Official Title of Study:

A Phase 1/2a Dose Escalation and Cohort Expansion Study of the Safety, Tolerability, and Efficacy of Anti-LAG-3 Monoclonal Antibody (BMS-986016) Administered Alone and in Combination with Anti-PD-1 Monoclonal Antibody (Nivolumab, BMS-936558) in Advanced Solid Tumors

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CLINICAL PROTOCOL CA224020

A Phase 1/2a Dose Escalation and Cohort Expansion Study of the Safety, Tolerability, and Efficacy of Anti-LAG-3 Monoclonal Antibody (BMS-986016) Administered Alone and in Combination with Anti-PD-1 Monoclonal Antibody (Nivolumab, BMS-936558) in Advanced Solid Tumors

Protocol Amendment: 15

Incorporates Administrative Letters 08 and 09

[redacted]

Bristol-Myers Squibb
Route de Perreux 1
2017 Boudry, Switzerland
Telephone (office): [redacted]

Clinical Trial Physician - Medical Monitor
[redacted]
Bristol-Myers Squibb
3401 Princeton Pike
Lawrence Township, NJ 08648
Telephone: [redacted]

24-hr Emergency Telephone Number
USA: [redacted]
International: [redacted]

Bristol-Myers Squibb Research and Development
Route 206 & Province Line Road
Lawrenceville, NJ 08543

Avenue de Finlande 4
B-1420 Braine-l'Alleud, Belgium

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Protocol Amendment 15	16-Feb-2024	Incorporates Administrative Letters 08 and 09 and the following changes: • Updated the Post Study Access to Therapy section to include rollover option. • Removed female partner contraception requirements to align with the latest relatlimab/nivolumab contraceptive guidance. • Replaced the EudraCT number by EU Trial Number, and the legal framework Directive 2001/20/EC by Regulation 536/2014.
Administrative Letter 09	25-Jan-2024	Updated study personnel information and updated nivolumab packaging (BMS-936558-01).
Administrative Letter 08	12-May-2023	Updated study personnel information.
Protocol Amendment 14	28-Oct-2022	Incorporates the following changes: • Clarified the study duration for patients remaining on treatment beyond 5 years. • Updated contraceptive language. • Added COVID-19 vaccination language. • Removed rechallenge period. Patients currently receiving rechallenge treatment will be allowed to continue and patients currently in rechallenge-eligible Survival Follow-up as of this Protocol Amendment remain eligible for rechallenge. • Limited PK/immunogenicity collection maximum to up to 24 months of treatment and removed PK/immunogenicity collections upon the occurrence of ≥ Grade 3 AEs. • Addition of Appendix 8: Country Specific Requirements/Differences, which includes France and Italy (Site Specific Amendment 9 and 10) in the list of countries.
Protocol Amendment 13	29-Jul-2021	Incorporates the following changes: • Provided information on the background/rationale for this amendment. [redacted]

Document	Date of Issue	Summary of Change
Revised Protocol 12	05-Feb-2020	Incorporates the following changes: • Typographical and grammatical errors were corrected, and edits were made for consistency and clarity. • Added DOR as secondary objective for Part E. • Clarified when survival follow-up visits will be scheduled. • PK and Biomarker samples will be taken coincident with the occurrence of a study drug-related ≥ Grade 3 adverse event. • When recent archival samples are submitted at baseline, [redacted] • Clarified that for subjects who discontinue at the investigator's discretion with CR, PR, or SD, imaging must be performed every 12 weeks until disease progression. Added information to bring in line with current program standards and template language.
Revised Protocol 11	01-Oct-2019	Incorporates the following changes: • Typographical and grammatical errors were corrected, and edits were made for consistency and clarity. • Updated information about the safety of BMS-986016 480 mg + nivolumab 480 mg Q4W dosing regimen • Removed from Treatment period references to up to twelve 8-week treatment cycles. • Removed confirmed complete response and completion of the maximum number of twelve 8 week cycles from discontinuation criteria • Removed from re-challenge period statement that subjects could receive therapy for up to 6 additional eight-week cycles • Changed criteria for Adjuvant/Neoadjuvant therapy in Part D1, D2, and E. • Added the following criterion to Part E for melanoma participants that have not received prior systemic anticancer therapy for unresectable or metastatic melanoma: Uveal melanoma subjects are NOT eligible • Outlined procedures for tumor assessments done outside of scheduled assessments, if clinically indicated.
Revised Protocol 10	15-Feb-2019	Incorporates the following changes: • Added four additional Part B combination dosing cohorts: 480 mg BMS-986016 (relatlimab) + 480 mg nivolumab, 960 mg BMS 986016 + 480 mg nivolumab, 1440 mg BMS-986016 + 480 mg nivolumab, and 1600 mg BMS-986016 + 480 mg nivolumab every four weeks (Q4W). • Changed the dose escalation statistical methodology from 3+3+3 to an adaptive Bayesian Logistic Regression Model (BLRM) Copula design for Part B. • Changed DLT period from 8 weeks to 6 weeks.

Document	Date of Issue	Summary of Change
		• Added Part E, exposure response evaluation cohorts (untreated metastatic melanoma and subjects who experienced progression on prior anti-PD-1 therapy).
Administrative Letter 07	18-Oct-2018	Study personnel updates
Revised Protocol 09	31-Jan-2018	Incorporates Administrative Letters 05 - 06 and the following changes: • The testing of the nivolumab/relatlimab fix dose combination (FDC) drug product into Part D1 has been added. • Compare the safety of the FDC drug product with co-administration of relatlimab and nivolumab. • Additional analyses are added/clarified to assess PK of the FDC drug product as well as confirm the efficacy and safety of the every four-week dosing schedule.
Administrative Letter 06	19-Jan-2018	Clarify language regarding the mandatory tissue collection requirements for clinical trial participation.
Administrative Letter 05	14-Sep-2017	Correction to numbering of Inclusion Criteria
Revised Protocol 08	31-Jul-2017	Incorporates Administrative Letter 04 and the following changes: • Added a bladder cohort to Part C and added Part D (melanoma prior IO expansion cohorts) to the study design, • Introduced co-administration to Part D • Updated to allow adolescent subjects (age 12 and above) to enroll in Parts C and D. • Modified inclusion/exclusion criteria • Updated statistical section and made administrative changes as applicable
Administrative Letter 04	01-Mar-2017	• Clarified biopsy requirements and updated inclusion criteria for Non-small cell lung cancer (NSCLC) naive to IO
Revised protocol 07	20-Dec-2016	Incorporates Amendment 11
Amendment 11	20-Dec-2016	The following changes were made: • Updated nivolumab and BMS 986016 safety information • Added a Q4W dosing regimen in Part B of the study • Updated dose delay guidelines and study discontinuation criteria to align with nivolumab program • Modified inclusion/exclusion criteria for Part C of study • Modified to mandate fresh tumor biopsy collection from every subject • Updated statistical section and made administrative changes as applicable
Revised protocol 06	25-May-2016	Incorporates Amendment 07 and Administrative letter 03

Document	Date of Issue	Summary of Change
Amendment 07	25-May-2016	The following changes were made: • Revision of exclusion criteria regarding cardiovascular history • Addition of echocardiogram and troponin level monitoring at baseline • Addition of ECG and troponin level monitoring through Cycle 1 • Correction of typographical errors
Revised protocol 05	12-Feb-2016	Incorporates Amendment 06 and Administrative letter 02
Amendment 06	12-Feb-2016	The following changes were made: • Revised study design to remove Parts D, E, F and G, and updated Part C expansion cohort populations. • Updated DLT criteria • Included adaptive language for dose selection for Part C of the study • Nivolumab infusion time was reduced from 60 minutes to 30 minutes starting for Part C of the study • Updated statistical sections, to align with revised study design
Administrative letter 02	20-Nov-2015	Change of Medical Monitor/Study Director
Revised protocol 04	24-Aug-2015	Incorporates Amendment 04
Amendment 04	24-Aug-2015	The following changes were made: • Revised study design to include new Parts/cohorts and updated expansion cohort populations; introduced adaptive design of Stage 1 and Stage 2. • Updated biomarker and pharmacokinetic collections • Updated anti-LAG-3 and nivolumab safety information • Updated statistical sections to reflect new study design
Revised protocol 03	08-Sep-2014	Incorporates Amendment 03 and Administrative letter 01
Amendment 03	08-Sep-2014	The following changes were made: • Revised the starting dose of anti-LAG-3 in the first combination cohort of Part B from 3 mg to 20 mg. • Removed the 3 mg anti-LAG-3/240 mg nivolumab cohort in Part B
Administrative letter 01	16-Jul-2014	Addition of EUDRACT number and minor clerical edits.
Revised Protocol 02	23-May-2014	Incorporates Amendment 02
Amendment 02	23-May-2014	The following changes were made: • Addition of fourth additional subject at beginning of each dose level • Revision of inclusion and exclusion criteria • Updated WOCBP definition and contraception methods, and revised Appendix 1 • Revised DLT criteria

Document	Date of Issue	Summary of Change
		• Added study drug dosing instructions for combination of anti-LAG-3 and nivolumab. • Incorporated new biomarker sample collections for Part C of study • Revised subject criteria for Part B and expansion cohorts in Part C of study • Modified PK and ADA Table 5.5.1-1 • Added Appendix 4- Nivolumab Management Algorithms
Revised Protocol 01	11-Sep-2013	Incorporates Amendment 01
Amendment 01	11-Sep-2013	The following changes were made: • Addition of Grade 4 anemia to dose-limiting toxicity criteria • Addition of neurological examination performed by a neurologist for subjects in Part B or C who develop study drug-related Grade 2 or higher neurological AEs • Extension of vital sign monitoring on Cycle 1 Day 1 from 60 minutes to 120 minutes for subjects in the first cohort in Part B • Modifications to inclusion criteria to specify that subjects in all parts of the study must have an incurable solid malignancy and that subjects in Parts B and C may have refused standard therapy for advanced or metastatic disease
Original Protocol	10-Jul-2013	Not applicable

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 15:

The study protocol has been updated to describe potential options post-CA224020 closure for 1) participants remaining on treatment to continue to receive study treatment, and 2) participants in rechallenge-eligible Survival Follow-up to remain eligible to receive rechallenge study treatment for up to 5 years from their first dose. This includes the option to participate in a Bristol-Myers Squibb sponsored rollover trial.

Additionally, this revised protocol reflects the changes included in approved administrative letters 08 and 09 and are not included in the summary of key changes listed below.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 15		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	Replaced EudraCT number by EU Trial Number. Added Sponsor location for Research and Development.	Applied the new administrative reference to comply with EU Clinical Trial Regulation (EU CTR), following the transition to EU CTR. To update address.
Section 2.1: Good Clinical Practice	Replaced the European Union Directive 2001/20/EC by European Union Regulation 536/2014.	Applied the new administrative reference to comply with EU CTR, following the transition to EU CTR.
Section 3.2: Post Study Access to Therapy	Updated to include options for continued study treatment after the conclusion of CA224020 study.	To allow participants remaining on treatment an option to continue treatment post CA224020 study, and participants in rechallenge-eligible Survival Follow-up an option to remain eligible for a rechallenge treatment for up to 5 years from the first dose.
Section 3.3.1: Inclusion Criteria	Criterion (3)(g): Added language that pregnancy reporting from female partners of childbearing potential is not required.	For consistency with Sponsor asset language.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 15		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 3.6: Post Treatment Study Follow up	Removed the Study Follow-up after study treatment discontinuation in a rollover study.	Text removed because no further collection of survival follow-up data via a rollover study is planned.
Section 6.4: Pregnancy	Removed the last paragraph pertaining to female partner contraception requirements.	Aligned with latest relatlimab/nivolumab contraceptive guidance.
Throughout	Minor formatting and typographical corrections.	Minor, therefore not summarized.

SYNOPSIS

Clinical Protocol CA224020

Protocol Title: A Phase 1/2a Dose Escalation and Cohort Expansion Study of the Safety, Tolerability, and Efficacy of Anti-LAG-3 Monoclonal Antibody (BMS-986016) Administered Alone and in Combination with Anti-PD-1 Monoclonal Antibody (Nivolumab, BMS-936558) in Advanced Solid Tumors

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

BMS-986016 (anti–lymphocyte activation gene 3 [LAG-3] antibody) is supplied as a sterile 10-mg/mL formulation to be administered as an intravenous (IV) infusion.

Nivolumab (BMS-936558) is available as a sterile 10-mg/mL formulation to be administered as an IV infusion.

BMS-986213 (relatlimab 80 mg/nivolumab 240 mg vial) is available as a 16-mg/mL fixed-dose combination (FDC) drug product. It contains relatlimab and nivolumab at a protein-mass ratio of 1:3 in a single vial.

In Part A, monotherapy dose escalation, BMS-986016 will be administered at doses of 20, 80, 240, and 800 mg once every 2 weeks (Q2W), in 8-week cycles.

In Part A1, monotherapy cohort expansion, BMS-986016 will be administered at the maximum administered dose (MAD) of 800 mg as determined in Part A. Study therapy will be administered once Q2W, in 8-week cycles.

In Part B, dose escalation of combination with nivolumab administered by sequential infusion, nivolumab will be administered at a dose of either 80 mg or 240 mg followed by infusion of BMS-986016 at doses of 20, 80, and 240 mg, once Q2W, in 8-week cycles. This part of the study will also have a dose escalation with a nivolumab dose of 480 mg followed by infusion of BMS-986016 at doses of 160, 240, 320, 480, 960, 1440, and 1600 mg once every 4 weeks (Q4W), in 8-week cycles.

In Part C, cohort expansion of combination with nivolumab administered by sequential infusion, nivolumab and BMS-986016 will be administered at the combination doses selected from Part B, which may represent the maximum tolerated dose (MTD), MAD, or an alternative dose selected from dose escalation. Study therapy will be administered once Q2W or Q4W with infusion of nivolumab first followed by BMS-986016 administration, in 8-week cycles.

In Part D, melanoma prior immuno-oncology (IO) extended expansion cohorts, most subjects will receive coadministration of BMS-986016 and nivolumab in a single IV bag at 2 different select doses, either at Q2W or Q4W, in 8-week cycles; some subjects will receive BMS-986213 FDC product. Part D1 employs focused eligibility criteria to build upon eligible subjects from the Part C melanoma prior IO cohort. If subjects do not meet the more focused eligibility of Part D1, they may be eligible for Part D2, which is more flexible in the allowed prior therapies and performance

status. Part D2 will test safety and efficacy in this broader patient population and will employ the more convenient Q4W dosing in 2 different dose combinations.

In Parts C, D, and E, adolescents (12 to < 18 years of age) weighing less than 40 kg will be dosed based on weight (1 mg/kg BMS-986016 and 3 mg/kg of nivolumab Q2W, 2 mg/kg BMS-986016 and 6 mg/kg of nivolumab Q4W, and 6 mg/kg BMS-986016 and 6 mg/kg of nivolumab Q4W) up to maximum doses of the respective adult flat doses.

In Part E advanced melanoma, exposure response evaluation cohorts, subjects will receive coadministration of BMS-986016 and nivolumab in a single IV bag at different select doses, Q4W, in 8-week cycles.

Study Phase: Phase 1/2a

Research Hypotheses: It is anticipated that anti-LAG-3 antibody (BMS-986016), administered as a single agent or in combination with anti-programmed cell death protein 1 (PD-1) antibody (nivolumab), will demonstrate adequate safety and tolerability, as well as a favorable benefit-risk profile, to support further clinical testing. No prospective hypotheses are being formally evaluated.

Part D1: Treatment with BMS-986016 in combination with nivolumab will lead to clinical benefit, as demonstrated by a clinically meaningful objective response rate (ORR), including durable responses with substantial magnitude of tumor burden reduction, in melanoma subjects who progressed while on anti-PD-1 antibody therapies.

Part D1: Treatment with BMS-986213 (FDC) will demonstrate no clinically relevant differences in safety relative to coadministration of nivolumab and BMS-986016.

Part E: Treatment with BMS-986016 in combination with nivolumab (coadministration) will lead to clinical benefit in melanoma subjects. This will be demonstrated by higher doses of relatlimab (eg, 480 mg BMS 986016 + 480 mg nivolumab Q4W) producing greater clinical benefit, manifested by a clinically meaningful ORR, including durability of response and substantial magnitude of tumor burden reduction.

Objectives:

Primary Objectives:

Parts A and B:

The primary objective is to determine the safety, tolerability, dose-limiting toxicities (DLTs), and MTD of BMS-986016 administered alone and in combination with nivolumab in subjects with advanced solid tumors.

Part A1:

The primary objective of BMS-986016 monotherapy cohort expansion is to gather additional safety, tolerability, and preliminary efficacy information of BMS-986016 monotherapy.

Part C:

The primary objective is to further establish adequate safety and tolerability of BMS-986016 in combination with nivolumab administered sequentially.

The coprimary objective in Dose Expansion Part C is to investigate the preliminary efficacy of BMS-986016 in combination with nivolumab as measured by ORR, disease control rate (DCR), and duration of response (DOR) in multiple tumor types.

Part D:

The primary objective in Part D is to assess safety and tolerability of a more convenient dosing regimen (ie, coadministration and Q4W dosing interval).

Part D1-Q2W: The coprimary objective in Part D1-Q2W is to demonstrate preliminary clinical evidence of the treatment effect, measured by ORR, as determined by Blinded Independent Central Review (BICR) using Response Evaluation Criteria for Solid Tumors (RECIST) version 1.1 that may represent substantial improvement over available therapies in advanced melanoma subjects with LAG-3 expression who progressed while on anti-PD-1 antibody therapies.

Part D1-Q4W: The primary objective in Part D1-Q4W is to evaluate the difference in safety of coadministration relative to FDC as measured by the incidence of adverse events (AEs) in the Broad Scope Medical Dictionary for Regulatory Activities (MedDRA) Anaphylactic Reaction Standardized MedDRA Query (SMQ) occurring within 2 days after dosing in advanced melanoma subjects who progressed while on anti-PD-1 antibody therapies.

Part D1-Q4W: The coprimary objective in Part D1-Q4W is to confirm with Q4W dosing of BMS-986016 160 mg in combination with nivolumab 480 mg the safety of the Q2W dosing of BMS-986016 80 mg in combination with nivolumab 240 mg in advanced melanoma subjects who progressed while on anti-PD-1 antibody therapies.

Part E:

The primary objective of Part E is to demonstrate that the 480 mg BMS 986016 + 480 mg nivolumab Q4W dosing regimen provides significantly greater clinical benefit, manifested as an increased ORR, to participants as compared with the 160 mg BMS 986016 + 480 mg nivolumab Q4W dose by interdose cohort comparison in melanoma participants who have not received prior systemic anticancer therapy for unresectable or metastatic melanoma and to historical control for melanoma participants who experienced disease progression on prior anti-PD-1 therapy.

Secondary Objectives:

The secondary objectives are:

To characterize the pharmacokinetics (PK) of BMS-986016 administered alone and in combination with nivolumab

To investigate the preliminary ORR and/or DCR of BMS-986016 administered alone and in combination with nivolumab in subjects with advanced solid tumors in Parts A and B, Dose Escalation

To characterize the immunogenicity of BMS-986016 administered alone and in combination with nivolumab

In Parts A and B, to assess the effect of BMS-986016 administered alone and in combination with nivolumab on QTc

Part D1:

To evaluate DOR, DCR, and progression-free survival (PFS) rates at prespecified time points (eg, 24 weeks) based on BICR assessments using RECIST v1.1 in advanced melanoma subjects with LAG-3 expression who progressed while on anti-PD-1 antibody therapies

To evaluate ORR, DCR, DOR, and PFS rates at prespecified time points (eg, 24 weeks) based on BICR assessments using RECIST v1.1 in advanced melanoma subjects with a lack of LAG-3 expression and overall, regardless of LAG-3 expression

To evaluate ORR, DCR, DOR, and PFS rates at prespecified time points (eg, 24 weeks) based on Investigator assessments using RECIST v1.1 in advanced melanoma subjects with LAG-3 expression, a lack of LAG-3 expression, and overall regardless of LAG-3 expression

To assess the 1-year and 2-year landmark overall survival (OS) in advanced melanoma subjects with LAG-3 expression, a lack of LAG-3 expression, and overall regardless of LAG-3 expression

Part D1-Q4W: To confirm with Q4W dosing of BMS-986016 160 mg in combination with nivolumab 480 mg the efficacy of the Q2W dosing of BMS-986016 80 mg in combination with nivolumab 240 mg in advanced melanoma subjects who progressed while on anti-PD-1 antibody therapies

Part D1-Q4W: To evaluate the difference in safety of coadministration relative to FDC as measured by the incidence of AEs in the Narrow Scope MedDRA Anaphylactic Reaction SMQ and the incidence of the select AEs in the hypersensitivity/infusion reaction category occurring within 2 days after dosing during the combination in advanced melanoma subjects who progressed while on anti-PD-1 antibody therapies

Part D1-Q4W: To evaluate Grade 3 - 5 AE incidence rate (drug related and all causality) defined using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0 criteria

Part D1-Q4W: To determine PK comparisons of nivolumab and BMS-986016 administered as FDC to that of coadministered nivolumab and BMS-986016

Part D1: To assess PK of nivolumab and BMS-986016 in Part D1-Q4W dosing and Part D1-Q2W dosing

Part D2:

To assess safety and tolerability of more convenient dosing regimen in a wider range of population in advanced melanoma subjects who progressed while on anti-PD-1/PD-L1 antibody therapies

To evaluate ORR, DCR, DOR, and PFS rates at prespecified time points (eg, 24 weeks) based on BICR assessments using RECIST v1.1 in a wider range of population in advanced melanoma subjects with LAG-3 expression, a lack of LAG-3 expression, and overall regardless of LAG-3 expression

To evaluate ORR, DCR, DOR, and PFS rates at prespecified time points (eg, 24 weeks) based on Investigator assessments using RECIST v1.1 in a wider range of population in advanced melanoma subjects with LAG-3 expression, a lack of LAG-3 expression, and overall regardless of LAG-3 expression

To assess the 1-year and 2-year landmark OS in advanced melanoma subjects with LAG-3 expression, a lack of LAG-3 expression, and overall regardless of LAG-3 expression

Part E:

To evaluate the clinical benefit of the 480 mg BMS-986016 + 480 mg nivolumab Q4W dosing regimen using DOR in melanoma participants who have not received prior systemic anticancer therapy for unresectable or metastatic melanoma and for melanoma participants who experienced disease progression on prior anti-PD-1 therapy

Exploratory Objectives:

To assess the pharmacodynamic effects of BMS-986016 alone and in combination with nivolumab based on select biomarkers in the peripheral blood and tumor biopsy specimens

[redacted]

To assess the 1-year and 2-year landmark OS in subjects treated with BMS-986016 alone and in combination with nivolumab

To characterize nivolumab PK and immunogenicity when administered in combination with BMS-986016

To explore exposure-response relationships in subjects treated with BMS-986016 as monotherapy or in combination with nivolumab

To investigate the relationship between clinical efficacy and peripheral and tumor biomarkers

[redacted]

To evaluate ORR, DCR, DOR, and PFS rates at prespecified time points (eg, 24 weeks) based on iRECIST assessments based on BICR

To predict milestone survival at 1 year and 2 years using tumor growth dynamic-survival model

Study Design:

This is a Phase 1/2a, open-label study of BMS-986016 administered as a single agent and in combination with nivolumab to subjects with advanced solid tumors.

Part A and **Part B** consist of a 3 + 3 + 3 dose escalation design and, implemented in site-specific amendment #15 (dated 13 August 2018) and superseding the 3 + 3+ 3 dose escalation design, the Bayesian Logistic Regression Model (BLRM)-Copula design (for Part B only), evaluating BMS-986016 administered as a single agent (Part A) or in combination with nivolumab (Part B) as sequential infusions in subjects with advanced solid tumors. Treatment in Part B will be initiated upon the decision to escalate to the third dose cohort in Part A (in accordance with dose escalation rules); subsequently, escalation in the 2 parts will proceed in parallel. Testing of the Q2W and

Q4W dosing schedules in Part B can proceed concurrently with independent escalation decisions based upon review of the current total safety experience and following consultation and agreement between Investigators and the Sponsor. Treatment in Part B will be initiated after the decision is made to escalate to the third dose cohort in Part A (in accordance with dose escalation rules).

Part A1 consists of cohort expansion with BMS-986016 monotherapy in 2 disease-restricted cohorts of approximately 6-12 subjects each. Treatment in Part A1 will be initiated at the MAD determined in Part A (ie, 800 mg). The dose selected for Part A1 will not exceed the MAD in Part A, but dose selection may change according to assessment of other data, including toxicities and PK and pharmacodynamic data from Parts A and A1. Subjects in Part A1 may cross over to combination therapy with nivolumab and BMS-986016 in sequential infusion if they meet predefined criteria.

Part C consists of cohort expansion in disease-restricted cohorts using a multistage approach, treated with sequential infusion of nivolumab and BMS-986016. Cohorts deemed futile (see sample size section for further details) at Stage 1 will be discontinued, whereas those deemed promising may be expanded further up to 90 to 120 subjects in total after careful evaluation of all available data, including the totality of efficacy, safety profile, and PK/pharmacodynamics. Otherwise, additional subjects may be treated to collect more data during Stage 2 in order to make decisions for further expansion. The doses selected for Part C will not exceed the Part B MTD or MAD, and specific doses selected may incorporate assessment of other data, including toxicities and PK and pharmacodynamic data from Parts A and B. Subjects in Part C cannot cross over to Part A1 either.

