcr	creatinine clearance
Cmaxss	maximum observed concentration at steady state
Cminss	minimum observed concentration at steady state
CMV	cytomegalovirus
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CR	Complete Response
CRF	Case Report Form, paper or electronic

Term	Definition
CRO	Contract Research Organization
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated protein-4
CYP	cytochrome p-450
DLBCL	diffuse large B-cell lymphoma
DDI	drug-drug interaction
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOOR	duration of objective response
DTIC	Dacarbazine (5-(3,3 dimethyl-l-triazeno)-imidazole-4-carboxamide)
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDTA	ethylene diamine tetra-acetic acid
ELISA	enzyme-linked immunosorbent assay
EOI	end of infusion
EORTC-QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
eGFR	estimated glomerular filtration rate
ePRO	electronic patient-reported outcome
EQ-5D-3L	EuroQoL 5-dimensions 3-levels (quality of life questionnaire)
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
FFPE	formalin fixed paraffin-embedded
FISH	fluorescent in situ hybridization
FSH	follicle stimulating hormone
G6PD	glucose 6-phosphate dehydrogenase
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen

Term	Definition
HBV	hepatitis B virus
HCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	Human Immunodeficiency Virus
HL	Hodgkin Lymphoma
HPV	human papilloma virus
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator Brochure
ICH	International Conference on Harmonisation
IDO1	indoleamine-1,2-dioxygenase 1 (enzyme)
IEC	Independent Ethics Committee
IFN	interferon
IHC	immunohistochemistry
IL	interleukin
IMAE	immune-mediated adverse event
IMP	investigational medicinal product
IO	Immuno-oncology
IP	investigational products
IRB	Institutional Review Board
IRT	Interactive Response Technology
IU	international units
IV	intravenous
K^+	potassium
LDH	lactate dehydrogenase
LFT	liver function test
MID	minimal important difference
MLR	mixed lymphocyte reaction
mmHg	millimeters of mercury
MRI	magnetic resonance imaging

Term	Definition
MTD	maximum tolerated dose
Na^+	sodium
NA	not applicable
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cells
PCR	polymerase chain reaction
PD	pharmacodynamics
PD-1	programmed cell death protein-1
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetics
PO	per os (by mouth route of administration)
PPK	population pharmacokinetics
PR	Partial Response
QD, qd	quaque die, once daily
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
SAE	serious adverse event
SD	standard deviation
SNP	single nucleotide polymorphism
SUSAR	Suspected, unexpected serious adverse reaction
TCR	T-cell receptor
TIL	tumor infiltrating lymphocyte
TMB	tumor mutational burden
Treg	regulatory T-cell
TSH	thyroid stimulating hormone
TTR	time to objective response

Term	Definition
ULN	upper limit of normal
VAS	visual analog scale
Vss	volume of distribution at steady state
WNOCBP	women not of childbearing potential
WOCBP	women of childbearing potential
WPAI(:GH)	Work Productivity and Activity Impairment (:General Health) questionnaire

APPENDIX 2 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:

- 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 serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

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

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (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 for
- 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 to subjects, their legally acceptable representatives (as per country guidelines) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the 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.

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 drug 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 .Certain CRF pages and/or electronic files may serve as the source documents:

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 (CTA) 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 CTA.

APPENDIX 3 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 treatment, 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).

Any component of a study endpoint that is considered related to study therapy should be reported as SAE (e.g., death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported).

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 treatment 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 4 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.*****

Note: Hormone-based contraceptives are <u>not</u> considered highly effective methods of contraception for WOCBP participants receiving BMS-986205 in this study.

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly*[a]
• **Not for participants receiving BMS-986205:** Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal

• **Not for participants receiving BMS-986205:** Progestogen-only hormonal contraception associated with inhibition of ovulation[b] – oral – injectable
Highly Effective Methods That Are User Independent
• **Not for participants receiving BMS-986205:** Implantable progestogen-only hormonal contraception associated with inhibition of ovulation [b] • **Not for participants receiving BMS-986205:** 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) [b] • Intrauterine device (IUD) • 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. Due to the potential interaction with study drug(s), these are only considered highly effective methods for female partners of male subjects participating in this study. Hormonal contraception should not be used by female participants of child-bearing potential.

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)

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

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 latex or synthetic male condom during each episode of sexual activity for study duration and until end of relevant systemic exposure defined as 7 months after the end of study treatment. This applies even if the participant has undergone a successful vasectomy.
- 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 latex or synthetic male condom during each episode of sexual activity during the treatment and until 7 months after the end of study treatment.
- Refrain from donating sperm for the duration of the study treatment and until 7 months after the end of study treatment.