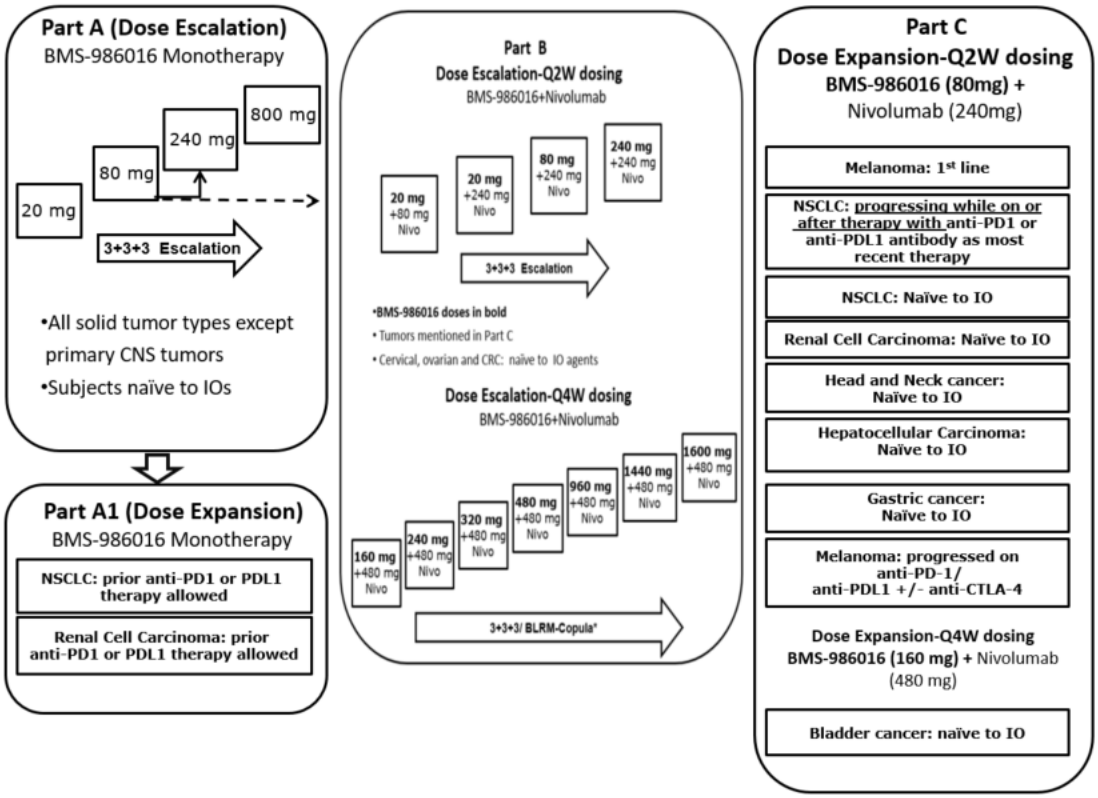
Part D consists of melanoma subjects who progressed on prior IO therapy. There is a Part D1 and a Part D2 within Part D. Most subjects in Part D will receive coadministration of BMS-986016 and nivolumab. Part D1 employs a focused set of eligibility criteria to build upon eligible subjects from the Part C melanoma prior IO cohort with the primary goal of testing the efficacy of 80 mg BMS-986016 + 240 mg nivolumab Q2W regimen. Enrollment may continue until the following criteria are met: (a) 90 efficacy-evaluable LAG-3-positive subjects have been treated, (b) 60 efficacy-evaluable LAG-3-positive and BRAF wild-type subjects have been treated, and (c) 60 efficacy-evaluable LAG-3-positive and ipilimumab-pretreated subjects have been treated. Part D1 will also have 2 other cohorts: 1) 160 mg BMS-986016 with 480 mg of nivolumab Q4W coadministration and 2) BMS-986213 (relatlimab 160 mg/nivolumab 480 mg) Q4W.

If subjects do not meet the more focused eligibility of Part D1, they may be eligible for Part D2, which is more flexible with respect to the allowed prior therapies and performance status. Part D2 will test safety and efficacy in this broader patient population and will employ the more convenient Q4W dosing in 2 different dose combinations (160 mg BMS-986016 + 480 mg nivolumab and subsequently 240 mg BMS-986016 + 480 mg of nivolumab). Adolescents (12 to < 18 years of age) weighing less than 40 kg will receive body weight-based dosing, equivalent to the conversion from a median adult weight of 80 kg (1 mg/kg BMS-986016 and 3 mg/kg of nivolumab Q2W, 2 mg/kg BMS-986016 and 6 mg/kg of nivolumab Q4W, or 6 mg/kg BMS-986016 and 6 mg/kg of nivolumab Q4W for corresponding fixed doses of 80/240 Q2W, 160/480 Q4W, and 240/480 Q4W, respectively). This adolescent dosing scheme also applies to BMS-986213. The doses and schedule

selected for Part D will not exceed the Part B MTD or MAD, and dosing of the cohorts may be altered in collaboration between the Investigators and Sponsor, based upon the overall ongoing study data, including evaluation of toxicities, PK, and pharmacodynamics. A schematic of the study is provided in Figure 1.

Part E consists of advanced melanoma participants. Two cohorts of melanoma participants will be enrolled in Part E: melanoma participants who experienced disease progression on prior anti-PD-1 therapy and melanoma participants who have not received prior systemic anticancer therapy for unresectable or metastatic melanoma. In Part E, melanoma participants will be administered either 160 mg BMS-986016 with 480 mg of nivolumab Q4W or 480 mg BMS-986016 with 480 mg of nivolumab Q4W; the specific dosing regimen will be dependent on 1) whether the subject had progressive disease on an earlier anti-PD-1 therapy and 2) randomization.

Figure 1: Study Schematic

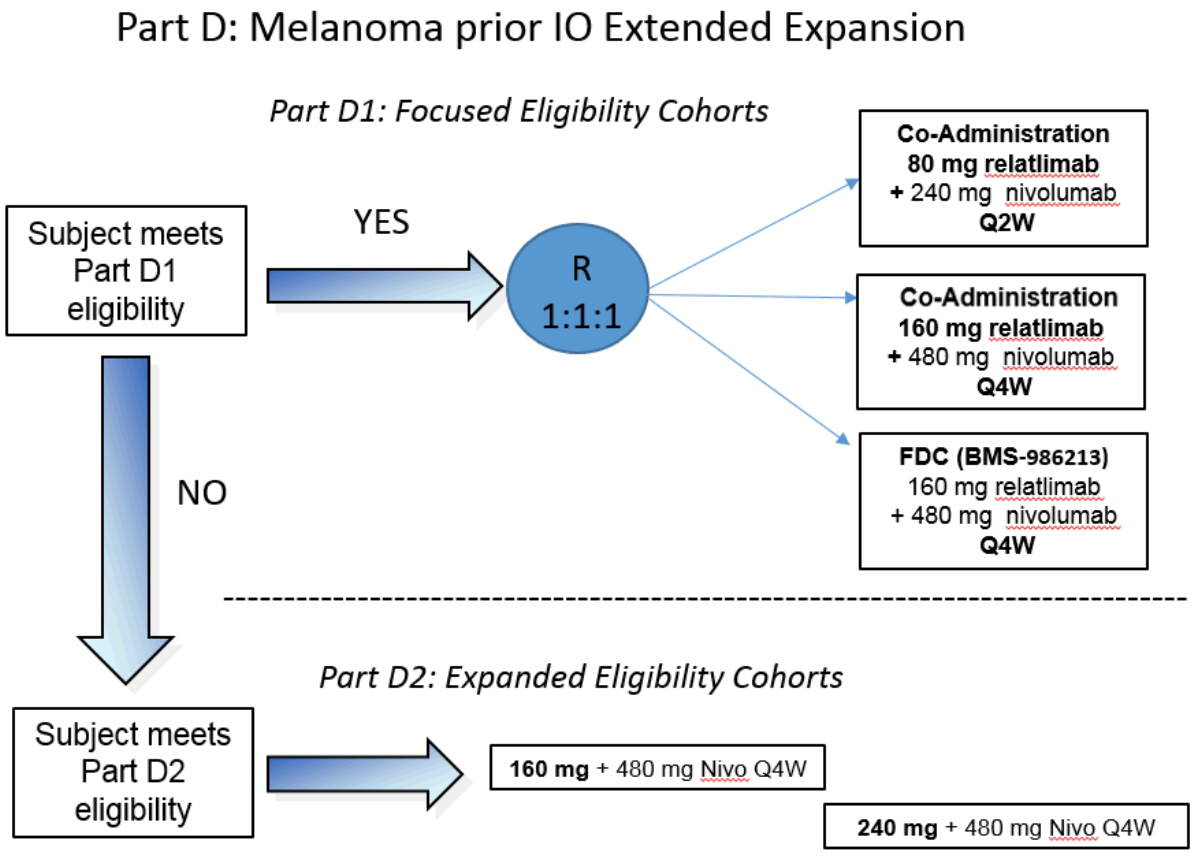


Sequential = sequential administration of nivolumab first, followed by BMS-986016 infusion within 15 to 30 minutes of completing nivolumab infusion. For doses of 960 mg relatlimab + 480 mg nivolumab Q4W and higher doses, BMS-986016 infusion should be administered no sooner than 30 minutes following completion of nivolumab infusion.

IO = immuno-oncology agents (such as, but not limited to, anti-cytotoxic T lymphocyte–associated antigen 4 (CTLA-4), anti–PD-1, anti–PD-L1, anti–PD-L2, anti-KIR, anti-CD137, anti-LAG-3, and/or anti-OX40 antibodies).

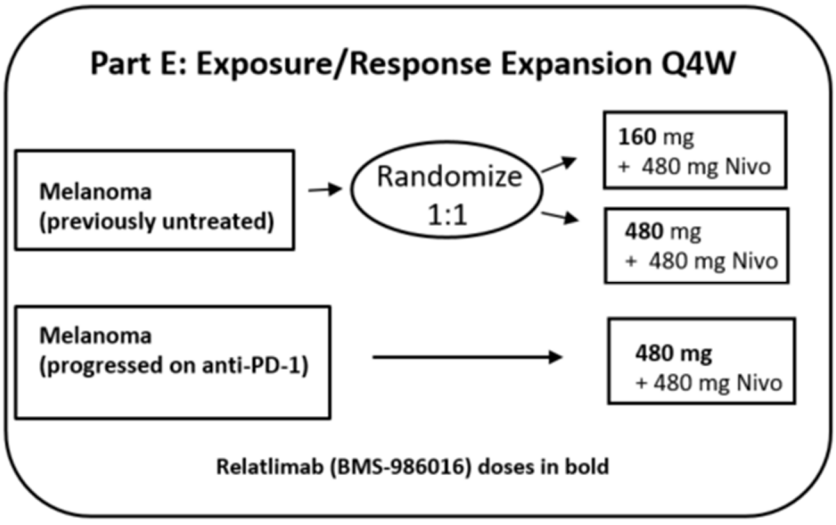
* Subsequent to site-specific amendment #15 (dated 13 August 2018), the dose escalation design was changed to BLRM-Copula from the 3 + 3 + 3 design.

Figure 2: Part D



- **Relatlimab (BMS-986016) doses in bold**
- BMS-986213: Fixed Dose Combination (FDC) vials
- Part D1: Randomized 1:1:1 to one of the three treatment Arms described above.
- Part D2: The **240mg** /480mg Q4W cohort will start enrollment once the **160mg** /480mg Q4W cohort has completed enrollment

Figure 3: Part E



Part E consists of advanced melanoma participants. Two cohorts of melanoma participants will be enrolled in Part E: melanoma participants who experienced disease progression on prior anti-PD-1 therapy and melanoma participants who have not received prior systemic anticancer therapy for unresectable or metastatic melanoma.

Melanoma participants who experienced disease progression on prior anti-PD-1 therapy will all receive 480 mg BMS 986016 + 480 mg nivolumab Q4W dose regimen.

Melanoma participants who have not received prior systemic anticancer therapy for unresectable or metastatic melanoma will be randomized to 1 of the 2 following treatment arms:

160 mg BMS-986016 + 480 mg nivolumab Q4W
480 mg BMS 986016 + 480 mg nivolumab Q4W

Subjects will complete up to 4 periods of the study: **Screening** (up to 28 days), **Treatment**, **Clinical Follow-up** (135 days), and **Survival Follow-up** (up to 5 years following the first dose of study drug). Two independent periods, **Crossover** and **Rechallenge** may be conducted in selected cases at progression. **As of Protocol Amendment 14, rechallenge is not permitted.**

In the **Treatment Period,** each treatment cycle comprises 4 doses of either BMS-986016 alone (Parts A and A1) or in combination with nivolumab (Part B and C except bladder cohort), administered on Days 1, 15, 29, and 43 of each treatment cycle. [redacted]. In Parts B and C when both study drugs are given as sequential infusion, nivolumab will be given first, followed by BMS-986016 within 15 to 30 minutes of completing the infusion of nivolumab. In Part B, for doses of 960 mg relatlimab + 480 mg nivolumab Q4W and higher doses, BMS-986016 infusion should be administered no sooner than 30 minutes following completion of nivolumab infusion. Part D, the melanoma prior IO extended expansion, will have 2 sections: Part D1 will have a focused eligibility criteria with a cohort of 80 mg of BMS-986016 with 240 mg nivolumab Q2W, a cohort of 160 mg BMS-986016 with 480 mg of nivolumab Q4W, and a cohort of BMS-986213 (160 mg relatlimab/480 mg nivolumab) Q4W; Part D2 will have an expanded eligibility criteria with 2 cohorts in sequence: 160 mg BMS-986016 with 480 mg of nivolumab Q4W and 240 mg BMS-986016 and 480 mg of nivolumab Q4W. In Part D, study drugs are given as a coadministration or single infusion of BMS-986213 over approximately 60 minutes. In Part E, melanoma subjects will be administered either 160 mg BMS-986016 with 480 mg of nivolumab Q4W or 480 mg BMS-986016 with 480 mg of nivolumab Q4W; the specific dosing regimen will be dependent on whether the subject previously received anti-PD-1 therapy in the advanced, unresectable, or metastatic setting and had progressive disease on that earlier treatment regimen and randomization, as previously described. Adolescents (12 to < 18 years of age) weighing less than 40 kg will be dosed based on weight (1 mg/kg BMS-986016 and 3 mg/kg of nivolumab Q2W, 2 mg/kg BMS-986016 and 6 mg/kg of nivolumab Q4W, or 6 mg/kg BMS-986016 and 6 mg/kg of nivolumab Q4W). In Parts C, D, and E, Q4W dosing, BMS-986016 and nivolumab will be

administered on Days 1 and 29 of each treatment cycle; visits will occur every 2 weeks to assess safety for the first cycle of treatment, and thereafter visits will only be on Day 1 and Day 29 of each subsequent cycle. [redacted] Tumor response will be evaluated using RECIST v1.1. Subjects will be allowed to continue study therapy until the first occurrence of either: 1) progressive disease (PD), 2) clinical deterioration, and/or 3) meeting other criteria for discontinuation (Section 3.5). Treatment beyond progression may be allowed in select subjects with initial RECIST v1.1-defined PD who are receiving clinical benefit as assessed by the Investigator, tolerating treatment, and meeting other criteria specified in Section 4.3.4. Subjects who discontinue treatment will enter a 135-day **Clinical Follow-up** period.

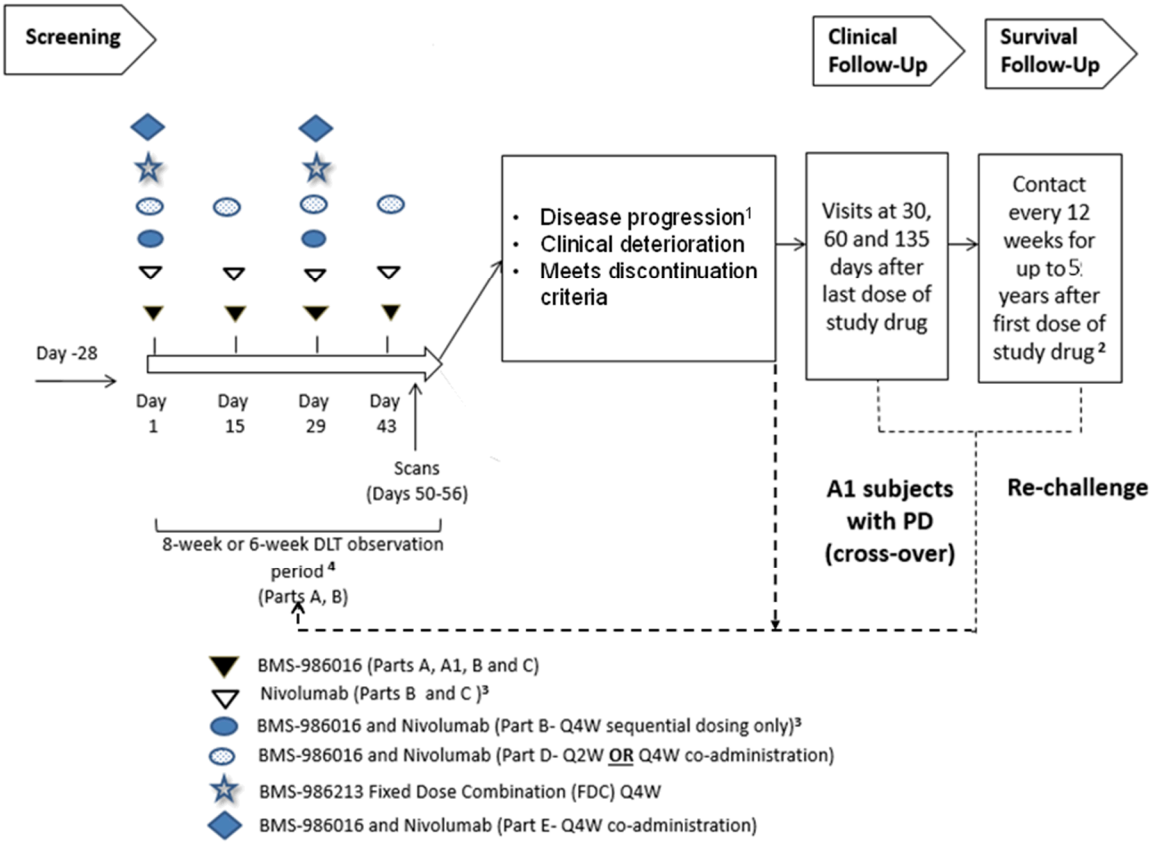
After completion of the **Clinical Follow-up** period, subjects will enter the **Survival Follow-up** period. During this period, clinic visits or telephone contact every 12 weeks will be performed to assess survival status. Survival follow-up visits will be scheduled based on the last clinical follow-up visit. The duration of this period may continue for up to 5 years from the first dose. **Diagnostic imaging must be performed every 8 weeks until disease progression. For subjects who discontinue treatment at the Investigator's discretion with a complete response (CR), partial response (PR), or stable disease (SD) by RECIST v1.1, imaging must be performed every 12 weeks until disease progression.** If subjects progress during the Clinical Follow-up period or the Survival Follow-up period, they could further receive therapy with BMS-986016 alone or in combination therapy (**Rechallenge** period) as long as the benefit-risk ratio is considered favorable by the Investigator and the Medical Monitor and eligibility criteria are met (Section 3.1.2.4). The rechallenge-eligible Survival Follow-up period may continue for up to 5 years from the first dose of study drug. The original dose and schedule and protocol rules would apply accordingly. Subjects will not be rechallenged a second time. Collection of archival tissue (baseline) and tumor biopsies (baseline and on-treatment) will be optional for subjects enrolled for rechallenge. PK and biomarker monitoring will be limited (Sections 5.5 and 5.7). **As of Protocol Amendment 14, rechallenge is not permitted.** All subjects who discontinue primary study treatment following implementation of Protocol Amendment 14 will not be eligible for rechallenge. Subjects currently receiving rechallenge treatment will be allowed to continue, and subjects currently in the rechallenge-eligible Survival Follow-up as of this Protocol Amendment remain eligible for rechallenge.

For patients remaining on treatment beyond 5 years, subjects may continue on study treatment, as long as the benefit-risk ratio is considered favorable by the Investigator and continues to meet the criteria outlined in the protocol.

Also, subjects receiving therapy with BMS-986016 alone in expansion Part A1 may **cross over** to combination therapy at confirmed progression (Section 3.1.2.1).

A study schematic is shown in Figure 4.

Figure 4: Detailed Study Schematic



[1] Treatment beyond progression may be considered in select subjects as described in Section 4.3.4.

[2] Diagnostic imaging must be performed every 8 weeks until disease progression, and in subjects who discontinue study treatment at the Investigator's discretion with a CR, PR, or SD via RECIST 1.1, imaging must be performed every 12 weeks until disease progression.

[3] For treatment visits in Parts B and C where BMS-986016 and nivolumab are administered sequentially, nivolumab will be administered first over 30 minutes, followed by BMS-986016 administration within 15 to 30 minutes after completion of the nivolumab infusion. For doses of 960 mg relatlimab + 480 mg nivolumab Q4W, BMS-986016 infusion should be administered no sooner than 30 minutes following completion of nivolumab infusion.

[4] Note the 6-week DLT period will be initiated with the 960 mg BMS-986016 dose level.

Note: As of Protocol Amendment 14, rechallenge is not permitted.

Study Parts:

Dose Escalation Part A: In Part A, a 3 + 3 + 3 design will be used to assess the safety of BMS-986016 given as single agent. A fourth subject may be enrolled at the beginning of a dose escalation cohort following agreement between the Investigator and the Sponsor/Medical Monitor, if the subject is able to start the first day of dosing within approximately 1 week of the third subject in the same dose escalation cohort. The dosages during dose escalation are provided in Table 1. Three subjects (or 4, if applicable) will initially be treated in each dose cohort; in Dose Cohort 1,

each of the first 3 subjects (or 4, if applicable) will be designated as sentinel subjects and will begin treatment at least 5 days apart. Subjects in subsequent cohorts will not be required to observe the 5-day interval between treatment start dates.

Dose escalation in Part A will proceed as follows: if none of the 3 (or 4, if applicable) subjects experience a DLT, a new cohort of 3 subjects (or 4, if applicable) will be treated at the next higher dose level. If 1 of 3 (or 4, if applicable) subjects experiences a DLT, that cohort will be expanded to 6 subjects (or 7, if applicable). If 2 of 6 (or 7, if applicable) subjects experience a DLT, that cohort will be expanded to 9 subjects. If ≥ 2 of 3 (or 4, if applicable), ≥ 3 of 6 (or 7, if applicable), or ≥ 3 of 9 subjects experience DLTs within a cohort, then that dose level will be determined to have exceeded the MTD.

Table 1: Dose Escalation and Dose Expansion Schedules for Part A and Part A1 BMS 986016 Monotherapy

Part A Dose Escalation Cohort Number	Total Subjects	BMS-986016 Dose (IV; mg)
1	n = approximately 3-9	20
2	n = approximately 3-9	80
3	n = approximately 3-9	240
4	n = approximately 3-9	800
Total	N = approximately 12-36	
Part A1: Dose Expansion Cohorts		
Non-small cell lung cancer (NSCLC): prior anti-PD-1 or PD-L1 therapy allowed[a]	n = approximately 6-12	800
Renal cell carcinoma (RCC): prior anti-PD-1 or PD-L1 therapy allowed[a]	n = approximately 6-12	800
Total	N = approximately 12-24	

[a] See Section 3.3 for detailed eligibility criteria.

Prior to declaring the MTD (or MAD), and in consultation with Investigators, the Sponsor has the option to expand any cohort previously established to be safe in order to obtain additional experience or to investigate dose levels intermediate to those defined in the protocol. Dose escalation rules (cohort size, observation for DLTs, etc.) will apply to these expanded or additional cohorts. A maximum of 9 subjects will be enrolled in any additional or expanded dose cohorts.

Cohort Expansion Monotherapy (Part A1): The purpose of cohort expansion is to gather additional safety, tolerability, preliminary efficacy, PK, and pharmacodynamic information of BMS-986016 monotherapy. The doses selected for Part A1 will not exceed the MTD or MAD in Part A but may incorporate assessment of other data, including toxicities and PK and pharmacodynamic data from Part A. Doses to be considered may include doses intermediate to those evaluated in Part A, if recommended by the Investigators and the Sponsor. Modeling may

be used to help inform the selection of the combination dose level to carry forward in Part A1 if a dose below the MTD is chosen. Two expansion cohorts will be restricted to the tumor types listed in Table 1.

Subjects in Part A1 may cross over to Part C if all of the following criteria are met: 1) subject has confirmed disease progression (Investigator-assessed RECIST 1.1-defined progression confirmed at least 4 weeks after the initial tumor assessment showing progression; 2) subject has not experienced BMS-986016–related AEs leading to permanent discontinuation; 3) subject is not continuing to derive any clinical benefit from BMS-986016 single-agent therapy as assessed by the Investigator; 4) the individual case has been discussed with the Medical Monitor prior to crossover (Section 3.1.2.1); 5) at least an 8-week period in between the last dose of monotherapy and the first dose of combination therapy. Subjects will not be rechallenged a second time. **As of Protocol Amendment 14, rechallenge is not permitted.** Subjects crossing over to combination therapy will start treatment at Cycle 1 Day 1 as described for subjects in Part C. Subjects who cross over will receive combination therapy in sequential infusion at the doses that have been declared safe in dose escalation and/or dose expansion parts at the time of crossover. The original protocol rules will apply accordingly. Subjects who crossed over and subsequently have an objective response in combination therapy will not be considered in the decision making for Part C proceeding to Stage 2. Subjects in Part C cannot cross over to Part A1.

Dose Escalation Sequential (Part B): Treatment in Part B will be initiated upon the decision to escalate to the third dose cohort in Part A in accordance with dose escalation rules. Subsequently, escalation in the 2 parts will proceed in parallel. Treatment assignments for subjects eligible for both Part A and Part B will alternate between the 2 parts, with consecutively treated subjects assigned to different parts through interactive voice response system, whenever possible. If there are no openings available in the part to which the subject would be assigned by this algorithm, then the subject will be assigned to the next open cohort or part.

In Part B, a 3 + 3 + 3 design or BLRM-Copula design, effective with site-specific amendment #15 (dated 13 August 2018), will also be used to assess the safety of BMS-986016 given in combination with nivolumab as a sequential infusion Q2W and Q4W. A fourth subject may be enrolled at the beginning of a dose escalation cohort following agreement between the Investigator and the Sponsor/Medical Monitor, if subject is able to start the first day of dosing within approximately 1 week of the third subject in the same dose escalation cohort. The potential dose levels evaluated during dose escalation are provided in Table 2. Intermediate and lower dose levels may be assessed following agreement between the Investigator and the Sponsor/Medical Monitor based upon ongoing review of safety data. As in Part A, each of the first 3 subjects (or 4, if applicable) in the first dose cohort in Part B will be designated as sentinel subjects and will begin treatment at least 5 days apart.

Table 2: Dose Escalation Schedule for Part B — BMS-986016 in Combination with Nivolumab Q2W and Q4W

Dose Cohort Number	Total Subjects	BMS-986016 Dose (IV; mg)	Nivolumab Dose (IV; mg)
	Dose Escalation Schedule for Part B — BMS-986016 in Combination with Nivolumab Q2W Dosing		
1	n = approximately 3-9	20	80
2	n = approximately 3-9	20	240
3	n = approximately 3-9	80	240
Intermediate	n = approximately 3-9	160	240
4	n = approximately 3-9	240	240
	Dose Escalation Schedule for Part B — BMS-986016 in Combination with Nivolumab Q4W Dosing		
1	n = approximately 3-9	160	480
2	n = approximately 3-9	240	480
3	n = approximately 3-9	320	480
4	n = approximately 3-12	480	480
5	n = approximately 3-15	960	480
6	n = approximately 3-15	1440	480
7	n = approximately 3-15	1600	480
Total	**N = approximately 36-120**		

In Part B, if the MTD is exceeded in Dose Cohort 2, the subsequent cohort will be treated with 80 mg of BMS-986016 and 80 mg of nivolumab. If this dose combination is found to be safe, and following consultation and agreement between Investigators and the Sponsor, escalation may proceed at the previously defined BMS-986016 doses, maintaining the nivolumab dose at 80 mg, or an intermediate dose level. Testing of the Q2W and Q4W dosing schedules can proceed concurrently with independent escalation decisions based upon review of the current total safety experience and following consultation and agreement between Investigators and the Sponsor.

Prior to declaring the MTD (or MAD), and in consultation with Investigators, the Sponsor has the option to expand any cohort previously established to be safe in order to obtain additional experience or to investigate dose levels intermediate to those defined in the protocol. Dose escalation rules (cohort size, observation for DLTs, etc.) will apply to these expanded or additional cohorts. A maximum of 9 subjects will be enrolled in any additional or expanded dose cohorts.

Cohort Expansion Sequential (Part C): The purpose of cohort expansion is to gather additional safety, tolerability, preliminary efficacy, PK, and pharmacodynamic information in subjects treated with sequential infusion of nivolumab first, followed by administration of BMS-986016.

The initial doses selected for specific Part C cohorts will not exceed the MTD or MAD in Part B but may incorporate consideration of other data, including (but not necessarily limited to) toxicities, PK, and pharmacodynamic data from Parts A and B and can be chosen while additional Part B dose escalation cohorts continue to be explored. Part C expansion cohort doses to be considered will include those doses shown to be safe in Part B (or intermediate to those doses) as recommended by the Investigators and the Sponsor. Dosing of subsequent patients within an expansion cohort, or between cohorts, can be increased (if deemed safe in Part B) or decreased (based upon ongoing reviews of the totality of the safety data), all to be decided in agreement between the Investigators and the Sponsor. There will be no dose adjustments for individual subjects.

In Part C, a multistage design will be used to assess treatment efficacy. Cohorts deemed futile at Stage 1 will be discontinued, whereas those deemed promising may be expanded up to 90 to 120 subjects in total after careful evaluation of all available data, including the totality of efficacy, safety profile, and PK/pharmacodynamics. Otherwise, additional subjects may be treated to collect more data during Stage 2 in order to make a decision for further expansion. Enrollment to Stage 2 or further expansion in a given cohort can continue even if the other cohorts are still in Stage 1. Subjects who crossed over to combination therapy in Part A1 and subsequently have an objective response will not be considered in the decision making for Part C. Subjects in Part C cannot cross over to Part A1 either.

All Cohort Expansion Parts (Parts A1, C, D, and E)

Continuous evaluation of toxicity events in the cohort expansions will be performed throughout enrollment in the expansion cohorts. If, at any time, the aggregate rate of treatment-related toxicities meeting DLT criteria exceeds 33% across all subjects treated in any of these cohort expansions, the findings will be discussed, and further enrollment must be interrupted in that particular cohort and other relevant cohorts. Depending on the nature and grade of the toxicity, and after assessing the benefit-risk ratio, a new dose(s) for all cohorts may be initiated at a previously tested lower dose level or at a dose level intermediate to previously tested lower dose levels.

Rechallenge in Dose Escalation (Parts A, B, and E) and Cohort Expansion (Parts A1, C, and D)

If, after discontinuing study treatment at the Investigator's discretion, subjects that have disease progression during the Clinical Follow-up period or the Survival Follow-up period, subjects could further receive therapy with BMS-986016 alone or in combination therapy (**Rechallenge**) as long as the benefit-risk ratio is considered favorable by the Investigator and the Medical Monitor and the following eligibility criteria are met: 1) subject has confirmed disease progression (Investigator-assessed RECIST 1.1-defined progression confirmed at least 4 weeks after the initial tumor assessment showing progression; 2) subject has not experienced BMS-986016–related AEs leading to permanent discontinuation. The rechallenge-eligible Survival Follow-up may continue for up to 5 years from the first dose of study drug. The original dose and schedule of therapy and protocol rules will apply. For the rechallenge, collection of archival tissue (baseline) and tumor

biopsies (baseline and on-therapy) will be optional for subjects crossing over, and PK and biomarker monitoring will be limited (Sections 5.5 and 5.7). **As of Protocol Amendment 14, rechallenge is not permitted.** All subjects who discontinue primary study treatment following implementation of Protocol Amendment 14 will not be eligible for rechallenge. Subjects currently receiving rechallenge treatment will be allowed to continue, and subjects currently in the rechallenge-eligible Survival Follow-up as of this protocol amendment remain eligible for rechallenge.

Subjects who are rechallenged and who subsequently have an objective response will not be included in the primary analysis of efficacy. Responses to rechallenge will be evaluated in a separate analysis. Subjects will not be rechallenged a second time.

Part D Melanoma Prior IO Extended Expansion Coadministration or Treatment with FDC (BMS-986213)

In Part D, advanced melanoma subjects with progression on prior anti-PD-1 therapy will be enrolled into 2 subparts, D1 and D2, based on eligibility criteria. If eligible for the focused (more restricted eligibility) D1 subpart, subjects will be randomized across 3 arms:

Arm 1: relatlimab 80 mg + nivolumab 240 mg given by coadministration Q2W

Arm 2: relatlimab 160 mg + nivolumab 480 mg given by coadministration Q4W

Arm 3: BMS-986213 (relatlimab 160 mg/nivolumab 480 mg) given Q4W; BMS-986213 contains both relatlimab and nivolumab in the same solution at a ratio of 1:3 (relatlimab:nivolumab)

Part E Exposure Response Evaluation (Coadministration)

Two cohorts of melanoma subjects will be enrolled in Part E: melanoma participants who experienced disease progression on prior anti-PD-1 therapy and melanoma participants who have not received prior systemic anticancer therapy for advanced, unresectable, or metastatic melanoma. Melanoma participants who experienced disease progression on prior anti-PD-1 therapy in the advanced, unresectable, or metastatic setting will only receive 480 mg BMS 986016 + 480 mg nivolumab Q4W. Melanoma participants who have not received prior systemic anticancer therapy for locally advanced, unresectable, or metastatic melanoma will be randomized to 1 of the following 2 treatment arms:

160 mg BMS-986016 + 480 mg nivolumab Q4W

480 mg BMS-986016 + 480 mg nivolumab Q4W

Randomization will be unblinded. Enrollment and randomization to Arm 1 may continue until the following criteria are met: (a) 90 efficacy-evaluable LAG-3-positive subjects have been treated, (b) 60 efficacy-evaluable LAG-3-positive and BRAF wild-type subjects have been treated, and (c) 60 efficacy-evaluable LAG-3-positive and ipilimumab-pretreated subjects have been treated. Enrollment and randomization across Arms 2 and 3 may continue until the following criteria are met: (a) 90 efficacy-evaluable LAG-3-positive subjects have been treated, (b) 60 efficacy-evaluable LAG-3-positive and BRAF wild-type subjects have been treated, and (c) 60 efficacy-evaluable LAG-3-positive and ipilimumab-pretreated subjects have been treated. Prior to Revised

Protocol 09, Part D1 subjects are being enrolled only into Arm 1. Subsequent to activation of this revised protocol, and until the enrollment to Arm 1 is completed, subjects in Part D1 will be randomized 1:1:1 across the 3 arms. Once enrollment to Arm 1 is completed, subjects will be randomized 1:1 to Arms 2 and 3. If enrollment to Arms 2 and 3 is completed prior to Arm 1, then enrollment to Arm 1 will be completed as a single arm. Prior to the start of randomization, a safety lead-in will be conducted with BMS-986213 (see Section 3.1.2.5). If subjects do not meet the more focused eligibility of Part D1, they may be eligible for Part D2, which is more flexible with respect to the allowed prior therapies and performance status. Part D2 will test safety and efficacy in this broader patient population and will employ the more convenient Q4W coadministration dosing. Initial dosing will be 160 mg BMS-986016 + 480 mg nivolumab. Once further safety is established at the BMS-986016 160 mg + nivolumab 480 mg dose, subsequently enrolled subjects will be treated with BMS-986016 240 mg + nivolumab 480 mg. The doses and schedule selected for Part D will not exceed the Part B MTD or MAD, and dosing of the cohorts may be altered in collaboration between the Investigators and Sponsor based upon the overall ongoing study data, including assessment of toxicities, PK, and pharmacodynamics. There will be no dose adjustments for individual subjects. Expansion cohorts in Part D will be restricted to advanced melanoma subjects (Section 3). Efficacy analyses are described in Section 8.4.2.

Dose-limiting Toxicities: BMS-986016 has the potential to augment the frequency and severity of previously described AEs associated with nivolumab or to produce new toxicities. For the purpose of guiding decisions regarding dose escalation in Parts A and B, DLTs will be determined based on the incidence, intensity, and duration of AEs that are related to study drug and that occur within 42 days (6 weeks) of initiation of study drug. The severity of AEs will be graded according to NCI CTCAE v4.0.

No intrasubject dose escalations are allowed. Subjects who withdraw from the study during the DLT evaluation interval for reasons other than a DLT may be replaced at the same dose level. In the case that an infusion cannot be administered at a scheduled visit during the DLT evaluation interval, it must be administered as soon as possible. Subjects may be dosed no more frequently than every 12 days in the Q2W regimen and no more frequently than every 25 days in the Q4W regimen and no more than 3 days from scheduled dose. If an infusion cannot be administered at a scheduled visit, it should be administered as soon as possible. Subsequent dosing visits will follow every 2 weeks or every 4 weeks after the delayed dose. A dose given more than 3 days after the intended dose date will be considered a delay. A maximum delay of 6 weeks between doses is allowed. Longer delays may be allowed following discussion with the Medical Monitor. For Q4W dosing cycles, subjects may be dosed within a ±3 day window. For the purpose of making decisions on dose escalation from a safety perspective, subjects will be considered evaluable if they have received 3 out of the 4 scheduled BMS-986016 doses in Part A (or 3 out of 4 schedules BMS-986016 and nivolumab doses in Part B Q2W dosing or 2 out of 2 scheduled BMS-986016 and nivolumab doses in Part B Q4W dosing) through the 6-week observation period, only if the 1 missed dose was secondary to progressive disease or nonmedical reasons. Unevaluable subjects may be replaced at the same dose level.

For the purpose of subject management, potential DLTs that occur at any time, whether during dose escalation (Parts A, B) or cohort expansion (Parts A1, C, D) will result in all study drug(s) being held pending evaluation of the event's relatedness to study drug, severity, duration, and in accordance with Section 4.3.2. Subjects must meet criteria for retreatment prior to reinitiation of study treatment (see Section 4.3.3). Any DLT that occurs after the initial 6-week DLT observation period, and after dosing in the next higher dose cohort has begun, will be accounted for and factored into the BLRM-Copula model in a post-hoc manner. Additionally, as a practical matter, it should be noted that the BLRM-Copula model, based on the absence of DLTs at a preceding dose level, may dictate that an entire dose level cohort be skipped.

Duration of Study: Subjects will be allowed to continue on therapy until PD, until clinical deterioration, or until meeting criteria for discontinuation as described in Section 3.5. Patients who discontinue treatment before 5 years will complete a 135-day clinical follow-up period, and a survival follow-up period for up to 5 years after the first dose. Patients who continue study treatment for longer than 5 years will complete a 135-day clinical follow-up period once the criteria for treatment discontinuation are met, but will not participate in a survival follow-up period. The study will end when all patients have completed their respective follow-up periods. The original dose, schedule, and protocol rules would apply.

If a subject has disease progression during the Clinical Follow-up period or the Survival Follow-up period, the subject could further receive therapy with BMS-986016 alone or in combination therapy (Rechallenge) as long as they meet eligibility criteria and the benefit-risk ratio is considered favorable by the Investigator and the Medical Monitor. The rechallenge-eligible Survival Follow-up may continue for up to 5 years from the first dose of study drug. The original dose and schedule and protocol rules would apply accordingly. Subjects will not be rechallenged a second time. **As of Protocol Amendment 14, rechallenge is not permitted.** All subjects who discontinue primary study treatment following implementation of Protocol Amendment 14 will not be eligible for rechallenge. Subjects currently receiving rechallenge treatment will be allowed to continue, and subjects currently in the rechallenge-eligible Survival Follow-up as of this protocol amendment remain eligible for rechallenge.

Number of Subjects: Approximately up to 1200 subjects may be dosed (up to approximately 100 subjects during dose escalation Parts A and B, approximately 300 subjects in Part C cohort expansions, and approximately 550 subjects in Part D and approximately 225 subjects in Part E).

Study Population: For Parts A, B, C, D, and E, males and females ≥ 18 years at the time of informed consent. Additionally, for Parts C (melanoma only), D, and E, males and females ≥ 12 years at the time of informed consent if local regulations and/or institutional policies allow for participants < 18 years of age (pediatric population). All subjects must have histologic or cytologic confirmation of advanced, nonresectable, or metastatic solid tumors and measureable disease who meet all eligibility criteria will be eligible to participate in the study. Unless otherwise stated in the inclusion/exclusion criteria for each study part, subjects must be naive to prior IO agents such as, but not limited to, anti-CTLA-4, anti-PD-1, or anti-PD-L1; anti-PD-L2, anti-KIR, anti-CD137, anti-LAG-3, and/or anti-OX40 antibodies.

Dose Escalation-Monotherapy (Part A): Subjects with any solid tumor type (with the exception of primary central nervous system [CNS] tumors or with CNS metastases as the only site of active disease) are eligible to enroll. Subjects must not have prior exposure to IOs.

Dose Expansion-Monotherapy (Part A1): Subjects with 1) NSCLC with prior anti-PD-1 or PD-L1 therapy allowed; 2) Subjects with renal cell carcinoma with prior anti-PD-1 or PD-L1 therapy allowed.

Dose Escalation-Sequential Infusion (Part B): Subjects with any solid tumor type (with the exception of primary CNS tumors or with CNS metastases as the only site of active disease) were eligible to enroll in the first 2 cohorts. Subjects naive to IOs, subjects with melanoma progressing while on or after anti-CTLA-4 and/or anti-PD-1/anti-PD-L1 antibody therapy, and subjects with NSCLC progressing while on anti-PD-1 or anti-PD-L1 antibody therapy as their most recent are allowed (full criteria described in Section 3.3.1) were also eligible in the first 2 cohorts.

For subsequent cohorts, eligible tumor types (and all subtypes) will include: 1) NSCLC naive to IOs; 2) NSCLC whose disease progresses while on therapy with anti-PD-1 (limited to nivolumab or pembrolizumab) or anti-PD-L1 antibody therapy; 3) melanoma first line; 4) melanoma progressing while on or after receiving anti-CTLA-4 and/or anti-PD-1 (limited to nivolumab or pembrolizumab)/anti-PD-L1 antibody therapies; 5) RCC naive to IOs; 6) other tumors naive to IO agents, including head and neck, gastric, hepatocellular, cervical, ovarian, bladder, and colorectal cancers. Participants must also weigh ≥ 40 kg. Subjects can have received anti-PD-1 (limited to nivolumab or pembrolizumab) or anti-PD-L1 antibody but cannot have had therapy discontinued due to serious and/or life-threatening anti PD-1 or anti-PD-L1 antibody related to toxicity.

Cohort Expansion - Sequential Infusion (Part C): Tumor types include: 1) melanoma first line; 2) RCC naive to IO; 3) squamous cell carcinoma head and neck (SCCHN) naive to IO; 4) NSCLC naive to IO; 5) NSCLC whose disease progressed while on or after therapy with anti-PD-1 or anti-PD-L1 antibody as most recent therapy; 6) gastric cancer naive to IO; 7) hepatocellular carcinoma (HCC) naive to IO; 8) melanoma previously progressed on anti-PD-1/anti-PD-L1 antibody alone or anti-PD-1/anti-PD-L1 antibody in combination with anti-CTLA-4 antibody therapy; and 9) bladder cancer naive to IO.

Part D Melanoma Prior IO Extended Expansion - Coadministration (BMS-986016 and Nivolumab): Tumor types include unresectable or metastatic advanced melanoma. Part D1, Focused Eligibility Criteria: 1) documented progression while on a prior anti-PD-1 (limited to nivolumab and pembrolizumab) containing regimen (monotherapy or combination therapy). Documentation of prior anti-PD-1 therapy should include start, stop, and progression dates of the prior anti-PD-1 therapy with unequivocal progression and a radiological progression date no more than 3 months after the last dose of anti-PD-1 therapy; 2) only 1 line of a prior anti-PD-1 (limited to nivolumab or pembrolizumab) containing regimen is allowed; 3) BRAF wild-type and mutant subjects are eligible; 4) if BRAF mutant, progression on a single line of a BRAF inhibitor, administered with or without a MEK inhibitor, is required; 5) Eastern Cooperative Oncology Group performance status (ECOG PS) 0-1. Part D2 Expanded Eligibility Cohort: 1) anti-PD-L1 therapy or combination-containing regimen can substitute for anti-PD-1 therapy (limited to

nivolumab or pembrolizumab); 2) BRAF wild-type and mutant subjects are eligible, but prior targeted BRAF therapy is not required; 3) ECOG PS 0-2. Please see Section 3.3 for full eligibility criteria.

Part E Exposure Response Evaluation in Melanoma Participants: Eligibility for melanoma participants who experienced disease progression on prior anti-PD-1 therapy: 1) documented progression while on a prior anti-PD-1 (limited to nivolumab and pembrolizumab) containing regimen (monotherapy or combination therapy). Documentation of prior anti-PD-1 therapy should include start, stop, and progression dates of the prior anti-PD-1 therapy **with unequivocal** progression, and a radiological progression date **no more than 3 months after the last dose of anti-PD-1 therapy**; 2) only 1 line of a prior anti-PD-1 (limited to nivolumab or pembrolizumab) containing regimen is allowed; 3) BRAF wild-type and mutant subjects are eligible; 4) if BRAF mutant, progression on a single line of a BRAF inhibitor, administered with or without a MEK inhibitor, is required; 5) ECOG PS 0-1.

Eligibility for melanoma participants who have not received prior systemic anticancer therapy for unresectable or metastatic melanoma: Participants must have an ECOG PS ≤ 1/Lansky Performance Score ≥ 80% for minors (ages 12-17) ONLY and 2) histologically confirmed Stage III (unresectable) or Stage IV melanoma, as per American Joint Committee on Cancer staging system.

As of Protocol Amendment 14, no contraception requirements for relatlimab and nivolumab are necessary for male participants.

Women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception for the duration of treatment with nivolumab and relatlimab, plus 5 half-lives of study treatment, for a total of 5 months post-treatment completion and agree not to donate eggs (ova, oocytes) for the purpose of reproduction for the same time period (refer to Appendix 1). Investigators shall counsel WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% per year when used consistently and correctly (see Appendix 1).

Please see Section 3.3 for full eligibility criteria and additional details regarding prior lines of treatments.

Study Assessments:

Safety Outcome Measures: Safety assessments will be based on medical review of AE reports and the results of vital sign measurements, electrocardiograms (ECGs), physical examinations, and clinical laboratory tests. AEs will be assessed continuously during the study and for 135 days after the last treatment. AEs will be coded using the most current version of MedDRA and reviewed for potential significance and importance. Both AEs and laboratory tests will be graded using the NCI CTCAE v4.0.

Efficacy Measures: Disease assessment using computed tomography (CT) and/or magnetic resonance imaging (MRI), as appropriate, will be performed at baseline and every 8 weeks regardless of dose delays during the treatment period after first dose of study medication. Tumor

responses will be determined by the Investigator for subjects with adequate data as defined by RECIST v1.1. For selected disease cohorts in Part C, tumor responses will also be determined by BICR using RECIST v1.1. **Diagnostic imaging must be performed every 12 weeks, until disease progression, in subjects who discontinue treatment at the Investigator's discretion with a confirmed CR, PR, or SD by RECIST v1.1.**

Pharmacokinetic Measures: Serial serum samples will be collected from all subjects at specified time points to evaluate concentrations of BMS-986016 and nivolumab. PK parameters such as Cmax, Ctrough, Tmax, AUC(TAU), CLT, and AI will be derived from serum concentration vs time data. Sparse serum samples will be collected from subjects in Parts B and C to evaluate concentrations of nivolumab. As per Protocol Amendment 14, PK sample collection upon the occurrence of a ≥ Grade 3 AE is not required.

Immunogenicity Measures: Serum samples to evaluate development of positive antidrug antibody (ADA) response to BMS-986016 and nivolumab will be collected at specified time points.

Biomarker Measures: The sample collection and biomarker assessment strategy is designed to address mechanisms of action, pharmacodynamic changes associated with BMS-986016, and the potential identification of predictive safety and efficacy biomarkers associated with BMS-986016, and to evaluate potential mechanisms of resistance to BMS-986016 and nivolumab. To address these key questions, peripheral blood, serum, and biopsy samples will be collected prior to and during study drug treatment during this study.

Statistical Considerations: Sample Size:

Dose Escalation (Parts A and B)

Sample size at each dose depends on observed toxicity and cannot be precisely determined. Part A will have 3 to 9 subjects in each cohort. Part B will have 3 to 15 subjects in each cohort.

In the Part B dose escalation using BLRM-Copula, the sample size at each dose depends on observed toxicity and posterior inference. Initially, approximately 3 subjects will be treated at the starting dose level (using the new BLRM-Copula design) of BMS-986016 in combination with nivolumab. Due to the potential for early discontinuation, an additional subject(s) may be enrolled to ensure approximately 3 evaluable subjects at each dose level.

Cohort tolerability assessment and subsequent dose recommendation will occur when 2 evaluable subjects within a set have completed the DLT evaluation period. If the potential DLT occurring in any third evaluable subject regarding the specific dose level does not influence the dose recommendation by BLRM-Copula, the BLRM-Copula recommended next dose level may proceed without waiting for the third subject to complete the corresponding DLT observation period, after discussion and agreement between Sponsor and Investigators. Continuous reassessment of dose recommendation by BLRM-Copula in the combination phase will be carried out at each dose level.

During dose escalation, BLRM could recommend escalating to the next dose or skipping an entire dose level altogether. In that case, a new cohort of approximately 3 subjects will be treated at the recommended new dose. BLRM could also recommend staying at the same dose level, in which case an additional increment of approximately 3 subjects will be treated at that dose. At least 6

DLT-evaluable subjects will be treated in the selected dose cohort(s) chosen for expansion. Up to 15 subjects may be treated at any dose level for further evaluation of safety and pharmacodynamic/PK parameters as required.

Cohort Expansion Monotherapy (Part A1)

A sample size of 6 subjects per cohort allows for estimation of the proportion of subjects with objective response (ie, best overall response [BOR] of CR + PR) within a cohort such that the maximum distance between the estimated rate and either limit of the exact 2-sided 95% Clopper-Pearson confidence interval (CI) is 47.5%.

A sample size of 12 subjects per cohort allows for estimation of the proportion of subjects with objective response (ie, BOR of CR + PR) within a cohort such that the maximum distance between the estimated rate and either limit of the exact 2-sided 95% Clopper-Pearson CI is 32.2%.

Cohort Expansion (Part C)

The objective of this expansion in combination with nivolumab is to support further clinical testing by demonstrating adequate safety and tolerability as well as favorable benefit-risk by assessing preliminary efficacy measured by ORR and other clinically relevant efficacy measures such as DOR and DCR. However, the sample size is strictly based on efficacy, specifically based on the target ORR relative to historic ORR.

Disease- and prior IO therapy-restricted cohorts will be investigated in the Part C cohort expansion: NSCLC progressing on IO therapy; melanoma progressing on anti-PD-1/anti-PD-L1; RCC naive to IO therapies; NSCLC naive to IO therapies; melanoma first line; SCCHN naive to IO therapies; gastric cancer naive to IO therapies; HCC naive to IO therapies; and bladder (urothelial) cancer naive to IO therapies. The NSCLC progressing on IO therapy cohort will be analyzed as a whole and as 2 separate subgroups, refractory and relapsed, as defined in Section 3.3.1. All disease cohorts will be handled independently, and there will be no multiplicity adjustment.

A multistage design will be used as a guide for each expansion cohort in order to decide whether the treatment of BMS-986016 in combination with nivolumab warrants more extensive development. At first, a 2-stage design with a reasonable false positive rate (eg, < 10%) and false negative rate (eg, < 10%) will be used for the decision making based on assumptions of true (target) and historic/standard-of-care response rate for each cohort. The assumed historic and target response rates may change over time and may need to be adjusted by the time of response data from this study are available. Using a 2-stage design provides an option to stop early for futility as well as a signal of preliminary antitumor activity for strong-go early on. Enrollment may continue into Stage 2 while the planned number of subjects for Stage 1 is followed for efficacy-evaluable tumor assessments. There will be no stopping of a disease cohort for efficacy, although early plan for the next stage of clinical development may be initiated.

The ORRs considered to be of clinical value for further expansion of selected populations, sample size, and operational characteristics of using a 2-stage design, as an example, are provided in Table 3, although this is not for statistical hypothesis testing.

Once there is preliminary evidence of the treatment effect that may represent substantial improvement over available therapies, sufficient additional subjects will be treated to demonstrate a substantial and clinically meaningful effect in ORR that is supported by duration of the effect. The total sample size at this stage will be determined based on the ability to produce a CI, which would exclude an ORR of the historic response, and to provide sufficient information for a reliable understanding of the safety profile. With 90 to 120 subjects in total, this design yields a less than 5% of 2-sided Type I error rate and at least 80% power depending on tumor type with specified historic/standard of care and target rates. Table 4 summarizes the 95% exact CI for various observed ORRs with sample sizes of 90, 100, and 120.

Table 3: Example of a 2-stage Design Characteristics

Cohort	Historic/ Target Rate (%)	Stage	Cum Sample Size	Conclude Futility if Ra	Conclude Efficacy if R	PETb for Futility (%)	PEEc for Efficacy (%)
Gastric IO naive HCC IO naive Melanoma progressed on anti-PD-1/PD-L1	10/30	1 2	15 26	≤ 1 ≤ 5	≥ 4 ≥ 6	55	70
RCC IO naive	25/50	1 2	11 26	≤ 2 ≤ 9	≥ 6 ≥ 10	46	50
NSCLC IO refractory NSCLC IO relapsed	5/20	1 2	12 37	0 ≤ 3	≥ 3 ≥ 4	54	44
NSCLC 1/2L, IO naive	20/45	1 2	14 25	≤ 3 ≤ 7	≥ 7 ≥ 8	70	45
Melanoma 1L	40/65	1 2	13 28	≤ 5 ≤ 14	≥ 10 ≥ 15	57	28
SCCHN IO naive Bladder IO naive	20/40	1 2	20 36	≤ 4 ≤ 10	≥ 8 ≥ 11	63	58

[a] R is the cumulative number of responses at the end of stage.

[b] PET: probability of early termination.

[c] PEE: probability of early expansion.