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 6 PERFORMANCE STATUS SCALES

STATUS	SCALES		STATUS
	KARNOFSKY	ZUBROD-ECOG-WHO	
Normal, no complaints; no evidence of disease	100	0	Normal activity
Able to carry on normal activities. Minor signs or symptoms of disease	90	0	
Normal activity with effort; some signs or symptoms of disease	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 personal 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	Symptomantic. Needs to be in bed > 50% of the day, but not bedridden
Severely disabled. Hospitalization indicated although death not imminent	30	3	
Very sick. Hospitalization necessary. Active supportive treatment necessary	20	4	Unable to get out of bed
Moribund. Fatal processess progressing rapidly	10	4	
Dead	0	5	Dead

APPENDIX 7 AJCC MELANOMA STAGING (CANCER STAGING MANUAL 8TH EDITION)

[From AJCC Cancer Staging Manual, 8th Edition. Amin MB, Edge S, Greene F, Byrd DR, Brookland RK, Washington MK, et al. editors. Springer International Publishing. 2017 (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 12 RESPONSE EVALUATION CRITERIA IN SOLID TUMORS GUIDELINES (VERSION 1.1) WITH BMS MODIFICATIONS

1 EVALUATION OF LESIONS

Solid tumors will be evaluated using Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1) guideline with BMS modifications.[1]

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as follows:

1.1 Measurable

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

10 mm by CT/MRI scan (scan slice thickness no greater than 5 mm), or ≥2x slice thickness if greater than 5mm.

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

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT/MRI scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

Note: Lesions on X-Ray are not to be selected as Target or Non-Target Lesions.

1.2 Non-Measurable

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

Note: Lesions on X-Ray are not to be selected as Target or Non-Target Lesions.

1.3 Special considerations regarding lesion measurability

1.3.1 Bone lesions

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

1.4 Baseline Documentation Of 'Target' And 'Non-Target' Lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded).

Note: A maximum of two lesions can be selected per organ system. For example, a maximum of two lung lesions can be selected (selected from one lung or one lesion from each). A maximum of two lymph nodes can be selected at baseline, as the lymphatic system is considered one organ.

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

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

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

2. RESPONSE CRITERIA

2.1 Evaluation of Target Lesions

- **Complete Response (CR):** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- **Partial Response (PR):** At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive Disease (PD):** At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
- **Not Evaluable (NE):** If one or more target lesions cannot be measured or adequately assessed as either fully resolved or too small to measure (due to missing or poor quality images), and the sum of diameters of the remaining measured target lesions (if any) has not increased sufficiently to meet Progressive Disease as defined above.

2.1.1 Special Notes on the Assessment of Target Lesions

2.1.1.1 Lymph nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

2.1.1.2 Target lesions that become 'too small to measure'

While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned as the reference diameter. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This

default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

2.1.1.3 Lesions that split or coalesce on treatment

When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

2.2 Evaluation of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

- **Complete Response (CR):** Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (< 10mm short axis).
- **Non-CR/Non-PD:** Persistence of one or more non-target lesion(s)
- **Progressive Disease (PD):** Unequivocal progression of existing non-target lesions.

2.2.1 Special Notes on Assessment of Progression of Non-Target Disease

The concept of progression of non-target disease requires additional explanation as follows:

2.2.1.1 When the patient also has measurable disease

In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. Pleural effusions, pericardial effusions and ascites will not be followed as target or non-target lesions and will not contribute to response or progression. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

2.2.1.2 When the patient has only non-measurable disease

This circumstance arises in some trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition:

if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include, an increase in lymphangitic disease from localized to widespread, or may be described as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore the increase must be substantial.

2.2.2 New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

NOTE: Fluid collections (pleural effusions, pericardial effusions, and ascites) will not be considered new lesions and will not contribute to response or progression. In the event a new fluid collection is seen on a post-baseline imaging exam, a comment may be made, but the appearance of a new fluid collection alone should not result in an assessment of Progressive Disease (PD). A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline. A lesion identified on Chest X-Ray that was not present in prior CT can be considered a new lesion and will result in Progressive Disease (PD).

If a new lesion is equivocal, for example because of its small size, continued follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan. While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

1. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
2. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive

FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

2.3 Response Assessment

2.3.1 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until disease progression or the last response recorded, taking into account any requirement for confirmation and censoring rules regarding subsequent therapy. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement.