Table 4: Observed ORR with Exact 95% CI

Sample Size	Number of Responses	ORR	95% Exact CI
90	18	20%	[12.3%, 29.8%]
	27	30%	[20.8%, 40.6%]
	32	36%	[25.7%, 46.4%]
	37	41%	[30.8%, 52.0%]
	46	51%	[40.4%, 61.8%]
100	20	20%	[12.7%, 29.2%]
	30	30%	[21.2%, 40.0%]
	35	35%	[25.7%, 45.2%]
	40	40%	[30.3%, 50.3%]
	50	50%	[39.8%, 60.2%]
120	24	20%	[13.3%, 28.3%]
	36	30%	[22.0%, 39.0%]
	42	35%	[26.5%, 44.2%]
	48	40%	[31.2%, 49.3%]
	60	50%	[40.7%, 59.3%]

Melanoma Prior IO Extended Expansion (Part D)

The objective of this expansion in melanoma subjects whose disease is progressing while receiving anti-PD-1 (anti-PD-L1 allowed in Part D2) antibody therapies is to assess safety and tolerability of more convenient dosing regimen (ie, coadministration and Q4W dosing interval) and demonstrate preliminary clinical evidence of the treatment effect measured by ORR, as determined by BICR, that may represent substantial improvement over available therapies in subjects with LAG-3 expression (Part D1).

Melanoma Prior IO Extended Expansion (Part D1-Q2W)

Data from Part C melanoma subjects who progressed while receiving anti-PD-1 antibody therapies demonstrated preliminary evidence that subjects with LAG-3 expression are more likely to respond to treatment of BMS-986016 in combination with nivolumab. The biomarker prevalence using the initial 1% cut (ie, LAG-3 expression ≥ 1%) is estimated to be approximately 60% in this patient population.

In order to establish safety and tolerability of a more convenient dosing regimen and further characterize an enriched responder population, approximately a total of 150 subjects who meet the eligibility criteria for Part D1 will be treated with BMS-986016 80 mg + nivolumab 240 mg Q2W coadministered. A sample size of 150 is expected to provide approximately 90 subjects with LAG-3 expression using the initial cutoff of 1% and provide reasonable precision to examine the enrichment of patient population with LAG-3 expression.

Since the optimal LAG-3 biomarker cutpoint is not well known prior to the study, several different cutoffs may be explored, and, depending on the prevalence of the LAG-3 biomarker-positive using

these cutoffs, the initial total sample size may be modified in order to have an adequate precision for demonstrating preliminary clinical evidence of the treatment effect in the LAG-3 biomarker-positive population (ie, approximately 90 subjects). Although evaluation of the cutpoint will be based on the ORR, the decision of the cutpoint will be based on the totality of the efficacy data, including DOR and DCR.

Additionally, in an effort of exploring enriched patient population in advanced melanoma subjects who progressed while on anti-PD-1 antibody therapies in Part D1, other potential predictive biomarkers such as BRAF mutation status may be explored. Approximately 60 subjects among the 90 subjects with LAG-3 expression in Part D1 are expected to be BRAF wild-type.

For the purpose of demonstrating preliminary clinical evidence of the treatment effect, the primary efficacy population will be subjects with LAG-3 expression who progressed while on anti-PD-1 antibody therapies and receive BMS-986016 80 mg + nivolumab 240 mg Q2W in Part D1. A portion of subjects in Part C who meet the eligibility criteria of Part D1 will be included in a sensitivity analysis to further strengthen the evidence.

The sample size of 90 subjects with LAG-3 expression was determined based on the ability to produce a CI, which would exclude an ORR of the historic response, and to provide sufficient information for a reliable understanding of the safety profile.

There is no standard of care for advanced melanoma patients that have progressed during prior anti-PD-1 therapy; thus, the demonstration of effective and tolerable therapy in these patients remains a large unmet need. The only published or reported studies in this clinical setting employ anti-CTLA-4 therapy, namely ipilimumab, and they are small retrospective or exploratory ad hoc analyses. The patient population characteristics and results of ipilimumab monotherapy in these studies are listed in Table 5 below. There have been no prospective studies defining the benefit of anti-CTLA-4 therapy after disease progression during anti-PD1 therapy.

Table 5: Ipilimumab After Prior Anti-PD-1 Therapy

Study Population	ORR/CI/DOR	Toxicity	Source
Retrospective: Sequential treatment of anti-PD-1 (all progressed on clinical trials), then ipilimumab. 10% BRAF mutant. 42% with PD as BOR to prior anti-PD-1. 10% prior ipilimumab (response not reported).	10% (4/40 PRs) No CI reported DOR not reported	55% received all 4 doses of ipilimumab 35% had Grade 3-5 immune-related (ir)AE; 1 drug-related death due to pneumonitis	Bowyer et al 10.1038/bjc.2016.107
Retrospective: Documented progression on prior anti-PD1 as per RECIST v1.1 (details not provided). 15% BRAF mutant. 51% with PD as BOR to prior anti-PD1. 26% prior ipilimumab (response not reported).	16% (7/43 PRs) No CI reported DOR not reported Median DoDC 7 months 95% CI (2.8-22.8) months	53% received all 4 doses of ipilimumab (33% did not due to toxicity) Rates of irAEs were not reported	Zimmer et al 10.1016/j.ejca.2017.01.009
Exploratory post-hoc analysis of patients who received ipilimumab	13% (3 CRs and 10 PRs out of 97 patients)	Not reported	Long et al

Table 5: Ipilimumab After Prior Anti-PD-1 Therapy

Study Population	ORR/CI/DOR	Toxicity	Source
sequentially after pembrolizumab (91% with documented progression). Data from subsequent therapies case report forms. 16% BRAF mutant. 62% with PD as BOR to prior anti-PD1.	No CI reported DOR not reported		KEYNOTE-006 presentation at Society for Melanoma Research November 6-9, 2016
All treated subjects - nivolumab crossover to ipilimumab (the subjects randomized to nivolumab who received ipilimumab as subsequent therapy). 56% with PD as BOR to prior anti-PD-1.	10% (7/68 PRs) 95% CI (4.2%, 20.1%) DOR not reported	Not reported	CA209066 study Unpublished analysis

Combined analyses employing a standard response evaluable population definition across the multiple small studies of ipilimumab monotherapy in the setting of prior anti-PD1 therapy reveals an approximate 12% ORR. Durability of these responses is poorly documented.

In heavily pretreated patients, where clinical benefit is observed in only a subset of the population, safety is a significant concern. The reported rates of Grade 3 (or greater) TRAEs of approximately 35% from single-agent ipilimumab after anti-PD-1 therapy limits the overall utility of this approach.[59]

The majority of our patient population (approximately 60%) has also been previously treated with anti-CTLA-4 therapy. There are no reported effective therapies in this setting. In addition, antitumor responses with continued anti-PD1 therapy after initial progression on anti-PD1 therapy is relatively rare, with estimates of incidence of approximately 5%.[60] Thus, given a study population in which all subjects have progressed during prior anti-PD1 therapy, and the majority have received prior anti-CTLA-4 therapy as well, it is reasonable to target an ORR that excludes 10% as a lower bound within a 95% CI.

Table 6: Observed ORR with Exact 95% CI for Cohort D

Sample Size	Number of Responses	ORR	95% Exact CI
60	12	20%	[10.8%, 32.3%]
	15	25%	[14.7%, 37.9%]
	18	30%	[18.9%, 43.2%]
90	16	18%	[10.5%, 27.3%]
	18	20%	[12.3%, 29.8%]
	20	22%	[14.1%, 32.2%]
120	20	17%	[10.5%, 24.6%]
	24	20%	[13.3%, 28.3%]
	27	23%	[15.4%, 31.0%]

Table 6: Observed ORR with Exact 95% CI for Cohort D

Sample Size	Number of Responses	ORR	95% Exact CI
150	24	16%	[10.5%, 22.9%]
	27	18%	[12.2%, 25.1%]
	30	20%	[13.9%, 27.3%]
220	26	12%	[7.9%, 16.8%]
	29	13%	[9.0%, 18.4%]
	32	15%	[10.2%, 19.9%]

Melanoma Prior IO Focused Eligibility Expansion (Part D1-Q4W)

The coprimary objective in Part D1-Q4W is to evaluate the difference in safety between coadministration relative to FDC as measured by the incidence of AEs in the Broad Scope MedDRA Anaphylactic Reaction SMQ occurring within 2 days after dosing during the combination and to confirm with Q4W dosing of BMS-986016 160 mg in combination with nivolumab 480 mg the safety of the BMS-986016 80 mg in combination with nivolumab 240 mg Q2W in advanced melanoma subjects who progressed while on anti-PD-1 antibody therapies (see Appendix 5).

Prior to Revised Protocol 09, subjects are being enrolled into a single arm: Part D1 BMS-986016 80 mg + nivolumab 240 mg Q2W. Subsequent to this amendment, and until the enrollment to Part D1 BMS-986016 80 mg + nivolumab 240 mg Q2W is completed, subjects in Part D1 will be randomized 1:1:1 to Part D1 BMS-986016 80 mg + nivolumab 240 mg Q2W, Part D1 BMS-986016 160 mg + nivolumab 480 mg Q4W coadministration, or Part D1 BMS-986213 (relatlimab 160 mg/nivolumab 480 mg) Q4W. Once the enrollment to Part D1 BMS-986016 80 mg + nivolumab 240 mg Q2W is completed, subjects will be randomized 1:1 to Part D1 BMS-986016 160 mg + nivolumab 480 mg Q4W coadministration or Part D1 BMS-986213 (relatlimab 160 mg/nivolumab 480 mg) Q4W arms. If enrollment to Q4W arms is completed prior to arm BMS-986016 80 mg + nivolumab 240 mg Q2W arm, then enrollment to arm BMS-986016 80 mg + nivolumab 240 mg Q2W will be completed as a single arm.

Approximately 150 subjects will be randomized to the 2 treatment arms: Part D1 BMS-986016 160 mg + nivolumab 480 mg Q4W coadministration and Part D1 BMS-986213 (relatlimab 160 mg/nivolumab 480 mg) Q4W. This number of treated subjects was chosen to achieve a sufficient level of precision for a descriptive analysis to estimate the difference in rates of AEs in the Broad Scope MedDRA Anaphylactic Reaction SMQ between the 2 treatment arms. Seventy-five treated subjects per arm will allow estimation of the rate difference within 95% confidence limits of ± 15% or less and will be supplemented by a qualitative clinical assessment of the type and severity of events to evaluate benefit-risk.

From the Q2W expansion cohorts in Part C of the current study, AEs in the MedDRA Anaphylactic Reaction SMQ (Broad Scope) with onset within 2 days after sequential dosing of nivolumab 240 mg combined with BMS-986016 80 mg were reported in 14% of treated subjects. In Part D1, if

the observed rate of these events is equal to 14% among 75 treated subjects in each arm, and then the 95% CI for the difference in rates between arms will be (-11.1%, 11.1%).

Table 7 shows the precision that the sample size of 75 treated subjects per arm in Part D1-Q4W and 150 treated subjects each in Part D1-Q2W and Part D1-Q4W dosing will provide for estimating rates and rate differences between the treatment arms under different assumed observed rates. Enrollment and randomization across treatment arms Part D1 BMS-986016 160 mg + nivolumab 480 mg Q4W coadministration and Part D1 BMS-986213 (relatlimab 160 mg/nivolumab 480 mg) Q4W may continue until the following criteria are met: (a) 90 efficacy-evaluable LAG-3-positive subjects have been treated, (b) 60 efficacy-evaluable LAG-3-positive and BRAF wild-type subjects have been treated, and (c) 60 efficacy-evaluable LAG-3-positive and ipilimumab-pretreated subjects have been treated.

Table 7: 95% CI for Rate Differences When Observed in 75 Subjects per Arm and 150 Subjects per Dosing Regimen

75 Subjects per Arm		
Coadministration Arm	**Fixed Dose Combination Arm**	**Rate Difference (95% CI)**
14%	14%	0% (-11.1%, 11.1%)
14%	12%	2% (-8.8%, 12.8%)
16%	14%	2% (-9.4%, 13.4%)
18%	16%	2% (-10%, 14%)
20%	18%	2% (-10.6%, 14.6%)
150 Subjects Each in Part D1-Q4W and Part D1-Q2W		
Q2W	**Q4W**	**Rate Difference (95% CI)**
14%	14%	0% (-7.9%, 7.9%)
14%	12%	2% (-5.6%, 9.6%)
16%	14%	2% (-6.1%, 10.1%)
18%	16%	2% (-6.5%, 10.5%)
20%	18%	2% (-6.9%, 10.9%)

Also, with 75 subjects per arm, there is a 99% probability that the 95% CI for the geometric mean ratio of Cmax of FDC to coadministration is wholly contained within [0.8, 1.25]. log(Cmax) is assumed to follow a normal distribution and, with intrasubject coefficients of variation, is assumed to be no greater than 30%.

Melanoma Prior IO Expanded Eligibility (Part D2)

Part D2 will have expanded eligibility criteria with 2 cohorts in sequence: 160 mg BMS-986016 with 480 mg of nivolumab Q4W and 240 mg BMS-986016 with 480 mg of nivolumab Q4W. Subjects in Part D2 on average will have a worse performance status and be more heavily pretreated. Approximately 30 subjects will be initially treated with 160 mg BMS-986016 with 480

mg of nivolumab Q4W. Once this dose level is deemed safe, approximately up to 220 additional subjects will be treated with either 160 mg BMS-986016 with 480 mg or 240 mg BMS-986016 with 480 mg of nivolumab Q4W to establish safety and efficacy in this broader group of melanoma patients. With 30 subjects, there is approximately 96% chance to observe at least 1 occurrence of any AE that would occur with a 10% incidence in the population from which the sample is drawn. With 250 subjects, there is approximately 92% chance to observe at least 1 occurrence of any AE that would occur with a 1% incidence in the population from which the sample is drawn. Safety and efficacy data will be collected as in the other cohorts, and the data will be used as supportive evidence of safety and efficacy of the combination therapy.

Exposure/Response Expansion Q4W Dosing (Part E)

In Part E, 2 disease cohorts will be investigated: melanoma participants who experienced disease progression on prior anti-PD-1 therapy and melanoma participants who have not received prior systemic anticancer therapy for advanced, unresectable, or metastatic melanoma. The objective of this expansion is to support further clinical testing at higher dose of relatlimab in combination with nivolumab by demonstrating adequate safety and tolerability as well as favorable benefit-risk by assessing preliminary efficacy measured by ORR and other clinically relevant efficacy measures, such as DOR and DCR. However, the sample size is based on efficacy, specifically based on the target ORR relative to the ORR observed at the lower dose of relatlimab in combination with nivolumab. Both disease cohorts will be handled independently, and there will be no multiplicity adjustment. The sample size of the melanoma participants who experienced disease progression on prior anti-PD-1 therapy cohort is based on the comparison of the ORR of subjects who receive 480 mg BMS 986016 + 480 mg nivolumab Q4W vs the benchmark observed ORR of subjects who received 80 mg BMS 986016 + 240 mg nivolumab Q2W from the historical control in this study. A sample size of 75 melanoma participants who experienced disease progression on prior anti-PD-1 therapy will provide approximately 85% power for testing the ORR difference with a 2-sided alpha of 0.1, assuming ORR of 25% and 10% in the 480 mg BMS 986016 + 480 mg nivolumab Q4W arm and in the historical control arm, respectively.

The sample size of the melanoma participants who have not received prior systemic anticancer therapy for unresectable or metastatic melanoma cohort is based on the comparison of the ORR of subjects who receive 480 mg BMS 986016 + 480 mg nivolumab Q4W vs the ORR of subjects who receive 160 mg BMS 986016 + 480 mg nivolumab Q4W. A sample size of 150 melanoma subjects who have not received prior systemic anticancer therapy for advanced, unresectable, or metastatic melanoma, randomized in a 1:1 ratio in 2 arms, will provide approximately 81% power for testing the ORR difference with a 2-sided alpha of 0.1, assuming ORR of 67% and 47% in the 480 mg BMS 986016 + 480 mg nivolumab Q4W arm and in the 160 mg BMS 986016 + 480 mg nivolumab Q4W arm, respectively.

Endpoints:

Primary Endpoint:

The primary endpoint of this Phase 1/2a study is safety as measured by the rate of AEs, serious AEs (SAEs), and AEs leading to discontinuation of treatment, deaths, and laboratory

abnormalities, assessed during treatment and for up to for 135 days after the last treatment. All subjects who receive at least 1 dose of BMS-986016 or nivolumab will be analyzed for safety.

In Part C, the coprimary endpoints are ORR, DCR, and DOR by BICR using RECIST v1.1, where applicable, in selected disease cohorts.

In Part D1-Q2W, the coprimary endpoint is efficacy measured by ORR, as determined by BICR using RECIST v1.1, in advanced melanoma subjects with LAG-3 expression who progressed while on anti-PD-1 antibody therapies.

The primary endpoint in Part D1-Q4W of the study is the incidence of AEs in the Broad Scope MedDRA Anaphylactic Reaction SMQ occurring within 2 days after dosing. This incidence rate is defined as number of subjects who experienced at least 1 AE in the MedDRA Anaphylactic Reaction broad scope SMQ with onset on the day of or within 2 days after any study therapy infusion divided by number of treated subjects. The terms included in the MedDRA Anaphylactic Reaction SMQ based on the most current MedDRA version will be listed in the statistical analysis plan.

Secondary Endpoints:

Efficacy: The BOR, ORR, DCR, DOR, and PFS rates at prespecified time points by BICR when not designated as the primary in Parts C and D, and by the Investigator assessments using RECIST v1.1 are secondary endpoints. Additionally, the 1-year and 2-year landmark OS in Part D and DOR in Part E are secondary endpoints.

Pharmacokinetics: Select BMS-986016 PK parameters, such as Cmax, Ctrough, Tmax, AUC (TAU), CLT, and AI, will be assessed from concentration-time data during Cycle 1 and Cycle 3.

Immunogenicity: Incidence of ADA to either BMS-986016 or nivolumab will be assessed during treatment and for up to 135 days after their last treatment in post-treatment follow-up or for a maximum of up to 24 months of treatment, whichever comes first.

ECG: In Parts A and B, QTc will be assessed by a central reader for ECG collected at follow-up Visit 1, as well as on Day 1 of Cycle 1 and Cycle 3 at the predose and 4-hour postdose time points.

In Part D1-Q4W, PK of nivolumab and BMS-986016 coadministered will be assessed and compared to that of FDC of relatlimab and nivolumab. PK will be measured using serum concentration-time data. PK of nivolumab and BMS-986016 in Part D1-Q4W and Part D1-Q2W will also be assessed.

Exploratory Endpoints:

Biomarkers: [redacted] Biomarker endpoints from tumor biopsies may include, but will not be limited to, [redacted] expression of LAG-3, [redacted] and PD-L1. [redacted]

Pharmacokinetics: PK parameters will include nivolumab concentration-time data at select trough (Ctrough) and end-of-infusion (EOI) time points based on measurements collected for up to 135 days during the post-treatment follow-up or for a maximum of up to 24 months of treatment, whichever comes first.

Efficacy: The BOR, ORR, DCR, DOR, and PFS rates at prespecified time points will be explored by iRECIST assessments based on BICR. Landmark 1-year and 2-year OS rates will be assessed as exploratory efficacy endpoints in the study (except for Part D).

Analyses:

Unless otherwise specified, data from Part A (monotherapy dose escalation) and Part A1 (monotherapy dose expansion) will be presented separately from data collected in Parts B, C, and D (combination therapy). Safety data from the dose escalation phase will be summarized by dose and across all doses. Safety data from the dose expansion phase will be summarized for each disease cohort and overall by dose and across doses. Efficacy data from the dose expansion phase will be summarized for each disease cohort by dose and across doses. Efficacy data from the dose escalation phase will be summarized by dose and listed by tumor type.

Safety: All subjects who receive study drug therapy will be included in the analysis of safety endpoints. All recorded AEs will be coded according to the most current version of MedDRA and be graded using NCI CTCAE v4.0. AEs will be listed, and subjects with AEs will be summarized based on the event with worst CTCAE grade by system organ class (SOC) and preferred term (PT), counting once at the PT term level and once at the SOC level, for each dose, dosing regimen, and overall. The incidence of AEs in the Broad and Narrow Scope MedDRA Anaphylactic Reaction SMQ and select AEs in hypersensitivity/infusion reaction category occurring within 2 days after dosing by treatment arm, the difference in rates between arms, and the corresponding 95% CIs will be reported descriptively. The CIs for the rate estimates will be based on the Clopper-Pearson method. Vital signs and clinical laboratory test results will be listed and summarized by treatment. Any significant physical examination findings and results of clinical laboratory tests will be listed. Any ECG abnormalities identified by the Investigator will be listed. In Parts A and B, ECG will be assessed by a central reader at specific time points. All ECG data analyses, including summaries of each ECG parameters, frequency distributions of subjects' maximum values/changes, and scatter plots, will be performed following the current practice of ECG data analysis. Concentration-response analysis may be performed using mixed effect model, if appropriate. The details of ECG data analysis will be provided in the statistical analysis plan.

Efficacy Analyses: Individual BOR, DOR, and PFS will be determined based on RECIST v1.1 criteria for the primary and secondary analyses. iRECIST will be used as an exploratory analysis in Parts C and D and for exploratory analyses in other parts of the study. BOR outcomes will be summarized using frequency tables together with 2-sided 95% CIs. Time-to-event distribution (eg, PFS and DOR) will be estimated using Kaplan-Meier method. When appropriate, the median along with 95% CI will be provided using Brookmeyer and Crowley methodology (using log-log transformation for constructing the CIs). Rates at fixed time points (eg, PFS rate at 24 weeks and OS at 1 and 2 years) will be derived from the Kaplan-Meier estimate, and corresponding CI will

be derived based on Greenwood formula. Confidence intervals for binomial proportions will be derived using the Clopper-Pearson method.

For the purpose of demonstrating preliminary clinical evidence of the treatment effect in advanced melanoma subjects who progressed while on receiving anti-PD-1 antibody therapies, the primary efficacy population will be subjects with LAG-3 expression who progressed while on anti-PD-1 antibody therapies in Part D1 and receive BMS-986016 80 mg + nivolumab 240 mg Q2W. A portion of subjects in Part C who meet the eligibility criteria of Part D1 will be included in the sensitivity analysis to further strengthen the evidence. Efficacy analysis will also be performed for subjects with a lack of LAG-3 expression and also for all treated subjects regardless of LAG-3 expression to support the treatment effect of the combination therapy.

Initial cutpoint for the purpose of exploring an enriched population is LAG-3 expression ≥ 1%. However, as the optimal biomarker cutpoint is not well known prior to the study, several different cutoffs may be explored other than the initial cutpoint of 1% by examining receiver operating characteristics curves using the ORR, although the decision of the cutpoint will be based on the totality of the efficacy data, including DOR and DCR. Details of methodology will be described in the statistical analysis plan prior to any data exploration in Part D.

In an effort to explore an enriched patient population in advanced melanoma subjects who progressed while on anti-PD-1 antibody therapies in Part D1, other potential predictive biomarkers such as BRAF mutation status may be explored.

Subsequently, efficacy analysis for Part D1-Q4W will be done similarly to that for Part D1-Q2W. If the outcome of BOR in the Part D1-Q4W is deemed similar to that of the Part D1-Q2W, data from both Part D1-Q2W and Part D1-Q4W may be combined to strengthen the evidence.

Efficacy analysis for Part D2 will be done similarly to that for Part D1.

Pharmacokinetics: PK parameters for BMS-986016 will be calculated using noncompartmental analyses. Summary statistics will be tabulated for the PK parameters of BMS-986016 by treatment and study day/cycle. To describe the association of these parameters with dose of BMS-986016, scatter plots of Cmax and AUC(TAU) vs dose may be provided for each day measured. Dose proportionality of BMS-986016 when administered alone or coadministered with nivolumab may also be assessed based on a power model. Nivolumab end-of-infusion and trough (Ctrough) concentrations will be tabulated by treatment using summary statistics.

Nivolumab concentration-time data at scheduled trough (Ctrough) and end-of-infusion time points will be evaluated as an exploratory endpoint. Measurements will be collected on-treatment (up to 12 cycles) and for up to 135 days during the post-treatment follow-up or for a maximum of up to 24 months of treatment, whichever comes first. Model-predicted milestone survival at 1 year and 2 years using all available longitudinal tumor response data based on historical IO treatment-based tumor growth dynamic-survival relationship similarly to PFS data analysis. In Part D1-Q4W, PK comparisons will be summarized using descriptive summary statistics, and the point estimate and CI of geometric mean ratios of Cmax and AUC(TAU) will be presented to compare nivolumab and BMS-986016 administered as FDC to that of coadministered nivolumab and BMS-986016.

PK parameters will also be summarized using descriptive summary statistics for nivolumab and BMS-986016 administered in Part D1-Q2W and Part D1-Q4W dosing.

Immunogenicity Analyses: A listing will be provided for all available immunogenicity data. A baseline ADA-positive subject is defined as a subject with positive seroconversion detected in the last sample before initiation of treatment. An ADA-positive subject is a subject with at least 1 ADA-positive sample relative to baseline after initiation of the treatment. For each drug, frequency distribution of baseline ADA-positive subjects and ADA-positive subjects after initiation of the treatment will be summarized. To examine the potential relationship between immunogenicity and safety, a table summarizing the frequency and type of AEs of special interest may be explored by immunogenicity status. In addition, potential relationships between immunogenicity and efficacy and/or PK may also be explored.

Biomarker Analyses: The pharmacodynamic effect in subjects who undergo biopsy will be assessed using summary statistics and plots. [redacted]

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1 INTRODUCTION AND STUDY RATIONALE

Patients with metastatic or refractory solid tumors have very poor prognosis.[1] Despite advances in multimodal therapy, increases in overall survival (OS) in this patient population have been limited. To address this unmet medical need, compounds that have novel mechanisms of action will be evaluated in clinical studies with the goal of achieving better response rates and improved OS.

The use of immunotherapy in the treatment of cancer is based on the premise that tumors evade the endogenous immune response by being recognized as self, and not non-self. Tumors develop immune resistance using different mechanisms; the goal of immunotherapy is to counteract these resistance mechanisms, allowing the endogenous immune system to reject tumors. The recent success of immune-modulating agents in patients with refractory solid tumors has provided proof-of-concept of the efficacy of immune system activation as a therapeutic modality. Specifically, patients with metastatic melanoma had an increase in OS when treated with the anti-cytotoxic T lymphocyte–associated antigen 4 (CTLA-4) antibody, ipilimumab.[2] Moreover, the same patient population treated with the combination of ipilimumab and an anti–programmed cell death protein 1 (PD-1) antibody (nivolumab) achieved an unprecedented 53% response rate and prolonged responses.[3] These data suggest that combination therapy with immune-modulating agents may achieve more robust and prolonged responses than single-agent therapy in select cancer types and deserves to be further explored.

1.1 Study Rationale

1.1.1 Rationale for Nivolumab Therapy

Programmed cell death 1 is a cell surface signaling receptor that plays a critical role in the regulation of T cell activation and tolerance.[4] It is a type I transmembrane protein and, together with B and T lymphocyte attenuator (BTLA), CTLA-4, inducible T cell costimulator (ICOS), and CD28, makes up the CD28 family of T cell costimulatory receptors. PD-1 is primarily expressed on activated T cells, B cells, and myeloid cells.[5] It is also expressed on natural killer (NK) cells.[6] Binding of PD-1 by its ligands PD-L1 and PD-L2 results in phosphorylation of the tyrosine residue in the proximal intracellular immune receptor tyrosine inhibitory domain, followed by recruitment of the phosphatase SHP-2, eventually resulting in downregulation of T cell activation. One important role of PD-1 is to limit the activity of T cells in peripheral tissues at the time of an inflammatory response to infection, thus limiting the development of autoimmunity.[7] Evidence of this negative regulatory role comes from the finding that PD-1–deficient mice develop lupus-like autoimmune diseases, including arthritis and nephritis, along with cardiomyopathy.[8,9] In the tumor setting, the consequence is the development of immune resistance within the tumor microenvironment.

PD-1 is highly expressed on tumor-infiltrating lymphocytes (TILs), and its ligands are upregulated on the cell surface of many different tumors.[10] Multiple murine cancer models have demonstrated that binding of ligand to PD-1 results in immune evasion. In addition, blockade of this interaction

results in antitumor activity. These findings provided the rationale for testing PD-1 pathway blockade in clinical trials.

Nivolumab is a fully human monoclonal antibody (mAb) that binds to PD-1 with nanomolar affinity and a high degree of specificity, thus precluding binding of PD-1 to its ligands PD-L1 and PD-L2.[11] Nivolumab does not bind other related family members, such as BTLA, CTLA-4, ICOS, or CD28. Results from clinical trials have demonstrated complete response (CR), partial response (PR), and mixed response in patients with advanced solid tumors treated with nivolumab monotherapy, including all tumor types chosen for expansion in this study: non-small cell lung cancer (NSCLC), melanoma, renal cell carcinoma (RCC), hepatocellular carcinoma (HCC), squamous cell carcinoma of the head and neck (SCCHN), gastric cancer, and bladder cancer (Section 1.4.2.4).

1.1.2 LAG-3 and T Cell Exhaustion

Lymphocyte activation gene 3 (LAG-3; CD223) is also a type I transmembrane protein that is expressed on the cell surface of activated $CD4^+$ and $CD8^+$ T cells and subsets of NK and dendritic cells.[12,13] LAG-3 is closely related to CD4, which is a co-receptor for T helper cell activation. Both molecules have 4 extracellular Ig-like domains and require binding to their ligand, [redacted], for their functional activity. In contrast to CD4, LAG-3 is only expressed on the cell surface of activated T cells, and its cleavage from the cell surface terminates LAG-3 signaling. LAG-3 can also be found as a soluble protein, but it does not bind to [redacted], and its function is unknown.

It has been reported that LAG-3 plays an important role in promoting regulatory T cell (Treg) activity and in negatively regulating T cell activation and proliferation.[14] Both natural and induced Treg express increased LAG-3, which is required for their maximal suppressive function.[15,16] Furthermore, ectopic expression of LAG-3 on $CD4^+$ effector T cells reduced their proliferative capacity and conferred on them regulatory potential against third-party T cells.[16] Recent studies have also shown that high LAG-3 expression on exhausted lymphocytic choriomeningitis virus-specific $CD8^+$ T cells contributes to their unresponsive state and limits $CD8^+$ T cell antitumor responses.[17,18] In fact, LAG-3 maintained tolerance to self and tumor antigens via direct effects on $CD8^+$ T cells in 2 murine models.[18]

Immune tolerance observed in the setting of tumor development and tumor recurrence, however, seems to be mediated by the coexpression of various T cell negative regulatory receptors, not solely from LAG-3. Data from chronic viral infection models,[17,18,19] knockout mice,[20,21,22] tumor recurrence models,[23] and, to a more limited extent, human cancer patients[23,24,25] support a model wherein T cells that are continuously exposed to antigen become progressively inactivated through a process termed "exhaustion." Exhausted T cells are characterized by the expression of T cell negative regulatory receptors, predominantly CTLA-4, PD-1, and LAG-3, whose action is to limit the cell's ability to proliferate, produce cytokines, and kill target cells and/or to increase Treg activity. However, the timing and sequence of expression of these molecules in the development and recurrence of tumors have not been fully characterized.

It is hypothesized that CTLA-4 acts as the dominant off-switch for tolerance, but it is the strong synergy between the PD-1 and LAG-3 inhibitory pathways that seems to mediate tolerance to both self and tumor antigens.[20,21,23] Whereas CTLA-4 knockout mice die prematurely from multiorgan inflammation,[26] PD-1 and LAG-3 single knockout mice present minimal immunopathologic sequelae.[21] In contrast, dual knockout mice (LAG-3-/-PD-1-/-) abrogate self-tolerance with resultant autoimmune infiltrates in multiple organs and even lethality.[20,21] These dual knockout mice also show markedly increased survival from and clearance of multiple transplantable tumors.[20]

Conversely, extensive coexpression of PD-1 and LAG-3 on tumor-infiltrating $CD4^+$ and $CD8^+$ T cells has been shown in distinct transplantable tumors and samples from melanoma, RCC, HNC, NSCLC, and ovarian cancer patients.[23,27,28,29,30,31,32] Blockade of PD-1/PD-L1 interactions has been successfully used to restore antitumor immunity in preclinical and clinical studies. But the simultaneous blockade of PD-1 and LAG-3 pathways on T cells may exert an even more robust antitumoral immunity in naive as well as in recurrent tumors due to the possibility of reversing LAG-3–mediated T cell exhaustion. In 2 syngeneic mice models, for example, dual anti–LAG-3/anti–PD-1 antibody therapy is able to cure most mice of established tumors that are largely resistant to single antibody treatment.[20] Furthermore, recurrent tumors from a melanoma mouse model with increased Treg cell numbers and increased expression of checkpoint inhibitors PD-1, LAG-3, T cell immunoreceptor with Ig and immunoreceptor tyrosine-based inhibition motif domains, and T cell immunoglobulin domain and mucin domain 3 can be controlled by depletion of Tregs (via FoxP3-DTR) plus the administration of anti–PD-L1 antibody. But more importantly, tumor regression of these recurrent tumors can also be accomplished with the combination of anti-PD-L1 plus anti-LAG-3 antibodies (C9B7W mAb), which also increases T cell activity.[23]

Given the literature supporting synergistic activity of nivolumab and anti–LAG-3 antibody in viral models, it is hypothesized that this combination could have antitumor effects in virally related cancers, including human papilloma virus (HPV)-related tumors such as HPV+ head and neck cancer (HNC). Recent evidence has shown a role of immune inhibitory receptors (eg, PD-1/PD-L1) in the adaptive immune resistance seen in HNCs associated with HPV. In these cancers with high lymphocytic infiltration, there is PD-1 expression on the majority of CD8+ TILs and PD-L1 expression on both tumor cells and tumor-associated macrophages.[19] In a recent analysis, 33% to 47% of head and neck tumors showed a T cell-inflamed phenotype (TCIP) similar to melanoma, based on a gene expression signature. Interestingly, 75% of HPV (+) tumors showed a TCIP, compared with 23% of HPV (-) tumors.[28] Furthermore, various checkpoint molecules were universally coexpressed in these TCIP tumors, including PD-1, CTLA-4, LAG-3, PD-L2, and indoleamine 2,3-dioxygenase, as shown in gene expression analysis. Altogether, these data support a role for the PD-1:PD-L1 pathway in T cell exhaustion leading to both persistence of HPV infection and malignant progression in HNC patients. It is then possible that LAG-3 may also play a role in virally induced T cell exhaustion in these patients. Gastric cancer is another exploratory tumor suitable for T cell-directed therapy based on preliminary objective responses observed in patients treated with anti-PD-L1 antibody therapy.[33] In addition, LAG-3 expression ≥

1% by immunohistochemistry (IHC) has been documented in ~35% of gastric cancer samples.[29] A subtype of gastric cancer is also associated with Epstein-Barr virus (EBV) infection.[34] This subtype is characterized by massive lymphocyte infiltration, better prognosis than EBV-negative tumors, and worldwide distribution, particularly in Asia. So, similar to HNC, the expression of checkpoint inhibitors may be leading to the persistence of EBV infection and/or malignant progression of these tumors which could be halted by T cell-directed therapy.

Hepatocellular carcinoma is another virally associated tumor suitable for combination therapy with BMS-986016 and nivolumab. On one hand, it has been shown that LAG-3 is selectively upregulated on tumor-infiltrating CD8+ T cells and that HBV-specific CD8+ TILs have an impaired effector function in subjects with HCC.[35] Furthermore, T cell–directed therapy with anti-CTLA-4 antibody (tremelimumab; NCT01008358)[36] or with nivolumab in HCC subjects has displayed an acceptable safety profile as well as antitumor and antiviral activity in clinical studies. In a Phase I trial,[31] nivolumab produced durable responses across all dose levels and HCC cohorts (objective response rate [ORR] 19%), with a favorable 12-month OS rate of 62%, regardless of the underlying viral status.

Checkpoint molecules are also key immunomodulators in RCC, particularly PD-1 and LAG-3. By IHC, it has been documented that LAG-3 expression ≥ 1% is found in ~60% of RCC samples. [redacted] has demonstrated that PD-1 and LAG-3 were expressed by a significantly higher percentage of CD8+ TILs as compared with [redacted] obtained from RCC patients or healthy individuals.[36] Also, subjects with RCC primary tumors and lung metastases associated with extensive CD8+ T cell infiltrate were correlated with poor prognosis only if they had high expression of LAG-3 and PD-L2.[37] Finally, nivolumab produced durable responses across all doses (ORR 29%), with a favorable 3-year OS rate of 52%.[38]

The efficacy and improved OS obtained with nivolumab in second-line treatment of squamous NSCLC has led to its recent approval in the US.[39] Nivolumab has also demonstrated a significant OS benefit in nonsquamous tumors in the CheckMate 057 trial.[32] So, considering that approximately 47% of the immune infiltrate in NSCLC is PD-L1 positive and that these tumors also express other immune checkpoints such as LAG-3, TIM3, B7-H3, B7-H4, and CTLA-4,[40] it is possible that dual blockade could improve the outcomes already seen with nivolumab single agent in these subjects.

More recently, nivolumab has received accelerated approval for locally advanced and metastatic urothelial carcinoma in the setting of advanced disease progression during or following platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant platinum-containing treatment. The accelerated approval was based on an ORR of 19.6% with a 10-month duration of response (DOR).[41] Despite clinical activity of PD-1/PD-L1–targeted therapy in this disease, most patients do not benefit, and resistance mechanisms remain poorly characterized. LAG-3 expression and PD-L1 expression were both highly positively correlated with CD8A expression within inflamed urothelial carcinomas, providing a strong rationale for combination therapy.[42]

Altogether, these data argue strongly that dual blockade of the PD-1 and LAG-3 pathways could be a promising combinatorial strategy for multiple malignancies.

1.1.3 Rationale for Anti-LAG-3 Antibody (BMS-986016) Therapy

BMS-986016 (relatlimab; these terms are interchangeably used throughout the document) is a fully human antibody specific for human LAG-3 that was isolated from immunized transgenic mice expressing human immunoglobulin genes. It is expressed as an IgG4 isotype antibody that includes a stabilizing hinge mutation (S228P) for attenuated Fc receptor binding in order to reduce or eliminate the possibility of antibody- or complement-mediated target cell killing. BMS-986016 binds to a defined epitope on LAG-3 with high affinity (Kd, 0.25 to 0.5 nM) and specificity and potently blocks the interaction of LAG-3 with its ligand, [redacted] (IC50, 0.7 nM). The antibody exhibits potent in vitro functional activity in reversing LAG-3–mediated inhibition of an antigen-specific murine T cell hybridoma overexpressing human LAG-3 (IC50, 1 nM). In addition, BMS-986016 enhances activation of human T cells in superantigen stimulation assays when added alone or in combination with nivolumab (anti–PD-1 antibody).

1.1.5 Summary

Combined inhibition of T cell checkpoint molecules, such as CTLA-4, PD-1, and LAG-3, in preclinical models provides synergistic improvement in T cell activity, control of virus replication, and tumor inhibition in animal models. These observations led to the discovery of one of the key signature molecules associated with T cell exhaustion, the negative T cell regulator, LAG-3, and to the development of the antagonistic LAG-3 antibody, BMS-986016.

An initial evaluation of the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics will be conducted with an escalation arm of BMS-986016 monotherapy. It is proposed that this antibody should be considered for the treatment of multiple malignancies in combination with nivolumab (an anti–PD-1 antibody) as a T cell-core therapy with the aim to: 1) increase the number, type, and DORs in tumors known to respond to T cell checkpoint inhibitors; 2) rescue an adaptive response where patients are refractory to T cell checkpoint inhibitors and have progressed clinically; and/or 3) enhance the antitumor immunity in malignancies associated with chronic viral infections (eg, HPV, EBV, HCV, HBV, etc).

1.1.6 Rationale for Part D Expansion

As of the cutoff date of 15-Jun-2017, preliminary proof-of-concept efficacy has been revealed in the Part C combination treatment expansion cohort of advanced melanoma with prior treatment with anti-PD-1/PD-L1. All subjects were treated with BMS-986016 80 mg + nivolumab 240 mg every 2 weeks (Q2W). The overall ORR was 11.5% (7/61 response evaluable), with a disease control rate (DCR) of 49%. Biomarker analyses suggested that subjects whose TIL expressed more LAG-3 had a higher response rate, with a greater than 3-fold increase in ORR observed in subjects with evidence of LAG-3 expression in at least 1% of nucleated cells within the tumor margin,

compared with less than 1% LAG-3 expression (18.2% [6/33] and 5.0% [1/20], respectively). PD-L1 expression did not appear to enrich for response. The treatment group had the following characteristics: 1) most subjects had M1C disease (68%), 2) the cohort was heavily pretreated (77% with 2 or more prior therapies and 57% with prior anti-CTLA-4 therapy), 3) all subjects had progressed while receiving anti-PD-1/PD-L1, and 4) progressive disease (PD) was the best response to prior anti-PD-1/PD-L1 in 46% of subjects. Overall, anti-LAG-3 (BMS-986016) in combination with nivolumab demonstrated encouraging initial efficacy with a safety profile similar to nivolumab monotherapy.[43]

Based on initial efficacy signal in advanced melanoma subjects who progressed on anti-PD-1/PD-L1 therapy, additional subjects in this subset population for further clinical testing are justified. Assessment in this population will be extended in 2 subparts: Part D1 and D2. D1 will test the combination in a focused eligibility population, whereas D2 will allow assessment in a broader population under expanded eligibility criteria.

Given the improved response rate in subjects whose tumor-associated immune cells express more LAG-3, efficacy analysis in Part D1 will be the primary focus. Subjects whose tumors are LAG-3 negative will also be evaluated to determine the role of LAG-3 expression on the antitumor activity of BMS-986016. Part D2 will explore safety and efficacy in a broader patient population, including those with Eastern Cooperative Oncology Group performance status (ECOG PS) up to 2 and among those with a more diverse set of prior therapies.

1.1.7 Rationale for Part E (Melanoma Expansion)

At the time of incorporation of Part E into this protocol, the majority of the melanoma patients evaluated within the BMS-986016 clinical development program have been treated with the BMS-986016 160 mg + nivolumab 480 mg every 4 weeks (Q4W) dosing regimen or BMS-986016 80 mg + nivolumab 240 mg Q2W dosing regimen. Although preliminary evidence indicates that BMS-986016 160 mg + nivolumab 480 mg Q4W is a reasonable dose, it is possible that higher doses may produce additional clinical benefit for melanoma participants. Accordingly, in an effort to more fully elucidate the dose-response curve in melanoma participants, Part E of this protocol includes the evaluation of the BMS-986016 480 mg + nivolumab 480 mg Q4W dosing regimen.

The BMS-986016 480 mg + nivolumab 480 mg Q4W dosing regimen has been evaluated in Part B (Dose Escalation with DLT Criteria) of this study. Seven (7) subjects were treated, and no DLTs were observed.[29] Accordingly, the BMS-986016 480 mg + nivolumab 480 mg Q4W dosing regimen was determined by the Principal Investigators conducting Part B to have an acceptable safety profile that warranted dose escalation to the BMS-986016 960 mg + nivolumab 480 mg Q4W dosing regimen. Subsequently, the BMS-986016 960 mg + nivolumab 480 mg Q4W dosing regimen was evaluated. Three (3) subjects were treated, and there were no DLTs. Accordingly, the BMS-986016 960 mg + nivolumab 480 mg Q4W dosing regimen was determined by the Principal Investigators conducting Part B to have an acceptable safety profile that warranted dose escalation to the BMS-986016 1440 mg + nivolumab 480 mg Q4W dosing regimen.

Melanoma participants who experienced disease progression on anti-PD-1 therapy and melanoma participants with previously untreated metastatic or unresectable disease will be included in Part

E. More specifically, these 2 participant cohorts are defined, respectively, as an advanced melanoma participant who has progressed (radiologically confirmed) on prior anti-PD-1 therapy within 3 months of the last anti-PD-1 dose and an advanced melanoma participant who has not received prior systemic anticancer therapy for unresectable or metastatic melanoma. Please refer to Section 3.3 of this protocol for complete definitions of these participant cohorts and details on applicable inclusion/exclusion criteria.

In participants who experienced disease progression on prior anti-PD-1 therapy, only the BMS-986016 480 mg + nivolumab 480 mg Q4W dosing regimen will be evaluated. In the cohort of participants who have not received prior systemic anticancer therapy for unresectable or metastatic melanoma, both the BMS-986016 160 mg + nivolumab 480 mg Q4W and the BMS-986016 480 mg + nivolumab 480 mg Q4W dosing regimens will be evaluated.

The rationale for limiting the cohort of participants who experienced disease progression on anti-PD-1 therapy cohort to only the BMS-986016 480 mg + nivolumab 480 mg Q4W dosing regimen is that there is substantial clinical experience in melanoma participants who experienced disease progression on anti-PD-1 therapy with the BMS-986016 160 mg + nivolumab 480 mg Q4W dosing regimen. That substantial clinical experience will be used as a historical control for the purpose of elucidating the dose-response curve in this cohort of melanoma subjects. For the cohort of participants who have not received prior systemic anticancer therapy for unresectable or metastatic melanoma, where the clinical experience is more limited, participants will be randomized to 1 of the 2 dosing regimens.

1.1.8 Parts C, D, and E (Melanoma Only) Rationale for Inclusion of Adolescents

Patients under 18 years of age have often been excluded from adult oncology trials because of safety or regulatory concerns; a practice that leads to delays in pediatric studies. Separate adult and pediatric cancer centers, distinct cooperative research groups, and oncologists specializing in different populations do not often conduct unified adult–pediatric clinical trials or drug-development programs.[44]

Although rare, the incidence of childhood and adolescent melanoma in the United States has been increasing in the past 35 years. This trend is most prominent in the adolescent age range, specifically those 15 to 19 years of age. Single-center and industry-sponsored trials often exclude advanced melanoma adolescent patients for historical or empiric reasons. A recent genomic analysis of pediatric melanoma demonstrates that conventional melanoma in children and adolescents shares many of the genomic features that have been described in adult melanoma, including BRAF mutations. The abstract of this genomic analysis advocated for the opportunity for pediatric patients to be enrolled in pharmaceutically sponsored trials that incorporate novel agents. Many pediatric subjects who are diagnosed with melanoma are referred to and treated by medical oncologists vs pediatric oncologists, due to divergent expertise in the field.[45]

1.1.9 Rationale for Dose Selection

CA224020 currently consists of 6 parts. Part A and Part B consist of a 3 + 3 + 3 dose escalation design and, implemented in site-specific amendment #15 (dated 13 August 2018) and superseding the 3 + 3+ 3 dose escalation design, the Bayesian Logistic Regression Model (BLRM)-Copula design, with BMS-986016 administered as a single agent (Part A) or in combination with nivolumab as sequential infusion (Part B) in subjects with advanced solid tumors. Part A1 consists of expansion cohorts of approximately 6 to 12 subjects in each disease-restricted population, with BMS-986016 monotherapy. Part C consists of expansion cohorts of approximately 25 to 40 subjects each in disease-restricted populations (and further expansion of up to approximately 90 to 120 subjects in selected cohorts based upon safety and efficacy profiles), with BMS-986016 administered in combination with nivolumab as sequential infusions. Part D consists of advanced melanoma subjects with progression on prior anti-PD-1 therapy enrolled into 2 subgroups based upon eligibility criteria. Part E consists of both melanoma participants who experienced disease progression on prior anti-PD-1 therapy and melanoma participants who have not received prior systemic anticancer therapy for unresectable or metastatic melanoma. The sequential infusion of BMS-986016 and nivolumab will be administered in Parts A, A1, B and C. In Part D, subjects will be administered BMS-986016 and nivolumab coadministration or BMS-986213 (fixed-dose combination [FDC] relatlimab/nivolumab at a 1:3 ratio in a single vial). In Part E, subjects will be administered BMS-986016 and nivolumab as a coadministration. See Section 4.1.1 for details.

1.1.9.1 Rationale for Flat Dosing

Therapeutic mAbs doses have been routinely calculated on a body size basis with a perception that this approach may reduce intersubject variability in drug exposure compared with a flat dose approach. However, recent analyses of marketed and experimental mAbs have demonstrated that body weight-based dosing did not always offer advantages over flat dosing in reducing exposure variability.[46,47] Since the magnitude of the impact of body weight on the human PK of BMS-986016 is not yet determined and it is unknown if body size-based dosing would increase or decrease intersubject variability, this study will utilize a flat dose escalation and expansion since it is the simpler of the 2 approaches and may result in fewer dosing errors. The impact of body weight on the PK of nivolumab is small, and the dose-response relationship is relatively shallow near the 3-mg/kg dose level, indicating that nivolumab can also be administered as a flat dose in combination with BMS-986016 in this study.

Flat doses for this study have been normalized for an average 80-kg adult cancer patient. A dataset from the nivolumab program used for preliminary population PK contained 325 subjects with a median weight of 81 kg. This value aligns well with a study by Bai et al, which found a median weight of 78 kg in 2519 adult patients with rheumatoid arthritis, breast cancer, colorectal cancer, NSCLC, ovarian cancer, and non-Hodgkin's lymphoma.[46]

Additionally, BMS-986016 flat dose of 20 to 800 mg as monotherapy and up to 480 mg in combination with nivolumab (both given Q2W) has been studied across the 40 to 120 kg weight range in adults.

1.1.9.2 Part A — BMS-986016 Dose

The first-in-human dose selected for this study is based on all available nonclinical data.

To balance the potential for pharmacologic activity and reasonable safety in this cancer patient population, a dose of 20 mg (0.25 mg/kg) was selected as the starting dose in monotherapy (Arm A). This dose is less than 1/10 of the human equivalent dose (HED) of the no-observed-adverse-effect level (NOAEL) in the 4-week toxicity study (636 mg; 8.0 mg/kg) and is below the HED after a linear adjustment of the NOAEL target exposure for the highest affinity difference estimate of 265-fold (24 mg; 0.30 mg/kg) between activated human and cynomolgus T cells. No additional safety factor was added to the affinity-adjusted calculation because a linear adjustment is expected to be a conservative approach. Based on the model from the mouse efficacy data, this dose has the potential to have antitumor activity in humans. The calculated safety multiple for the 20-mg (0.25 mg/kg) dose is 315-fold based on the NOAEL of 100 mg/kg/week in the 4-week repeat-dose monkey study without accounting for affinity differences. In addition, a staggered dosing (sentinel subject) approach will be used in the first dose cohort, as described in Section 3.1.1.1. The top dose of 800 mg (10 mg/kg) is projected to have the potential for 71% to 179% TGI from the most sensitive model in mouse.

1.1.9.3 Part B — BMS-986016 Dose (Applies to Only a Subset of Sites 1-6)

Administrative Note: Only a limited number of sites are conducting Part B of this protocol. Each investigational site that is participating in Part B will receive an administrative letter from BMS confirming their participation in Part B that can be submitted to their respective Institutional Review Board (IRB) or Independent Ethics Committee (IEC).

The starting doses for Part B were selected based on all nonclinical data available from studies of the combination and BMS-986016 monotherapy and on emerging clinical safety and PK data from Part A monotherapy. In the 4-week repeated-dose Good Laboratory Practice (GLP) toxicology study, a dose of 100 mg/kg/week of BMS-986016 + 50 mg/kg/week nivolumab was considered the severely toxic dose in 10% of the animals (STD10; refer to Section 1.4.1.2). The same approach to identifying HEDs as described for monotherapy was used. Using a linear adjustment of the STD10 for a 265-fold affinity difference results in a dose of 20 mg (~0.3 mg/kg).

Pharmacokinetic data from Part A monotherapy suggested that subjects treated at 20 mg BMS-986016 (flat dose) have significant lower exposure compare to exposure associated with toxicity in the GLP toxicology study with 100 mg/kg/week of BMS-986016 + 50 mg/kg/week nivolumab in cynomolgus monkey. Furthermore, BMS-986016 monotherapy was well tolerated in subjects treated with up to 800 mg BMS-986016 (flat dose) in Part A. The only high-grade related toxicity was an asymptomatic, self-limited, G3 lipase elevation in 1 subject treated at 20 mg flat dose. Therefore, the proposed starting dose for BMS-986016 in combination with nivolumab in Part B was 20 mg (~0.3 mg/kg) given Q2W. This dose cohort was initiated after the decision was made to escalate to the third dose cohort in Part A (monotherapy) in accordance with the dose escalation rules. Delaying initiation of the first dose cohort in Part B until after evaluation of the first 2 cohorts in Part A (ie, up to 80 mg flat dose) provided additional clinical safety data with single-agent BMS-986016 at doses 4-fold higher than the 20-mg dose prior to administration

of the combination. In addition, a staggered dosing (sentinel subject) approach will be used in the first dose cohort as described in Section 3.1.1.2.

While the majority of assessments in this study have been and will be conducted using Q2W dosing, a Q4W dosing regimen will also be assessed in this study. Specifically, extending the dosing interval to Q4W provides numerous benefits to patients, including increased flexibility between clinical visits compared with Q2W.