2.3.2 Time Point Response

At each protocol specified time point, a response assessment occurs. Table 2.3.2-1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline. When patients have non-measurable (therefore non-target) disease only, Table 2.3.2-2 is to be used.

Table 2.3.2-1: Time Point Response: Patients With Target (± Non-Target) Disease

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

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease and NE = inevaluable

Table 2.3.2-2: Time Point Response: Patients with Non-target Disease Only		
Non-Target Lesions	**New Lesions**	**Overall Response**
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD
CR = complete response, PD = progressive disease and NE = inevaluable		

[a] Non-CR/non-PD is preferred over SD for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

2.3.3 Best Overall Response

Best response determination of complete or partial response requires confirmation: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point of ≥ 4 weeks (28 days) later. In this circumstance, the best overall response can be interpreted as in Table 2.3.3-1. When SD is believed to be best response, it must meet the protocol specified minimum time from the date of first treatment or randomization date.

For example, if the first scheduled follow-up imaging visit is Week 6 (± 7 days) for a particular protocol, a Best Response of SD can only be made after the subject is on-study for a minimum of 6 weeks (42 days) minus 7 days, for an absolute minimum time on-study of 35 days from the reference start date (reference date is considered Day 1 on study). If the subject is not on-study for at least this amount of time, any tumor assessment indicating stable disease before this time period will have a Best Response of NE unless PD is identified.

Special note on response assessment: When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).

Table 2.3.3-1: Best Overall Response (Confirmation of CR and PR Required)		
Overall Response First Time Point	**Overall Response Subsequent Time Point**	**Best Overall Response**
CR	CR	CR
CR	PR	SD, PD OR PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD

Table 2.3.3-1: Best Overall Response (Confirmation of CR and PR Required)		
Overall Response First Time Point	**Overall Response Subsequent Time Point**	**Best Overall Response**
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE
CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable		

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

2.3.4 Confirmation Scans

Verification of Response: To be assigned a status of CR or PR, changes in tumor measurements must be confirmed by consecutive or subsequent repeat assessments that should be performed no less than 28 days after the criteria for response are first met. Subsequent documentation of a CR may provide confirmation of a previously identified CR even with an intervening NE or PR (e.g., CR NE CR or CR PR CR). Subsequent documentation of a PR may provide confirmation of a previously identified PR even with an intervening NE or SD (e.g., PR NE PR or PR SD PR). However, only one (1) intervening time point will be allowed between PR/CRs for confirmation.

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

[1] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45: 228-47.

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]

APPENDIX 16 REVISED PROTOCOL SUMMARY OF CHANGE HISTORY

[redacted]

Summary of key changes for Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 2, Table 2-1, Screening Procedural Outline	Note added to title indicating that enrollment was stopped, and any consented but non-randomized patients should be screen failed.	[redacted]
Section 2, Table 2-2, On-study Assessments	• [redacted] • Allowing for co-oximetry to be used for oxygen saturation. • Increase frequency of methemoglobin assessments for participants treated with BMS-986205	• [redacted]
Table 2-3, Follow-up Procedural Outline	• Survival visits removed. • Pregnancy testing for WOCBP added • [redacted] • Footnote added specifying no follow-up visits required for participants who screen fail.	[redacted]
Section 3.1.1, Change Per Revised Protocol 01	[redacted]	[redacted]
Section 6.1, Inclusion Criteria	Contraceptive guidance updated.	[redacted]
Section 7.1.2 Nivolumab Dosing	Guidance regarding monitoring for infusion reactions added.	Information provided for sites that do no [redacted]

Summary of key changes for Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
		[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Section 7.7.2 Other Restrictions and Precautions	Precautions regarding the development of and monitoring of serotonin syndrome added.	[redacted]
Section 8.1.1 BMS-986205 and Nivolumab Dose Discontinuation	Updated to contain the most recent criteria for nivolumab in combination with BMS-986205.	[redacted]
Section 8.1.2 BMS-986205 Dose Discontinuation	Updated to specify events that require discontinuation of BMS-986205.	[redacted]
Section 9.1.1	Imaging schedule updated to local standard of care. Updated with note that images will not be submitted to BIRC.	[redacted]
Section 9.2.5 Adverse Event of Special Interest	Added section regarding the adverse events of special interest.	[redacted]
Section 9.3 Overdose	Updated reporting requirements.	[redacted]
[redacted]	[redacted]	[redacted]
Section 10, Statistical considerations	Updated to indicate that efficacy analyses will not be conducted.	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Summary of key changes for Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]	[redacted]	[redacted]
Appendix 15	Adverse events of special interest	Guidance added to aid investigators in identifying adverse events of special interest.