The initial Q4W dose escalation (3 + 3 + 3 design) is as follows: 160, 240, and 320 mg. Upon completion of safety evaluation from these initial dose escalations, additional higher doses, including 480, 960, 1440, and 1600 mg Q4W, will be evaluated to assess a maximum tolerated dose (MTD). Proposed higher doses of 480 to 1600 mg Q4W are predicted to provide a dose-proportional increase in exposure by following linear PK. The top dose of 1600 mg is predicted to provide steady state average concentrations similar (< 5%) to the maximum administered dose (MAD) of 800 mg Q2W in human and steady state maximum observed concentration (Cmaxss) well below the observed exposure at the NOAEL dose in the 3-month repeat-dose toxicity studies in cynomolgus monkeys. [redacted] (Section 1.4.1.4). The increment of subsequent dose levels after the initial 320-mg dose level can be modified based on the BLRM-Copula recommendation.

1.1.9.4 Parts B, C — Nivolumab and Combination Dosing - Sequential Infusion

As mentioned previously, a dose of 100 mg/kg/week of BMS-986016 + 50 mg/kg/week nivolumab was considered the STD10 in the 4-week toxicity study. Known human nivolumab PK parameters were used to calculate the HED. The same approach to identifying HEDs as described for monotherapy was used. With an added 10-fold safety factor, the maximum recommended starting dose based on the STD10 is 320 mg (~4 mg/kg) in humans. The starting nivolumab dose for subjects in Part B is 80 mg (1 mg/kg) Q2W. All subsequent cohorts on Q2W schedule are planned to be administered 240 mg of nivolumab, which is equivalent to the well-tolerated global nivolumab monotherapy Phase 3 dose 3 mg/kg Q2W.[11] Most recently, the nivolumab dosage regimen was modified to a flat 240 mg Q2W as monotherapy for melanoma, NSCLC, and RCC in the US.[11] [USPI (Appendix 1)] In Part B with Q2W dose escalation cohorts, doses will be administered sequentially as nivolumab intravenous (IV) infusion over 60 minutes, followed by BMS-986016 infusion over 60 minutes.

In Part B, for the less frequent dosing regimen (Q4W), nivolumab dose of 480 mg will be administered in combination with BMS-986016. Based on PK modeling and simulations, while 480 mg Q4W is predicted to provide greater (approximately 40%) maximum steady state concentrations and lower (approximately 20%) steady state trough concentrations, these exposures are predicted to be within the exposure ranges observed at doses up to 10 mg/kg Q2W used in the Phase 1 nivolumab clinical program and are not considered to put subjects at increased risk. Similar to the nivolumab Q2W dosing monotherapy regimen, the exposures predicted following administration of nivolumab 480 mg Q4W are on the flat part of the exposure-response curves for previously investigated tumors (ie, melanoma and NSCLC) and are not predicted to affect efficacy.

Based on these data, nivolumab 480 mg Q4W is expected to have similar efficacy and safety profiles to nivolumab 240 mg or 3 mg/kg Q2W.[48]

The dosing and schedule for subjects in Part C will be agreed upon by Investigators and the Sponsor based upon dosing shown to be safe in Part B. In Part B and Part C, the sequential infusion of both drugs will start with nivolumab administration first, followed by infusion of BMS-986016. Based upon review of the available safety, PK, [redacted], Part C expansions commenced at combination dosing of 80 mg BMS-986016 and 240 mg nivolumab Q2W (see Section 1.4.1.4.2 of this protocol and the BMS-986016 Investigator Brochure [IB]).[29] The planned treatment for the bladder immuno-oncology (IO)-naive cohort will be sequential dosing of 160 mg BMS-986016 with 480 mg nivolumab Q4W. However, if 160 mg BMS-986016 with 480 mg nivolumab Q4W is deemed not safe, then the 80 mg BMS-986016 with 240 mg nivolumab Q2W regimen will be given.

1.1.9.5 Rationale for 30-minute Nivolumab Infusion

Administration of nivolumab using a 30-minute infusion time has been evaluated in subjects with cancer and was shown to be safe.[49]

1.1.9.6 Part D: Coadministration or Fixed-dose Combination

In Part D, advanced melanoma subjects with progression on prior anti-PD-1 therapy will be enrolled in 2 subgroups based on eligibility criteria. If eligible for the focused D1 group, subjects will be randomized across 3 arms (see Section 3.1.2.5 for details):

Arm 1: BMS-986016 80 mg + nivolumab 240 mg given by coadministration Q2W

Arm 2: BMS-986016 160 mg + nivolumab 480 mg given by coadministration Q4W

Arm 3: BMS-986213 (relatlimab 160 mg/nivolumab 480 mg) given Q4W; BMS-986213 contains both relatlimab and nivolumab in the same solution at a ratio of 1:3

The expanded eligibility Part D2 cohort will all be treated using the more convenient Q4W dosing in 2 different dose combinations: 160 mg BMS-986016 + 480 mg of nivolumab and subsequently 240 mg BMS-986016 + 480 mg of nivolumab (described in Section 3.1). The combination treatment in Part D2 will be coadministered.

The less frequent dosing regimen given Q4W was selected based on model predicted PK, [redacted] and acceptable safety profile up to BMS-986016 160 mg + nivolumab 240 mg given Q2W in this study and ongoing study CA224022. BMS-986016 160 mg + nivolumab 480 mg Q4W is predicted to provide similar steady state BMS-986016 exposure (ie, steady state average concentration [Cavgss]) [redacted] comparable to the levels achieved when BMS-986016 80 mg + nivolumab 240 is dosed Q2W. BMS-986016 240 mg + nivolumab 480 mg Q4W is predicted to maintain steady state exposure (ie, Cavgss) [redacted] below the levels achieved when BMS-986016 160 mg + nivolumab 240 mg is given Q2W, a dose shown to be tolerable in Part B. In addition, confirmation of the predicted safety of BMS-986016 240 mg + nivolumab 480 mg Q4W is ongoing, and employment of this dose will commence upon appropriate safety assessment in Part B. If BMS-986016 240 mg + nivolumab 480 mg Q4W is

considered toxic based on Section 3.1.2.3, then further expansion will resume at BMS-986016 160 mg + nivolumab 240 mg Q2W.

For coadministration treatments, BMS-986016 and nivolumab will be mixed in same infusion bag and will be administered over approximately 60 minutes. The decrease in infusion time will allow for increased convenience for patients, doctors, nursing staff, other health-care staff members, and pharmacists. Key advantages of a coadministration of this combination are as follows:

Patients benefit from reduced infusion time and less time in the clinic and/or doctor's office

Increased ease of administration

Pharmacists require less time in preparation of the IV solution to be administered to the patient

For the FDC drug product (BMS-986213) treatment, BMS-986213 will be administered over approximately 60 minutes. The advantages of the use of a single-vial drug product include easier and more rapid administration and infusion preparation, as well as decreased opportunity for dosing and administration errors.

Although coadministration and treatment with the FDC drug product (BMS-986213) would result in overlapping time of maximum observed concentration (Tmax) for BMS-986016 and nivolumab, the PK and exposure of both agent will be the same as when administered sequentially. Therefore, sequential administration vs coadministration (ie, single infusion bag) vs BMS-986213 (FDC) administration is not expected to impact the overall safety profile.

1.1.9.7 Part E: Coadministration of BMS-986016 and Nivolumab

Part E consists of advanced melanoma participants. Two cohorts of melanoma participants will be enrolled in Part E: melanoma participants who experienced disease progression on prior anti-PD-1 therapy and melanoma participants who have not received prior systemic anticancer therapy for unresectable or metastatic melanoma. Melanoma participants who experienced disease progression on prior anti-PD-1 therapy will only receive 480 mg BMS-986016 + 480 mg nivolumab Q4W. Melanoma participants who have not received prior systemic anticancer therapy for unresectable or metastatic melanoma will be randomized to 1 of 2 treatment arms:

- 160 mg BMS-986016 + 480 mg nivolumab Q4W
- 480 mg BMS-986016 + 480 mg nivolumab Q4W

Administration of 480 mg BMS-986016 + 480 mg nivolumab Q4W to participants in Part E is warranted based on an acceptable safety profile of this dose being established in Part B (ie, Dose Escalation with DLT Criteria) of this study; see Section 1.1.7 for details.

BMS-986016 and nivolumab will be mixed in same infusion bag and will be administered over approximately 60 minutes. The decrease in infusion time will allow for increased convenience for patients, doctors, nursing staff, other health-care staff members, and pharmacists. Key advantages of a coadministration of this combination are as follows:

Patients benefit from reduced infusion time and less time in the clinic and/or doctor's office
Increased ease of administration
Pharmacists require less time in preparation of the IV solution to be administered to the patient

1.1.9.8 Dose Rationale for Adolescents

The PK of drugs and many therapeutics proteins has been shown to be similar between adolescents and adults once the effect of body size on PK is taken into consideration.[50,51] Therefore, in general, adult doses would expected to achieve similar systemic exposures in adolescents. In this study, BMS-986016 in combination with nivolumab was administered as a flat dosing in adults; therefore, a minimum body weight threshold in adolescents (≥ 40 kg) is defined to receive the same adult flat dose to prevent exceeding target adult exposures. Adolescent subjects < 40 kg body weight will be given body weight–based dosing, equivalent to the conversion from a median adult weight of 80 kg. Therefore, the weight-based doses are 1 mg/kg BMS-986016 and 3 mg/kg nivolumab Q2W, 2 mg/kg BMS-986016 and 6 mg/kg nivolumab Q4W, and 6 mg/kg BMS-986016 and 6 mg/kg nivolumab Q4W for corresponding fixed doses of 80/240 Q2W, 160/480 Q4W, and 480/480 Q4W, respectively. This adolescent dosing scheme also applies to BMS-986213.

1.2 Research Hypotheses

It is anticipated that anti–LAG-3 antibody (BMS-986016, relatlimab), administered as a single agent or in combination with anti–PD-1 antibody (nivolumab) will demonstrate adequate safety and tolerability, as well as a favorable benefit-risk profile, to support further clinical testing. No prospective hypotheses are being formally evaluated.

Part D1: Treatment with BMS-986016 in combination with nivolumab will lead to clinical benefit, as demonstrated by a clinically meaningful ORR, including durable responses with substantial magnitude of tumor burden reduction in melanoma subjects who progressed while on anti-PD-1 antibody therapies.

Part D1: Treatment with BMS-986213 (FDC) will demonstrate no clinically relevant differences in safety relative to coadministration of nivolumab and BMS-986016.

Part E: Treatment with BMS-986016 in combination with nivolumab (coadministration) will lead to clinical benefit in melanoma subjects. This will be demonstrated by higher doses of relatlimab (eg, 480 mg BMS-986016 + 480 mg nivolumab Q4W) producing greater clinical benefit, as manifested by a clinically meaningful ORR, including durability of response and substantial magnitude of tumor burden reduction.

1.3 Objectives

1.3.1 Primary Objectives

Parts A and B:

The primary objective of Parts A and B is to determine the safety, tolerability, dose-limiting toxicities (DLTs), and MTD of BMS-986016 administered alone and in combination with nivolumab in subjects with advanced solid tumors.

Part A1:

The primary objective of BMS-986016 monotherapy cohort expansion is to gather additional safety, tolerability, and preliminary efficacy information of BMS-986016 monotherapy.

Part C:

The primary objective is to further establish adequate safety and tolerability of BMS-986016 in combination with nivolumab administered sequentially.

The coprimary objective in Dose Expansion Part C is to investigate the preliminary efficacy of BMS-986016 in combination with nivolumab as measured by ORR, DCR, and DOR in multiple solid tumor types.

Part D:

The primary objective in Part D is to assess safety and tolerability of a more convenient dosing regimen (ie, coadministration and Q4W dosing interval).

Part D1-Q2W: The coprimary objective in Part D1-Q2W is to demonstrate preliminary clinical evidence of the treatment effect, measured by ORR, as determined by Blinded Independent Central Review (BICR) using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, that may represent substantial improvement over available therapies in advanced melanoma subjects with LAG-3 expression who progressed while on anti-PD-1 antibody therapies.

Part D1-Q4W: The primary objective in Part D1-Q4W is to evaluate the difference in safety of coadministration relative to FDC as measured by the incidence of adverse events (AEs) in the Broad Scope Medical Dictionary for Regulatory Activities (MedDRA) Anaphylactic Reaction Standardized MedDRA Query (SMQ) occurring within 2 days after dosing in advanced melanoma subjects who progressed while on anti-PD-1 antibody therapies (see Appendix 5).

Part D1-Q4W: The coprimary objective in Part D1-Q4W is to confirm with Q4W dosing of BMS-986016 160 mg in combination with nivolumab 480 mg the safety of the Q2W dosing of BMS-986016 80 mg in combination with nivolumab 240 mg in advanced melanoma subjects who progressed while on anti-PD-1 antibody therapies.

Part E:

The primary objective of Part E is to demonstrate that the 480 mg BMS-986016 + 480 mg nivolumab Q4W dosing regimen provides significantly greater clinical benefit, manifested as an increased ORR, to participants as compared with the 160 mg BMS-986016 + 480 mg nivolumab Q4W dose by interdose cohort comparison in melanoma participants who have not received prior systemic anticancer therapy for unresectable or metastatic melanoma and to historical control for melanoma participants who experienced disease progression on prior anti-PD-1 therapy.

1.3.2 Secondary Objectives

The secondary objectives are:

To characterize the PK of BMS-986016 administered alone and in combination with nivolumab.

To investigate the preliminary ORR and/or DCR of BMS-986016 administered alone and in combination with nivolumab in subjects with advanced solid tumors in Parts A and B, Dose Escalation.

To characterize the immunogenicity of BMS-986016 administered alone and in combination with nivolumab.

In Parts A and B, to assess the effect of BMS-986016 administered alone and in combination with nivolumab on QTc.

Part D1:

To evaluate DOR, DCR, and progression-free survival (PFS) rates at prespecified time points (eg, 24 weeks) based on BICR assessments using RECIST v1.1 in advanced melanoma subjects with LAG-3 expression who progressed while on anti-PD-1 antibody therapies.

To evaluate ORR, DCR, DOR, and PFS rates at prespecified time points (eg, 24 weeks) based on BICR assessments using RECIST v1.1 in advanced melanoma subjects with a lack of LAG-3 expression and overall regardless of LAG-3 expression.

To evaluate ORR, DCR, DOR, and PFS rates at prespecified time points (eg, 24 weeks) based on investigator assessments using RECIST v1.1 in advanced melanoma subjects with LAG-3 expression, a lack of LAG-3 expression, and overall regardless of LAG-3 expression.

To assess the 1-year and 2-year landmark OS in advanced melanoma subjects with LAG-3 expression, a lack of LAG-3 expression, and overall regardless of LAG-3 expression.

Part D1-Q4W: To confirm with Q4W dosing of BMS-986016 160 mg in combination with nivolumab 480 mg the efficacy of the Q2W dosing of BMS-986016 80 mg in combination with nivolumab 240 mg in advanced melanoma subjects with LAG-3 expression who progressed while on anti-PD-1 antibody therapies.

Part D1-Q4W: To evaluate the difference in safety of coadministration relative to FDC as measured by the incidence of AEs in the Narrow Scope MedDRA Anaphylactic Reaction SMQ and the incidence of the select AEs in the Hypersensitivity/Infusion Reaction category occurring within 2 days after dosing during the combination in advanced melanoma subjects who progressed while on anti-PD-1 antibody therapies (see Appendix 5).

Part D1-Q4W: To evaluate Grade 3 - 5 AE incidence rate (drug related and all causality) defined using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0 criteria.

Part D1-Q4W: To determine PK comparisons of nivolumab and BMS-986016 administered as FDC to that of coadministered nivolumab and BMS-986016.

Part D1: To assess PK of nivolumab and BMS-986016 in Part D1-Q4W dosing and Part D1-Q2W dosing.

Part D2:

To assess safety and tolerability of more convenient dosing regimen in a wider range of population in advanced melanoma subjects who progressed while on anti-PD-1/PD-L1 antibody therapies.

To evaluate ORR, DCR, DOR, and PFS rates at prespecified time points (eg, 24 weeks) based on BICR assessments using RECIST v1.1 in a wider range of population in advanced melanoma subjects with LAG-3 expression, a lack of LAG-3 expression, and overall regardless of LAG-3 expression.

To evaluate ORR, DCR, DOR, and PFS rates at prespecified time points (eg, 24 weeks) based on investigator assessments using RECIST v1.1 in a wider range of population in advanced melanoma subjects with LAG-3 expression, a lack of LAG-3 expression, and overall regardless of LAG-3 expression.

To assess the 1-year and 2-year landmark OS in advanced melanoma subjects with LAG-3 expression, a lack of LAG-3 expression, and overall regardless of LAG-3 expression.

Part E:

To evaluate the clinical benefit of the 480 mg BMS-986016 + 480 mg nivolumab Q4W dosing regimen using DOR in melanoma participants who have not received prior systemic anticancer therapy for unresectable or metastatic melanoma and for melanoma participants who experienced disease progression on prior anti-PD-1 therapy.

1.3.3 Exploratory Objectives

Exploratory objectives are:

To assess the pharmacodynamic effects of BMS-986016 alone and in combination with nivolumab based on select biomarkers in the peripheral blood and tumor biopsy specimens.

[redacted]

To assess the 1-year and 2-year landmark OS in subjects treated with BMS-986016 alone and in combination with nivolumab.

To characterize nivolumab PK and immunogenicity when administered in combination with BMS-986016.

To explore exposure-response relationships in subjects treated with BMS-986016 as monotherapy or in combination with nivolumab.

To investigate the relationship between clinical efficacy and peripheral and tumor biomarkers.

[redacted]

To evaluate ORR, DCR, DOR, and PFS rates at prespecified time points (eg, 24 weeks) based on iRECIST assessments based on BICR.

To predict milestone survival at 1 year and 2 years using tumor growth dynamic-survival model.

1.4 Product Development Background

Information for nivolumab (BMS-936558, anti–PD-1 antibody), BMS-986016 (relatlimab, anti–LAG-3 antibody), and BMS-986213 (relatlimab/nivolumab) is provided in the sections below; additional details are provided in the respective IBs.[11,29,53]

1.4.1 BMS-986016 (Anti–LAG-3 Antibody)

1.4.1.1 Nonclinical Pharmacology

The ability of BMS-986016 to bind recombinant human LAG-3 antigen was determined using Biacore and enzyme-linked immunosorbent assay (ELISA). Binding to human and primate LAG-3+ transfectants and to activated human or primate T cells was measured using flow cytometric and Scatchard analyses. BMS-986016 binds to human LAG-3 with high affinity (Kd, 0.12 to 0.5 nM) and inhibits the binding of LAG-3 to cells expressing its ligand, [redacted] (IC50, 0.67 nM). BMS-986016 binds to cynomolgus LAG-3 on transfected Chinese hamster ovary cells and on activated cynomolgus T cells with a lower affinity (EC50, 21.5 to 34.3 nM) than to activated human T cells. A high concentration of BMS-986016, in the absence of secondary costimulation, elicits no measurable cytokine response from cultured human peripheral blood cells, nor does the drug mediate measurable antibody-dependent or complement-dependent killing of target cells. BMS-986016 promotes the activation of an antigen-specific mouse T cell hybridoma expressing human LAG-3 in co-culture with an [redacted]-positive antigen-presenting cell. In addition, BMS-986016 enhances activation of human T cells in superantigen stimulation assays when added alone or in combination with nivolumab (anti–PD-1 antibody). Detailed information can be found in the current version of the BMS-986016 IB.[29]

1.4.1.2 Toxicity

The nonclinical toxicology package for BMS-986016 consists of the following studies:

1) Four-week Intermittent (QW) Intravenous Exploratory Combination Pharmacodynamic and Toxicity Study in Cynomolgus Monkeys with Anti-LAG-3.1 Antibody (a precursor of the anti-LAG-3.5 antibody) and Nivolumab
2) GLP-compliant Four-week Intravenous Combination Toxicity Study in Cynomolgus Monkeys with a 6-week Recovery with BMS-986016 and Nivolumab
3) GLP-compliant Three-month Intravenous Toxicity Study in Cynomolgus Monkeys with BMS-986016

The key results were as follows:

- Single-agent BMS-986016 administered at up to 100 mg/kg/week did not result in adverse changes.
- Combined administration of BMS-986016 and nivolumab (100 and 50 mg/kg/week, respectively) resulted in moribundity of 1 male out of 9 monkeys on study Day 29. From Days 26 to 29, this monkey presented with elevated body temperature, shivers, red or clear nasal discharge, fecal changes (unformed, scant, or absent feces), decreased feeding behavior, mild dehydration, sneezing, decreased activity, and hunched posture. After

2 days of veterinary care and antibiotic treatment, this animal did not show any improvement and was euthanized on Day 29 for poor clinical condition. There were no remarkable gross necropsy findings. Histopathological findings in this monkey included slight lymphoplasmacytic inflammation of the choroid plexus; minimal to moderate lymphohistiocytic inflammation of the vasculature of the brain parenchyma, meninges, and spinal cord (cervical and lumbar); and minimal to moderate mixed cell inflammation of the epididymes, seminal vesicles, and testes. Clinical pathology changes indicated decreases in red blood cell count, hemoglobin concentration, and hematocrit whose cause was unclear and an increase in fibrinogen correlating with the inflammation observed in the central nervous system (CNS) and male reproductive tract.

- Additional histopathological findings upon combination administration of BMS-986016 and nivolumab (100 and 50 mg/kg/week, respectively) were limited to minimal to slight nonreversible lymphoplasmacytic inflammation of the choroid plexus in the brain in 7 of 8 remaining monkeys and minimal lymphohistiocytic inflammation of the vasculature of the brain parenchyma in 1 of 8 remaining monkeys, whose reversibility could not be assessed.
- NOAEL for single-agent BMS-986016 was considered to be 100 mg/kg/week (mean area under the concentration-time curve (AUC)[0-168h] = 474,000 μg·h/mL); NOAEL for single-agent nivolumab was considered to be 50 mg/kg/week (mean AUC[0-168h] = 193,000 μg·h/mL); NOAEL for combination of BMS-986016 and nivolumab was not determined.
- However, the combination therapy was generally well tolerated, and clinical signs of toxicity were observed in only 1 of 9 monkeys (approximately 10%). Therefore, 100/50 mg/kg/week BMS-986016/nivolumab (mean BMS-986016 AUC[0-168h] = 514,000 μg·h/mL; mean nivolumab AUC[0-168h] = 182,000 μg·h/mL) was considered the STD10.
- The doses administered (100 mg/kg BMS-986016 and 50 mg/kg nivolumab) are ≥ 10 times higher than the maximum doses proposed for the current study.
- In GLP-compliant toxicity studies up to 3 months in duration, single-agent BMS-986016 administered at up to 100 mg/kg/week did not result in adverse changes. In the 3-month study, 1 male monkey at 30 mg/kg exhibited transient clinical observations that were considered to be secondary to antidrug antibodies (ADAs) and, therefore, were not factored in determining the NOAEL. The NOAEL was considered to be 100 mg/kg/week (mean AUC[0-168h] = 1,180,000 □g•h/mL)

4) GLP-compliant Tissue Cross-reactivity Study in Human and Select Cynomolgus Monkey Tissues with BMS-986016.
   - Positive staining with BMS-986016-FITC was observed in the plasma membrane or plasma membrane granules of mononuclear leukocytes of most human tissues, including lymphoid tissues and hematopoietic cells of the bone marrow. In addition, staining with BMS-986016-FITC was observed in the cytoplasm of the human pituitary endocrine cell epithelium. Although BMS-986016 is not expected to have access to the cytoplasmic compartment in vivo and the repeat-dose toxicology studies in monkeys showed no effects on the pituitary gland, these findings may be of clinical significance and will be monitored.

- In Vitro Cytokine Release and Lymphocyte Activation Assessment with BMS-986016 Using Human [redacted]
- BMS-986016 did not induce cytokine release when presented to human [redacted] regardless of concentration, donor, or incubation time. The levels of cytokines observed were either at or near the assay lower limits of quantification, with no evidence of dose dependence or pattern across donors (interleukin [IL]-1β, IL-2, IL-5, IL-10, IL-12p70, and interferon gamma [IFN-γ]) or were generally overlapping with cytokine levels from [redacted] incubated with negative controls (IL-6, IL-8, TNF-α).
- Consistent with the lack of cytokine release, there was no evidence that BMS-986016 induced T or NK cell activation, as measured by surface expression of CD25 and CD69. Expression levels of these markers on T and NK cells following stimulation with BMS-986016 were similar to those observed upon stimulation with negative controls.
- Overall, these data indicate that BMS-986016 does not possess agonistic potential to induce either T or NK cellular activation or cytokine release.

Refer to the current BMS-986016 IB or additional information regarding nonclinical toxicity of BMS-986016.

1.4.1.3 Nonclinical Metabolism and Pharmacokinetics

In accordance with regulatory guidelines for biotechnology-derived pharmaceuticals,[52] no metabolism studies with BMS-986016 have been conducted in animals. The expected in vivo degradation of mAbs is to small peptides and amino acids via biochemical pathways that are independent of cytochrome P450 enzymes.

BMS-986016 demonstrated favorable PK properties in cynomolgus monkeys. From both single-dose and repeat-dose IV PK studies, BMS-986016 decayed bi-exponentially, and the exposure was approximately dose proportional. The systemic clearance (CLTp) ranges from 0.12 to 0.22 mL/h/kg and a terminal half-life (T-HALF) 133 to 414 hours. The volume of distribution at steady state was 62 to 72 mL/kg, suggesting limited distribution outside the plasma. Anti–BMS-986016 antibodies were detected in some monkeys, but the presence of anti–BMS-986016 antibodies appeared to have no impact on BMS-986016 exposure.

1.4.1.4 Clinical Pharmacology and Safety

1.4.1.4.1 Clinical Pharmacology

Relatlimab PK was well described by a 2-compartment model with time-varying linear and nonlinear clearance. The time-varying linear clearance was described by an empirical Emax model. The baseline covariate effects of body weight, sex, albumin, and lactate dehydrogenase (LDH) on baseline clearance and body weight on central volume of distribution were found to be statistically significant. The baseline covariate effects of race, age, ECOG PS, hepatic function, renal function, tumor type, and coadministration with nivolumab on relatlimab PK were not statistically significant.

[redacted]

Currently available data suggest that the immunogenicity rate of anti-relatlimab antibodies is approximately 7% and 21% when administered alone and in combination with nivolumab, respectively. A neutralizing antibody assay is currently being developed to further assess neutralizing potential of anti-relatlimab antibodies. The clinical significance of immunogenicity will be assessed using all available data on efficacy, safety, and time of immunogenicity occurrence.

1.4.1.4.2 Clinical Safety

Safety information is presented in detail in the BMS-986016 IB and focuses primarily on information obtained from Phase 1/2a studies (Studies CA224020 [advanced solid tumors] and CA224022 [advanced hematologic malignancies], as well a Phase 1 study conducted in Japan [Study CA224034]). As of the clinical data cutoff date of 18-Jun-2018, 942 subjects have been treated with relatlimab monotherapy or relatlimab in combination with nivolumab in these

3 ongoing studies. The large majority of the BMS-986016 safety data are derived from study CA224020, in which 837 total subjects have been treated, 25 with BMS-986016 monotherapy and 812 in combination with nivolumab.

Overall, the safety profile of relatlimab in combination with nivolumab is manageable in the 3 ongoing studies with combination therapy, with no MTD reached at the tested doses up to 960 mg relatlimab/480 mg nivolumab (Q4W). As of the clinical cutoff date of 18 June 2018, there was no dose relationship between the incidence, severity, or causality of AEs and combination therapy (see Section 5.5.1, Section 5.5.2, and Section 5.5.3 of the BMS-986016 IB). Most AEs were of low grade (Grade 1 to 2). A total of 91 out of the 876 subjects receiving combination therapy experienced a drug-related serious AE (SAE). Twenty Grade 1 and 31 Grade 2 infusion-related reactions were reported during infusion of the study drug and were manageable using the updated protocol guidelines.

In Studies CA224020, CA224022, and CA224034, a total of 273 deaths occurred in subjects treated with combination therapy (62 deaths within 30 days of last dose, 218 deaths within 135 days of last dose, and 55 deaths occurring > 135 days after last dose of study drug). A total of 19 subjects died for reasons other than disease progression. In Study CA224020, causes of death were reported as study drug toxicity in 3 subjects (Grade 5 dyspnea, Grade 4 myocarditis, and Grade 3 pneumonitis), unknown in 1 subject, and "other" in 13 subjects. In Study CA224022, 1 subject died due to an unknown cause, and 1 subject died due to a cause listed as "other." All other deaths were due to complications of disease progression and were considered by the Investigator to be not related to study drug.

1.4.1.4.3 Clinical Efficacy - Monotherapy (Part A) Versus Combination Therapy (Part B): CA224020 Study

Response Evaluation Criteria In Solid Tumors v1.1 criteria were used in Study CA224020 to evaluate response to treatment. As of the cutoff date of 15-Jun-2017, 25 subjects were treated with BMS-986016 monotherapy. In Part A, no responses were observed in subjects with advanced solid tumors treated with BMS-986016 monotherapy. [redacted]

As of the 16 June 2017 cutoff date, 262 subjects were treated with BMS-986016/nivolumab combination therapy in Part C. Preliminary proof-of-concept efficacy has been revealed in Part C of Study CA224020 in the combination treatment expansion cohort of advanced melanoma with prior treatment with anti-PD-1/PD-L1. The treatment group had the following characteristics: 1) most subjects had M1C disease (68%), 2) the cohort was heavily pretreated (77% with 2 or more prior therapies and 57% with prior anti-CTLA-4 therapy), 3) all subjects had progressed while receiving anti-PD-1/PD-L1, and 4) PD was the best response to prior anti-PD-1/PD-L1 in 46% of subjects. All subjects were treated with 80 mg BMS-986016/ 240 mg nivolumab Q2W. The overall ORR was 11.5% (7/61, response evaluable) with a DCR of 49%. Biomarker analyses suggested that subjects whose TIL expressed more LAG-3 had a higher response rate, with a greater than 3-fold increase in ORR observed in subjects with evidence of LAG-3 expression in at least 1% of nucleated cells within the tumor margin, compared with less than 1% LAG-3 expression (18.2% [6/33] and 5.0% [1/20], respectively). PD-L1 expression did not appear to enrich for response.

These data were presented at the 2017 annual ESMO conference.[43]

1.4.2 Nivolumab (BMS-936558, Anti–PD-1 Antibody)

1.4.2.1 Nonclinical Pharmacology, Metabolism, and Pharmacokinetics

Nivolumab is a fully human, IgG4 (kappa) isotype mAb that binds to PD-1. Additional details are provided in the current version of the nivolumab (BMS-936558) IB and OPDIVO® (nivolumab) package insert.[11,49]

1.4.2.2 Clinical Safety

Nivolumab has been studied in over 17,700 subjects and is widely approved in multiple indications. Extensive details on the safety profile of nivolumab are available in the IB[11] and OPDIVO package insert[49] and will not be repeated herein.

1.4.2.3 Clinical Pharmacokinetics

Details are provided in the current version of the nivolumab (BMS-936558) IB and OPDIVO package insert.[11,49]

1.4.2.4 Clinical Activity

Nivolumab has demonstrated clinical activity in subjects with a variety of malignancies, including melanoma, NSCLC, RCC, urothelial carcinoma, SCLC, gastric and esophageal cancer, HCC, colorectal cancer, glioblastoma, Merkel cell carcinoma, and combined malignant tumors as described in the nivolumab IB (detailed in Section 5.4),[11] appendices (USPI [Appendix 1]) and Summary of Product Characteristics (SmPC [Appendix 2]), and OPDIVO package insert.[49]

1.4.3 BMS-986213 (Fixed-dose Combination Product)

BMS-986213 contains both relatlimab and nivolumab in protein-mass ratio 1:3 in a single vial. Additional details including the formulation are provided in the current version of BMS-936213 IB.[53]

1.5 Overall Benefit-risk Assessment

This section summarizes the potential risks of treatment with relatlimab alone and in combination with nivolumab and the specific tests, observations, and precautions that are required in clinical studies.

As of the clinical cutoff date of 18-Jun-2018, across 3 safety studies (Studies CA224020, CA224022, and CA224034), relatlimab monotherapy has been administered to 66 subjects across doses: 20 mg (8 subjects), 80 mg (13 subjects), 240 mg (27 subjects), and 800 mg (18 subjects) relatlimab flat dose Q2W. The safety profile of relatlimab monotherapy appears manageable, with no MTD reached. The MAD was 800 mg Q2W. Following administration of up to 800 mg relatlimab flat dose in Study CA224022, AEs were mainly Grade 1 and Grade 2, with 4 drug-related Grade 3 to 4 events (anemia, amylase increased, and lipase increased following administration of 240 mg relatlimab, and aseptic meningitis following administration of 800 mg relatlimab). All AEs were reversible or manageable (in the setting of immune-mediated endocrine events) by withholding drug administration and following treatment algorithms specified in the protocols where applicable. There were 5 Grade 1 to Grade 2 infusion-related reactions with relatlimab monotherapy (1 in Study CA224020, 4 in Study CA224022, and 0 in Study CA224034), which were manageable and reversible with recommended treatment guidelines in the protocol. There were 4 drug-related SAEs in monotherapy: Grade 3 pneumonitis, Grade 2 pneumonitis, and Grade 3 allergic reaction in monotherapy in Study CA224020 at a dose of 800 mg relatlimab Q2W; and Grade 3 aseptic meningitis in monotherapy in Study CA224022 at a dose of 800 mg relatlimab Q2W. There was no apparent relationship in the incidence, severity, or causality of AEs to relatlimab at these dose levels. A total of 27 subjects died due to malignant neoplasm progression following relatlimab monotherapy (19 in Study CA224020, 7 in Study CA224022, and 1 in Study CA224034).

As of the clinical cutoff date of 18-Jun-2018, treatment with relatlimab in combination with nivolumab has been administered to 876 subjects in Studies CA224020 (812 subjects), CA224022 (45 subjects), and CA224034 (19 subjects). The safety profile of relatlimab combined with nivolumab is manageable, with currently no MTD reached, as combination dose evaluation remains ongoing.

Across Studies CA224020, CA224022, and CA224034 for both monotherapy and combination therapy, drug-related AEs were reported in 528 subjects. The most frequent drug-related AEs included fatigue, decreased appetite, pruritus, diarrhea, rash, rash maculopapular, anemia, asthenia, hypothyroidism, and hyperthyroidism. The types of drug-related AEs, as well as the rates of drug-related AEs, appeared comparable to historical nivolumab monotherapy rates. All drug-related AEs, except for 1 Grade 4 myocarditis (240 mg relatlimab/240 mg nivolumab Q2W) as well as 1 Grade 4 potential drug-induced liver injury (DILI), 1 Grade 5 dyspnea, and 1 Grade 3 pneumonitis (all at a dose level of 80 mg relatlimab/240 mg nivolumab Q2W), were reversible or manageable by withholding study drug administration, providing standard medical care, and/or following immune-related AE (irAE) algorithms.[29]

There is risk associated with tumor biopsies, including bleeding, infection, and pain. While there is no direct benefit to subjects who undergo these procedures, there is significant potential that data generated from these samples will guide the further development of these compounds and may be of direct benefit for others with advanced solid tumors. In particular, emerging evidence from tissue analysis is showing an enrichment of response in subjects expressing higher LAG-3 protein levels in tumor-associated immune cells.

The potential direct benefit to subjects who participate in the CA224020 study is that both single-agent and combined therapy with these investigational agents may result in a greater proportion of subjects with stabilization of disease, objective response, or increased DOR than those observed with nivolumab monotherapy. It is also possible that combination therapy may reverse LAG-3-mediated T cell exhaustion and achieve responses in 1) tumor types known to be unresponsive to nivolumab, 2) tumors refractory to anti-CTLA-4 and anti-PD-1 or anti-PD-L1 antibody therapy, and/or 3) virally associated tumors. In fact, multiple RECIST v1.1–defined clinical responses have been observed with BMS-986016 in combination with nivolumab, both in the immunotherapy naive as well as the anti-PD-1 resistant setting. More specifically, updated disclosure of the initial efficacy at ESMO 2017 showed an ORR of 11.5% in advanced melanoma subjects that have progressed on prior anti-PD-1/PD-L1, with an even more encouraging ORR of 18% in subjects with significant LAG-3 expression in tumor-associated immune cells. Thus, the potential for direct benefit in subjects with few if any alternative treatment options has been initially demonstrated, warranting continued evaluation of the combination across tumor types.

Lastly, the FDC drug product BMS-986213, with both relatlimab and nivolumab administered from the same vial, offers increased ease and speed of preparation with decreased opportunity for dosing errors. Given the theoretical risk of infusion reactions with the new formulation, an acute safety lead-in will be employed with continued monitoring for 1 hour after the completion of all infusions.

The effect of coronavirus disease 2019 (COVID-19) vaccines in participants taking relatlimab in combination with nivolumab is unknown. BMS has given consideration regarding the benefit-risk of COVID-19 vaccination during participation in BMS-986016 (relatlimab) and BMS-936558 (nivolumab) clinical trials. Based on the review of current available data and evidence to date, knowledge of the mechanisms of action of the COVID-19 vaccines and relatlimab in combination with nivolumab investigational medicinal product (IMP), a biological or pharmacological interaction occurring between the vaccine and the IMP that would negatively impact the benefit-risk for participants in BMS relatlimab in combination with nivolumab clinical trials is not expected; however, data will continue to be reviewed. Therefore, at this time, a COVID-19 vaccine given to subjects in this trial is considered a concomitant medication with no interaction.

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

This study will be conducted in accordance with:

- Consensus ethical principles from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines Good Clinical Practice (GCP);
- as defined by the International Council for Harmonisation (ICH); and
- in accordance with the ethical principles underlying European Union Regulation 536/2014,
- United States Code of Federal Regulations, Title 21, Part 50 (21CFR50), and
- applicable local requirements.

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subjects' informed consent forms (ICFs) will receive approval/favorable opinion by IRB/IEC and regulatory authorities according to applicable local regulations prior to initiation of the study.

All potential serious breaches must be reported to Bristol-Myers Squibb (BMS) immediately. A serious breach is a breach of the conditions and principles of GCP (occurring in any country) 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 1 or more subjects of the study or the scientific value of the study.

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

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

2.2 Institutional Review Board/Independent Ethics Committee

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

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

2.3 Informed Consent

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

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

BMS will provide the Investigator with an appropriate (ie, global or local) sample ICF, which will include all elements required by ICH, GCP, and applicable regulatory requirements. The sample ICF 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 subject is most proficient prior to clinical study participation. The language must be nontechnical and easily understood.

Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.

Obtain an ICF signed and personally dated by the subject or the subject'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 ICF 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 subject's legally acceptable representative or legal guardian and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject.

Revise the ICF whenever important new information becomes available that is relevant to the subject's consent. The Investigator, or a person designated by the Investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects' signed ICF and, in the US, the subjects' signed Health Insurance Portability and Accountability Act (HIPAA) Authorization.

The consent form must also include a statement that BMS and regulatory authorities have direct access to subject 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 ICF 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.

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

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

This is a Phase 1/2a, open-label study of BMS-986016 (relatlimab) administered as a single agent and in combination with nivolumab to subjects with advanced solid tumors. **Part A and Part B** consist of a 3 + 3 + 3 dose escalation design and, implemented in the site-specific amendment #15 (dated 13 August 2018) and superseding the 3+3+3 dose escalation design, the BLRM-Copula design (for Part B only), evaluating BMS-986016 administered as a single agent (Part A) or in combination with nivolumab (Part B) as sequential infusions in subjects with advanced solid tumors. Treatment in Part B will be initiated upon the decision to escalate to the third dose cohort in Part A (in accordance with dose escalation rules); subsequently, escalation in the 2 parts will proceed in parallel. Testing of the Q2W and Q4W dosing schedules in Part B can proceed concurrently, with independent escalation decisions based upon review of the current total safety experience and following consultation and agreement between Investigators and the Sponsor.

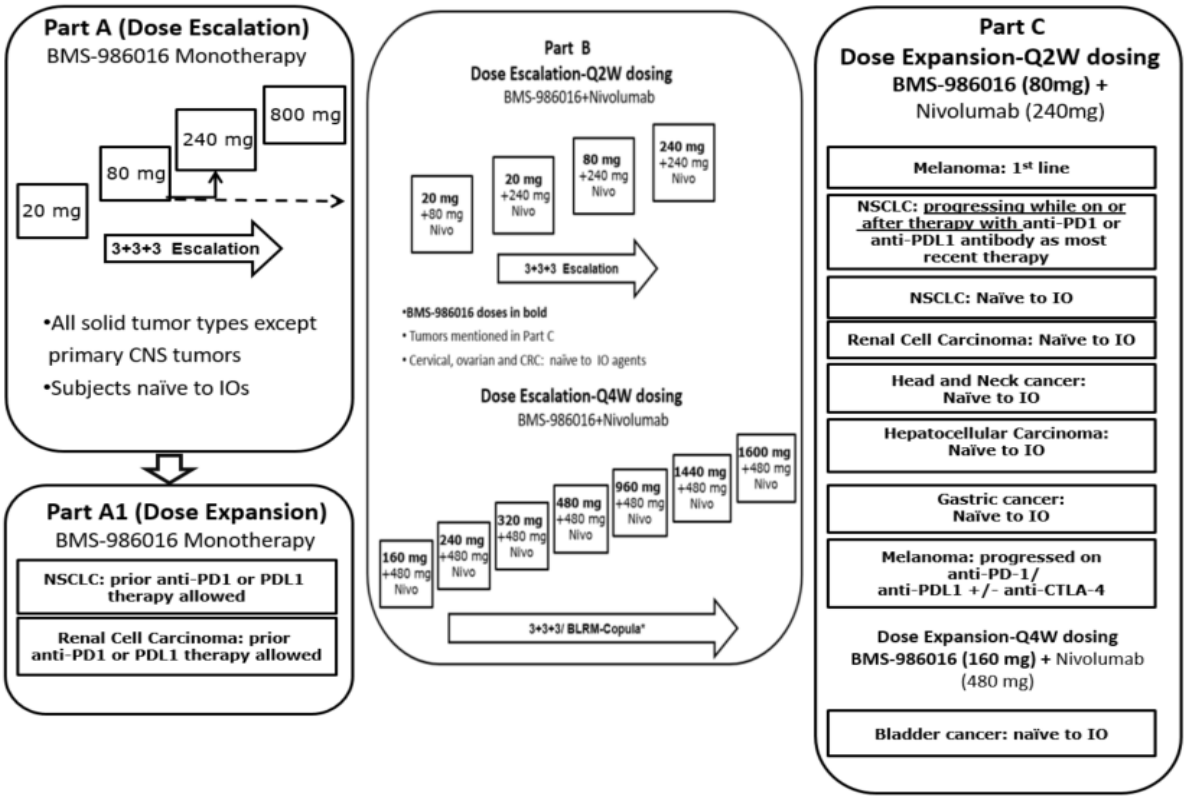
Part A1 consists of cohort expansion with BMS-986016 monotherapy in 2 disease-restricted cohorts of approximately 6 to 12 subjects each. Treatment in Part A1 will be initiated at the MAD determined in Part A (ie, 800 mg). The dose selected for Part A1 will not exceed the MAD in Part A, but dose selection may change according to assessment of other data, including toxicities and PK and pharmacodynamic data from Parts A and A1. Subjects in Part A1 who progress on monotherapy may cross over to combination therapy with nivolumab and BMS-986016 as long as they meet eligibility criteria and the benefit-risk ratio is considered favorable by the Investigator and the Medical Monitor. Subjects will receive combination therapy in sequential infusion at the doses that have been declared safe in dose escalation or dose expansion parts at the time of crossover. The original protocol rules will apply accordingly. Combination therapy may thus be administered for up to 12 additional 8-week cycles according to the protocol rules. Collection of archival tissue (baseline) and tumor biopsies (baseline and on-therapy) will be optional for subjects crossing over, and PK and biomarker monitoring will be limited (Sections 5.5 and 5.7).

Part B treatment will be initiated after the decision is made to escalate to the third dose cohort in Part A (in accordance with dose escalation rules). See Section 3.1.1.2.

Part C consists of cohort expansion in disease-restricted cohorts using a multistage approach, treated with sequential infusion of nivolumab and BMS-986016. Cohorts deemed futile (Section 8.1.2) at Stage 1 will be discontinued. Cohorts deemed promising may be expanded further up to 90 to 120 subjects in total after careful evaluation of all available data, including the totality of efficacy, safety profile, and PK/pharmacodynamics. Otherwise, additional subjects may be treated to collect more data during Stage 2 in order to make decision for further expansion. The doses and schedule selected for Part C will not exceed the Part B MTD or MAD, and specific doses selected may incorporate assessment of other data including toxicities, PK, and pharmacodynamic data from Parts A and B. Subjects who crossed over to combination therapy in Part A1 and subsequently have an objective response will not be considered in the decision making for Part C. Subjects in Part C cannot cross over to Part A1 either. A study schematic for Parts A-C is provided in Figure 3.1-1.

Part D consists of melanoma subjects who progressed on prior IO therapy. There is a Part D1 and a Part D2 within Part D. Most subjects in Part D will receive coadministration of BMS-986016 and nivolumab. Part D1 employs a focused eligibility to build upon eligible subjects from the Part C melanoma prior IO cohort, with the primary goal of testing the efficacy of 80 mg BMS-986016 + 240 mg nivolumab Q2W. Enrollment may continue until the following criteria are met: (a) 90 efficacy-evaluable LAG-3–positive subjects have been treated, (b) 60 efficacy-evaluable LAG-3–positive and BRAF wild-type (WT) subjects have been treated, and (c) 60 efficacy-evaluable LAG-3–positive and ipilimumab pretreated subjects have been treated. Part D1 will also have 2 other cohorts: 1) 160 mg BMS-986016 with 480 mg of nivolumab Q4W coadministration and 2) a cohort of BMS-986213 (relatlimab 160 mg/nivolumab 480 mg) Q4W. If subjects do not meet the more focused eligibility of Part D1, they may be eligible for Part D2, which is more flexible with respect to the allowed prior therapies and performance status. Part D2 will test safety and efficacy in this broader patient population and will employ the more convenient Q4W dosing in 2 different dose combinations (160 mg BMS-986016 + 480 mg nivolumab, and subsequently, 240 mg BMS-986016 + 480 mg of nivolumab). Adolescents (12 to < 18 years of age) weighing less than 40 kg will receive weight-based dosing (see Section 1.1.9.8). The doses and schedule selected for Part D will not exceed the Part B MTD or MAD, and dosing of the cohorts may be altered in collaboration between the Investigators and Sponsor, based upon the overall ongoing study data, including toxicities, PK, and pharmacodynamics. A schematic of Part D is provided in Figure 3.1-2.

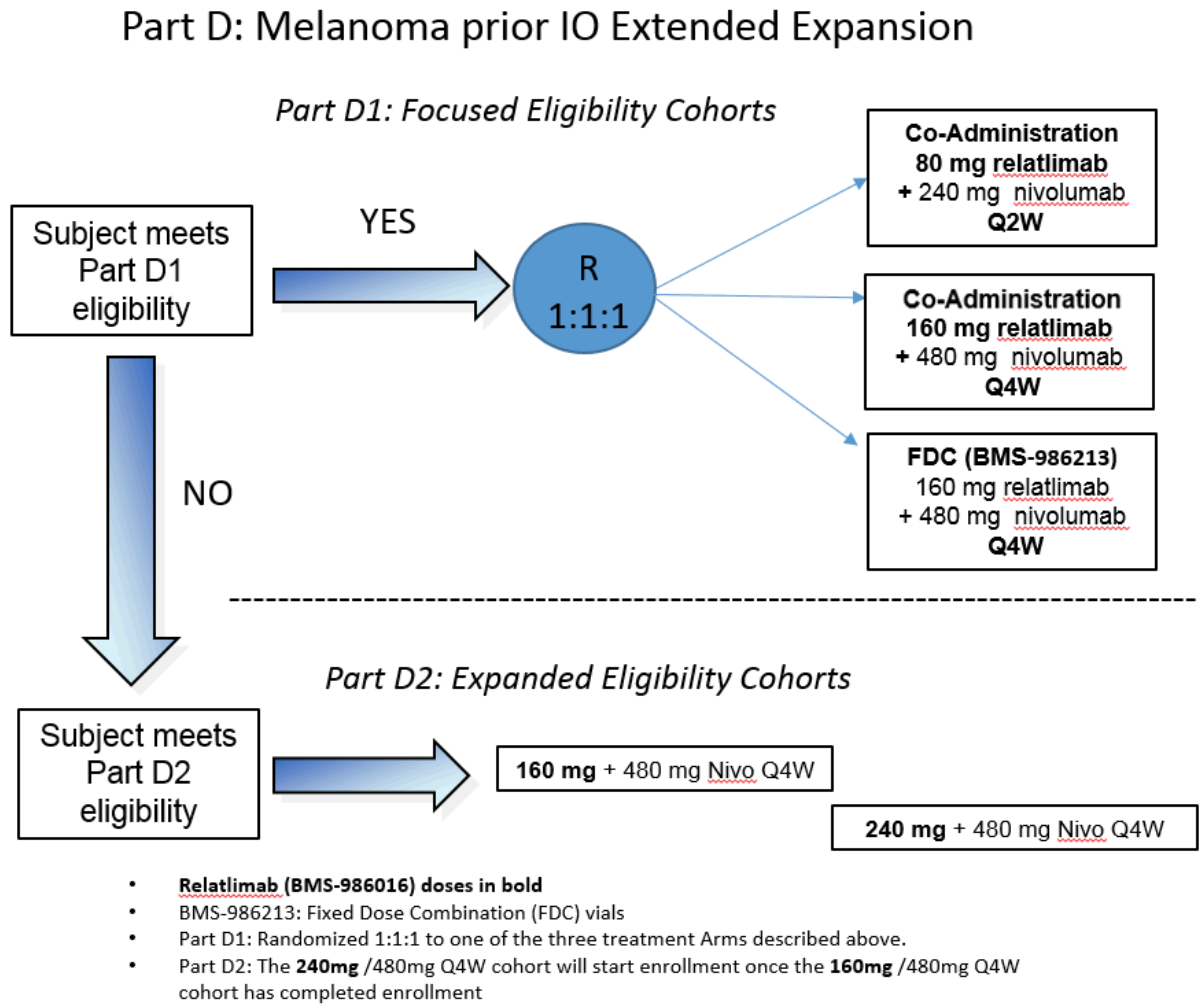
Figure 3.1-1: CA224020 Study Schematic



Sequential = sequential administration of nivolumab first followed by BMS-986016 infusion within 15 to 30 minutes of completing nivolumab infusion. For doses of 960 mg relatlimab + 480 mg nivolumab Q4W and higher doses, BMS-986016 infusion should be administered no sooner than 30 minutes following completion of nivolumab infusion.
IO = immuno-oncology agents (such as, but not limited to, anti-CTLA-4, anti–PD-1, anti–PD-L1, anti–PD-L2, anti-KIR, anti-CD137, anti-LAG-3, and/or anti-OX40 antibodies).

* Subsequent to site-specific amendment #15 (dated 13 August 2018), the dose escalation design was changed to BLRM-Copula from the 3 + 3 + 3 design.

Figure 3.1-2: Part D



Part E consists of advanced melanoma participants. Two cohorts of melanoma participants will be enrolled in Part E: melanoma participants who experienced disease progression on prior anti-PD-1 therapy and melanoma participants who have not received prior systemic anticancer therapy for unresectable or metastatic melanoma.

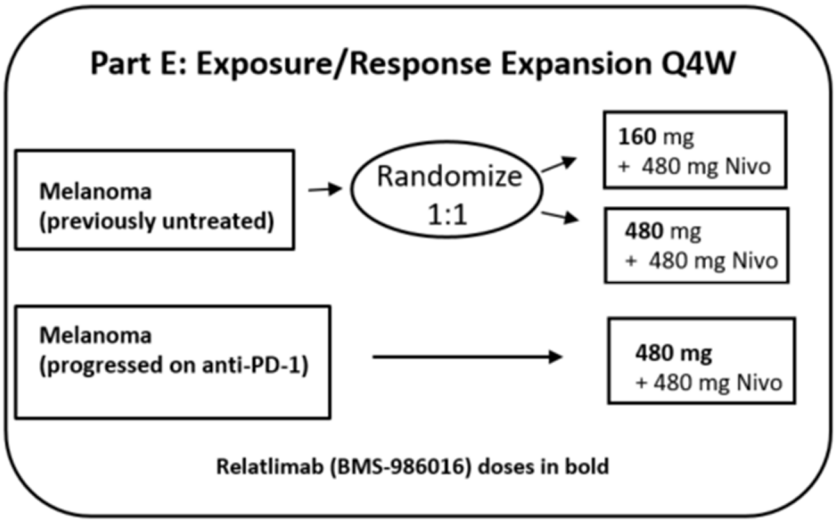
Melanoma participants who experienced disease progression on prior anti-PD-1 therapy will all receive the 480 mg BMS-986016 + 480 mg nivolumab Q4W dose regimen.

Melanoma participants who have not have not received prior systemic anticancer therapy for unresectable or metastatic melanoma will be randomized to 1 of the 2 following treatment arms:

- 160 mg BMS-986016 + 480 mg nivolumab Q4W
- 480 mg BMS-986016 + 480 mg nivolumab Q4W

A schematic for Part E is presented in Figure 3.1-3.

Figure 3.1-3: Part E



Subjects will complete up to 4 periods of the study: **Screening** (up to 28 days), **Treatment**, **Clinical Follow-up** (135 days), and **Survival Follow-up** (up to 5 years following the first dose of study drug). Two independent periods, **Crossover** and **Rechallenge**, may be conducted in selected cases upon disease progression. **As of Protocol Amendment 14, rechallenge is not permitted.**

In the **Treatment Period**, each treatment cycle comprises 4 doses of either BMS-986016 alone (Parts A and A1) or in combination with nivolumab (Part B and C except bladder cohort), administered on Days 1, 15, 29, and 43 of each treatment cycle. [redacted] In Parts B and C, when both study drugs are given as sequential infusion, nivolumab will be given first, followed by BMS-986016 within 15 to 30 minutes of completing the infusion of nivolumab. In Part B, for doses of 960 mg relatlimab + 480 mg nivolumab Q4W and higher doses, BMS-986016 infusion should be administered no sooner than 30 minutes following completion of nivolumab infusion. Part D, the melanoma prior IO extended expansion, will have 2 sections: Part D1 will have a focused eligibility criteria with a cohort of 80 mg of BMS-986016 with 240 mg nivolumab Q2W, a cohort of 160 mg BMS-986016 with 480 mg of nivolumab Q4W, and a cohort of BMS-986213 (relatlimab 160 mg/nivolumab 480 mg) Q4W; and Part D2 will have an expanded eligibility

criteria with 2 cohorts in sequence, 160 mg BMS-986016 with 480 mg of nivolumab Q4W and 240 mg BMS-986016 and 480 mg of nivolumab Q4W. In Part D, both study drugs are given as a coadministration or as FDC over approximately 60 minutes.

In Part E, melanoma subjects will be administered either 160 mg BMS-986016 with 480 mg nivolumab Q4W or 480 mg BMS-986016 with 480 mg of nivolumab Q4W; the specific dosing regimen will be dependent on 1) whether the subject previously received anti-PD-1 therapy in the advanced, unresectable, or metastatic setting and had PD on that earlier treatment regimen; and 2) randomization, as previously described.

Adolescents (12 to < 18 years of age) weighing less than 40 kg will be dosed based on weight (1 mg/kg BMS-986016 and 3 mg/kg nivolumab Q2W, 2 mg/kg BMS-986016 and 6 mg/kg nivolumab Q4W, or 6 mg/kg BMS-986016 and 6 mg/kg nivolumab Q4W. In Parts C, D, and E, Q4W dosing, BMS-986016 and nivolumab will be administered on Days 1 and 29 of each treatment cycle; visits will occur every 2 weeks to assess safety for the first cycle of treatment, and thereafter visits will only be on Day 1 and Day 29 of each subsequent cycle. [redacted] Tumor response will be evaluated using RECIST v1.1.

Subjects will be allowed to continue study therapy until the first occurrence of either 1) PD, 2) clinical deterioration, and/or 3) meeting other criteria for discontinuation. Refer to Section 3.5 for additional details. Treatment beyond progression should be considered in select participants with initial RECIST v1.1-defined PD who are receiving clinical benefit as assessed by the Investigator, tolerating treatment, and meeting other criteria specified in Section 4.3.4. Follow-up imaging should be obtained to confirm progression where appropriate (see Section 5.1). Subjects who discontinue treatment will enter a 135-day **Clinical Follow-up** period.

After completion of the Clinical Follow-up period, subjects enter the **Survival Follow-up** period. During this period, clinic visits or telephone contact every 12 weeks will be performed to assess survival status. Survival follow-up visits will be scheduled based on the last clinical follow-up visit. **Diagnostic imaging must be performed every 8 weeks until disease progression. For subjects who discontinue treatment at the Investigator's discretion with a CR, PR, or stable disease (SD) by RECIST v1.1, imaging must be performed every 12 weeks until disease progression.** The duration of this period may continue for up to 5 years from the first dose.

For patients remaining on treatment beyond 5 years, subjects may continue on study treatment, as long as the benefit-risk ratio is considered favorable by the Investigator and continues to meet the criteria outlined in the protocol. Patients who discontinue treatment before 5 years will complete a 135-day clinical follow-up period, and a survival follow-up period for up to 5 years after the first dose. Patients who continue study treatment for longer than 5 years will complete a 135-day clinical follow-up period once the criteria for treatment discontinuation are met, but will not

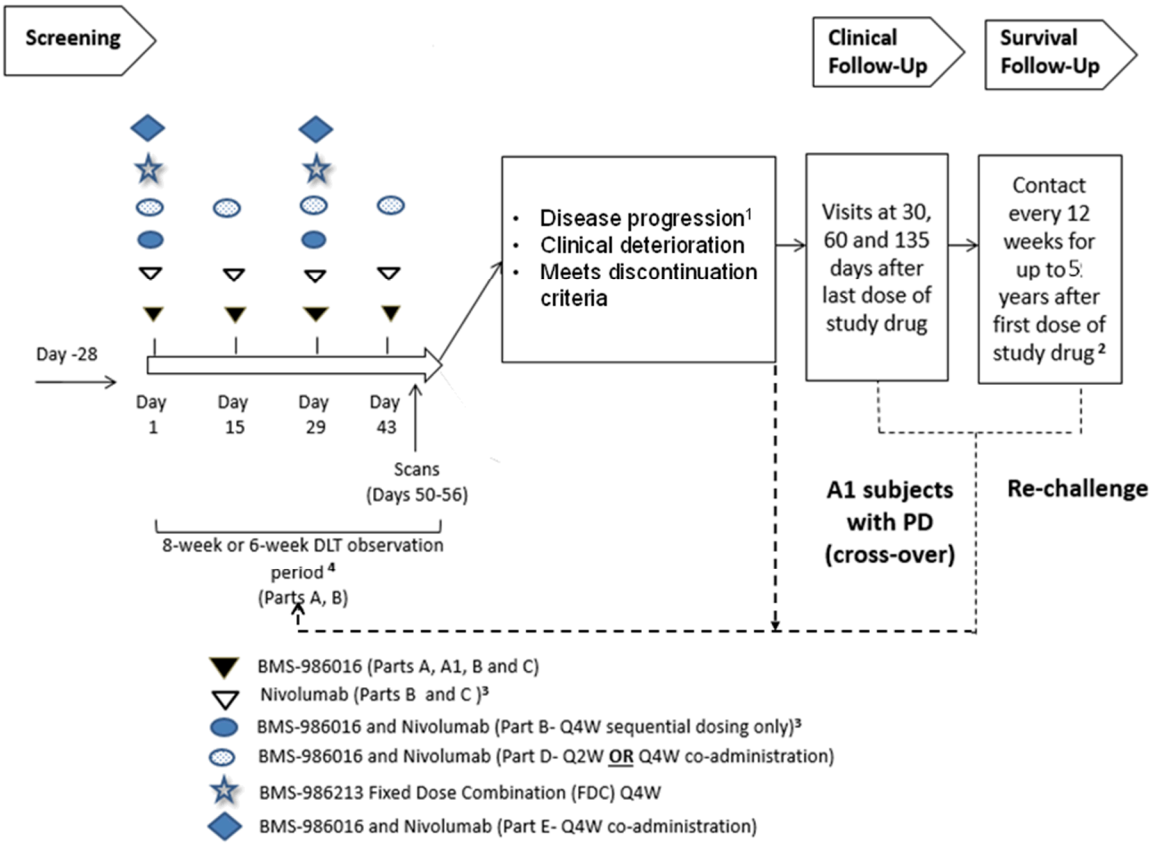
participate in a survival follow-up period. The study will end when all patients have completed their respective follow-up periods. The original dose, schedule and protocol rules would apply.

If subjects progress during the Clinical Follow-up period or the Survival Follow-up period, they could further receive therapy with BMS-986016 alone or in combination therapy (**Rechallenge** period) as long as the benefit-risk ratio is considered favorable by the Investigator and the Medical Monitor and eligibility criteria is met (Section 3.1.2.4). The rechallenge-eligible Survival Follow-up may continue for up to 5 years from the first dose of study drug. The original dose, schedule, and protocol rules would apply. Subjects will not be rechallenged a second time. Collection of archival tissue (baseline) and tumor biopsies (baseline and on-treatment) will be optional for subjects enrolled for rechallenge. Pharmacokinetic and biomarker monitoring will be limited (Sections 5.5 and 5.7). **As of Protocol Amendment 14, rechallenge is not permitted.** All subjects who discontinue primary study treatment following implementation of Protocol Amendment 14 will not be eligible for rechallenge. Subjects currently receiving rechallenge treatment will be allowed to continue, and subjects currently in the rechallenge-eligible Survival Follow-up as of this Protocol Amendment remain eligible for rechallenge.

Also, subjects receiving therapy with BMS-986016 alone in expansion Part A1 may cross over to combination therapy at confirmed progression (Section 3.1.2.1).

A study schematic is provided in Figure 3.1-4.

Figure 3.1-4: Detailed Study Schematic



[1] Treatment beyond progression may be considered in select subjects as described in Section 4.3.4.

[2] Diagnostic imaging must be performed every 8 weeks until disease progression, and in subjects who discontinue study treatment at the Investigator's discretion with a CR, PR, or SD via RECIST v1.1, imaging must be performed every 12 weeks until disease progression.

[3] For treatment visits in Parts B and C where BMS-986016 (relatlimab) and nivolumab are administered sequentially, nivolumab will be administered first over 30 minutes, followed by BMS-986016 administration within 15 to 30 minutes after completion of the nivolumab infusion. For doses of 960 mg relatlimab + 480 mg nivolumab Q4W, BMS-986016 infusion should be administered no sooner than 30 minutes following completion of nivolumab infusion.

[4] Note the 6-week DLT period will be initiated after completion of the 480 mg BMS-986016 dose level.

Note: As of Protocol Amendment 14, rechallenge is not permitted.

Assessments, including physical examinations, vital sign measurements, 12-lead electrocardiogram (ECG), and clinical laboratory evaluations, will be performed at selected times throughout the dosing interval. Subjects will be closely monitored for AEs throughout the study. Blood samples will be collected for up to 4 hours following the start of study drug administration for PK analysis.

Subjects will be allowed to continue on therapy until PD, clinical deterioration, or meeting criteria for discontinuation. Patients who discontinue treatment before 5 years will complete a 135-day clinical follow-up period, and a survival follow-up period for up to 5 years after the first dose. Patients who continue study treatment for longer than 5 years will complete a 135-day clinical follow-up period once the criteria for treatment discontinuation are met, but will not participate in a survival follow-up period. The study will end when all patients have completed their respective follow-up periods. Additional OS analysis may be conducted periodically until end of study.

3.1.1 Dose Escalation

3.1.1.1 Part A - Monotherapy

In Part A, a 3 + 3 + 3 design will be used to assess the safety of BMS-986016 given as single agent. A fourth subject may be enrolled at the beginning of a dose escalation cohort following agreement between the Investigator and the Sponsor/Medical Monitor, if the subject is able to start the first day of dosing within approximately 1 week of the third subject in the same dose escalation cohort.

The dosages during dose escalation are provided in Figure 3.1-1 and Table 3.1.1.1-1.

Three subjects (or 4, if applicable) will initially be treated in each dose cohort; in Dose Cohort 1, each of the first 3 subjects (or 4, if applicable) will be designated as sentinel subjects and will begin treatment at least 5 days apart. Subjects in subsequent cohorts will not be required to observe the 5-day interval between treatment start dates.

Dose escalation in Part A will proceed as follows:

If 0 of the first 3 (or 4, if applicable) subjects experiences a DLT within the DLT evaluation interval, a new cohort of 3 subjects (or 4, if applicable) will be treated at the next higher dose level.

If 1 of 3 (or 4, if applicable) subjects experiences a DLT within the DLT evaluation interval, that cohort will be expanded to 6 subjects (or 7, if applicable).

If 2 of 6 (or 7, if applicable) subjects experience a DLT within the DLT evaluation interval, that cohort will be expanded to 9 subjects.

If ≥ 2 of 3 (or 4, if applicable), ≥ 3 of 6 (or 7, if applicable), or ≥ 3 of 9 subjects experience DLTs within a dose cohort during the DLT evaluation interval, then that dose level will be determined to have exceeded the MTD.

Table 3.1.1.1-1: Dose Escalation and Dose Expansion Schedules for Part A and Part A1 BMS-986016 Monotherapy

Part A Dose Escalation Cohort Number	Total Subjects	BMS-986016 Dose (IV; mg)
1	n = approximately 3-9	20
2	n = approximately 3-9	80
3	n = approximately 3-9	240
4	n = approximately 3-9	800
Total	N = approximately 12-36	
Part A1 Dose Expansion Cohorts		
NSCLC: prior anti-PD-1 or PD-L1 therapy allowed[a]	n = approximately 6-12	800
RCC: prior anti-PD-1 or PD-L1 therapy allowed[a]	n = approximately 6-12	800
Total	N = approximately 12-24	

[a] See Section 3.3 for detailed eligibility criteria.

Prior to declaring the MTD (or MAD), and in consultation with Investigators, the Sponsor has the option to expand any cohort previously established to be safe in order to obtain additional experience or to investigate dose levels intermediate to those defined in the protocol. Dose escalation rules (cohort size, DLT evaluation interval, cohort expansion criteria, etc.) will apply to these expanded or additional cohorts. A maximum of 9 subjects will be enrolled in any additional or expanded dose cohorts.

No within-subject dose escalations will be permitted. If a dose level is found to exceed the MTD, subjects enrolled in that dose level may be treated at a lower dose following consultation and agreement between Investigators and the Sponsor.

3.1.1.2 Part B - Sequential Infusion

Treatment in Part B will be initiated after the decision is made to escalate to the third dose cohort in Part A (in accordance with dose escalation rules). Subsequently, escalation in the 2 parts will

proceed in parallel. Treatment assignments for subjects eligible for both Part A and Part B will alternate between the 2 parts, with consecutively treated subjects assigned to different parts through interactive voice response system (IVRS) whenever possible. If there are no openings available in the part to which the subject would be assigned by this algorithm, then the subject will be assigned to the next open cohort or part.

As in Part A, a 3 + 3 + 3 design, or a BLRM-Copula design, as implemented in the site-specific amendment #15 (dated 13 August 2018) and superseding the 3 + 3 + 3 dose escalation design will also be used in Part B to assess the safety of BMS-986016 given in combination with nivolumab as a sequential infusion. A fourth subject may be enrolled at the beginning of a dose escalation cohort following agreement between the Investigator and the Sponsor/Medical Monitor, if the subject is able to start the first day of dosing within approximately 1 week of the third subject in the same dose escalation cohort. The potential dose levels evaluated during dose escalation are provided in Table 3.1.1.2-1. Intermediate and lower dose levels may be assessed following agreement between the Investigator and the Sponsor/Medical Monitor based upon ongoing review of safety data.

Table 3.1.1.2-1: Dose Escalation Schedule for Part B — BMS-986016 in Combination with Nivolumab Q2W and Q4W

Dose Cohort Number	Total Subjects	BMS-986016 Dose (IV; mg)	Nivolumab Dose (IV; mg)
	Dose Escalation Schedule for Part B — BMS-986016 in Combination with Nivolumab Q2W Dosing		
1	n = approximately 3-9	20	80
2	n = approximately 3-9	20	240
3	n = approximately 3-9	80	240
Intermediate	n = approximately 3-9	160	240
4	n = approximately 3-9	240	240
	Dose Escalation Schedule for Part B — BMS-986016 in Combination with Nivolumab Q4W Dosing		
1	n = approximately 3-9	160	480
2	n = approximately 3-9	240	480
3	n = approximately 3-9	320	480
4	n = approximately 3-12	480	480
5	n = approximately 3-15	960	480
6	n = approximately 3-15	1440	480
7	n = approximately 3-15	1600	480
Total	**N = approximately 36-120**		

Three subjects (or 4, if applicable) will be treated initially in each dose cohort; in Dose Cohort 1, each of the first 3 subjects (or 4, if applicable), designated as sentinel subjects, will begin treatment at least 5 days apart. Subjects in subsequent cohorts will not be required to observe the 5-day interval between treatment start dates.

In Part B, if the MTD is exceeded in Dose Cohort 2, the potential subsequent cohort will be treated with 80 mg BMS-986016 and 80 mg nivolumab. If this dose combination is found to be safe, following consultation and agreement between Investigators and the Sponsor, escalation may proceed at the previously defined BMS-986016 doses, maintaining the nivolumab dose at 80 mg, or an intermediate dose level. Testing of the Q2W and Q4W dosing schedules can proceed concurrently with independent escalation decisions based upon review of the current total safety experience and following consultation and agreement between Investigators and the Sponsor.

Prior to declaring the MTD (or MAD), and in consultation with Investigators, the Sponsor has the option to expand any cohort previously established to be safe in order to obtain additional experience or to investigate dose levels intermediate to those defined in the protocol. Dose escalation rules (cohort size, DLT evaluation interval, cohort expansion criteria, etc.) will apply to these expanded or additional cohorts. A maximum of 9 (or 15, in case of BLRM-Copula) subjects will be enrolled in any additional or expanded dose cohorts.

No within-subject dose escalations will be permitted. If a dose level is found to exceed the MTD, subjects enrolled in that dose level may be reduced to a lower dose following consultation and agreement between Investigators and the Sponsor.

3.1.2 Cohort Expansion

3.1.2.1 Cohort Expansion (Part A1) - Monotherapy

The purpose of cohort expansion is to gather additional safety, tolerability, preliminary efficacy, PK, and pharmacodynamic information of BMS-986016 monotherapy. The doses selected for Part A1 will not exceed the MTD or MAD in Part A but may incorporate assessment of other data, including toxicities and PK and pharmacodynamic data from Part A. Doses to be considered may include doses intermediate to those evaluated in Part A, if recommended by the Investigators and the Sponsor. Two expansion cohorts will be restricted to the tumor types listed in Table 3.1.1.1-1.

Subjects with PD in Part A1 may cross over to combination therapy with sequential infusion of nivolumab and BMS-986016 if the following criteria are met: 1) subject has confirmed disease progression (investigator-assessed RECIST v1.1–defined progression confirmed at least 4 weeks after the initial tumor assessment showing progression); 2) subject has not experienced BMS-986016–related AEs leading to permanent discontinuation; 3) subject is not continuing to derive any clinical benefit from BMS-986016 single-agent therapy as assessed by the Investigator; 4) the individual case has been discussed with the Medical Monitor prior to crossover; 5) at least an 8-week period between the last dose of monotherapy and the first dose of combination therapy. Subjects crossing over to combination therapy will start treatment at Cycle 1 Day 1 as described for subjects in Part C. Subjects who cross over will receive combination therapy in sequential infusion at the doses that have been declared safe in dose escalation and/or dose expansion parts at the time of crossover. The original protocol rules will apply accordingly. Combination therapy

may thus be administered for up to 12 additional 8-week cycles according to the protocol rules. Subjects who crossed over and subsequently have an objective response in combination therapy will not be considered in the decision making for Part C. Subjects in Part C cannot cross over to Part A1.

Collection of archival tissue (baseline) and tumor biopsies (baseline and on-therapy) will be optional in subjects crossing over, and PK and biomarker monitoring will be limited (Sections 5.5 and 5.7).

3.1.2.2 Cohort Expansion (Part C) - Sequential Infusion

The purpose of cohort expansion is to gather additional safety, tolerability, preliminary efficacy, PK, and pharmacodynamic information in subjects treated with sequential infusion of nivolumab followed by administration of BMS-986016. The initial doses selected for specific Part C cohorts will not exceed the MTD (or MAD if no MTD is determined) in Part B but may incorporate consideration of other data, including (but not necessarily limited to) toxicities, PK, and pharmacodynamic data from Parts A and B and can be chosen while additional Part B dose escalation cohorts continue to be explored. Part C expansion cohort doses to be considered will include those doses shown to be safe in Part B (or intermediate to those doses) as recommended by the Investigators and the Sponsor. Dosing of subsequent patients within an expansion cohort, or between cohorts, can be increased (if deemed safe in Part B) or decreased (based upon ongoing reviews of the totality of the safety data), all to be decided in agreement between the Investigators and the Sponsor. There will be no dose adjustments for individual subjects. Expansion cohorts in Part C will be restricted to 7 tumor types in 8 cohorts (Section 3.1). Efficacy analyses in all cohorts will be guided by a multistage evaluation approach. Cohorts deemed futile at Stage 1 will be discontinued, whereas those deemed promising may be expanded up to 90 to 120 subjects in total after careful evaluation of all available data, including the totality of efficacy, safety profile, and PK/pharmacodynamics (Section 8.1.2). Otherwise, additional subjects may be treated to collect more data during Stage 2 in order to make a decision for further expansion. Enrollment to Stage 2 or further expansion in a given cohort can continue even if the other cohorts are still in Stage 1. Subjects who crossed over to combination therapy in Part A1 and subsequently have an objective response will not be considered in the decision making for Part C. Subjects in Part C cannot crossover to Part A1 either.

3.1.2.3 All Cohort Expansion Parts (A1, C, D, and E)

Continuous evaluation of toxicity events in the cohort expansions will be performed throughout enrollment in the expansion cohorts. **Not applicable as per Protocol Amendment 14:** Safety conference calls with the BMS Medical Monitor, Investigators, and representatives of the Sponsor are being held regularly during conduct of the study. In addition, separate BMS Medical Safety Teams routinely review safety signals across the BMS-986016 and nivolumab programs. If, at any time, the aggregate rate of treatment-related toxicities meeting DLT criteria exceeds 33% across all subjects treated in any of these cohort expansions, the findings will be discussed and further enrollment must be interrupted in that particular cohort and other relevant cohorts. Depending on the nature and grade of the toxicity and after assessing the benefit-risk ratio, a new dose(s) for all

cohorts may be initiated at a previously tested lower dose level or at a dose level intermediate to previously tested lower dose levels.

3.1.2.4 Rechallenge in Dose Escalation (Parts A and B) and Cohort Expansion Parts (A1, C, D, and E)

If, after discontinuing study treatment at the Investigator's discretion, subjects progress during the Clinical Follow-up period or the Survival Follow-up period, subjects could further receive therapy with BMS-986016 alone or in combination therapy (**Rechallenge**) as long as the benefit-risk ratio is considered favorable by the Investigator and the Medical Monitor and the following eligibility criteria are met: 1) subject has confirmed disease progression (Investigator-assessed RECIST v1.1–defined progression confirmed at least 4 weeks after the initial tumor assessment showing progression); 2) subject has not experienced BMS-986016–related AEs leading to permanent discontinuation. The rechallenge-eligible Survival Follow-up may continue for up to 5 years from the first dose of study drug. The original dose and schedule of therapy and protocol rules will apply. For the rechallenge, collection of archival tissue (baseline) and tumor biopsies (baseline and on-therapy) will be optional and PK and biomarker monitoring will be limited (Sections 5.5 and 5.7). **As of Protocol Amendment 14, rechallenge is not permitted.** All subjects who discontinue primary study treatment following implementation of Protocol Amendment 14 will not be eligible for rechallenge. Subjects currently receiving rechallenge treatment will be allowed to continue, and subjects currently in the rechallenge-eligible Survival Follow-up as of this protocol amendment remain eligible for rechallenge.

Subjects who are rechallenged and who subsequently have an objective response will not be included in the primary analysis of efficacy. Responses to rechallenge will be evaluated in a separate analysis. Subjects will not be rechallenged a second time.

3.1.2.5 Part D Melanoma Prior IO Extended Expansion (Coadministration or Treatment with Fixed-dose Combination [BMS-986213])

In Part D, advanced melanoma subjects with progression on prior anti-PD-1 therapy will be enrolled into 2 subparts, D1 and D2, based on eligibility criteria. If eligible for the focused (more restricted eligibility) D1 subpart, subjects will be randomized across 3 arms:

Arm 1: BMS-986016 80 mg + nivolumab 240 mg given by coadministration Q2W

Arm 2: BMS-986016 160 mg + nivolumab 480 mg given by coadministration Q4W

Arm 3: BMS-986213 (relatlimab 160 mg/nivolumab 480 mg) given Q4W; BMS-986213 contains both relatlimab and nivolumab in the same solution at a ratio of 1:3 (relatlimab:nivolumab)

Randomization will be unblinded. Enrollment and randomization to Arm 1 may continue until the following criteria are met: (a) 90 efficacy-evaluable LAG-3–positive subjects have been treated, (b) 60 efficacy-evaluable LAG-3–positive and BRAF WT subjects have been treated, and (c) 60 efficacy-evaluable LAG3–positive and ipilimumab-pretreated subjects have been treated.

Enrollment and randomization across Arms 2 and 3 may continue until the following criteria are met: (a) 90 efficacy-evaluable LAG-3–positive subjects have been treated, (b) 60 efficacy-

evaluable LAG-3–positive and BRAF WT subjects have been treated, and (c) 60 efficacy-evaluable LAG-3–positive and ipilimumab-pretreated subjects have been treated.

Prior to Revised Protocol 09, Part D1 subjects are being enrolled only into Arm 1. Subsequent to activation of this revised protocol and until the enrollment to Arm 1 is completed, subjects in Part D1 will be randomized 1:1:1 across the 3 arms. Once enrollment to Arm 1 is completed, subjects will be randomized 1:1 to Arms 2 and 3. If enrollment to Arms 2 and 3 is completed prior to Arm 1, then enrollment to Arm 1 will be completed as a single arm. Prior to the start of randomization, a safety lead-in will be conducted with BMS-986213.

If subjects do not meet the more focused eligibility of Part D1, they may be eligible for Part D2, which is more flexible with respect to the allowed prior therapies and performance status. Part D2 will test safety and efficacy in this broader patient population and will employ the more convenient Q4W combination coadministration dosing. Initial dosing will be 160 mg BMS-986016 + 480 mg nivolumab. Once further safety is established at the BMS-986016 160 mg + nivolumab 480 mg dose (see Section 8.1.4), subsequently enrolled subjects may be treated with BMS-986016 240 mg + nivolumab 480 mg. The doses and schedule selected for Part D will not exceed the Part B MTD or MAD, and dosing of the cohorts may be altered in collaboration between the Investigators and Sponsor, based upon the overall ongoing study data, including toxicities, PK, and pharmacodynamics.

There will be no dose adjustments for individual subjects. Expansion cohorts in Part D will be restricted to advanced melanoma subjects (Section 3). Efficacy analyses are described in Section 8.4.2.

Part D1 Safety Lead-in

Given the theoretical risk of infusion reactions with the administration of the BMS-986213, a safety lead-in will be employed for the first (up to) 9 subjects enrolling into subpart D1 and prior to the start of randomization.

The lead-in will follow a 3 + 3 + 3 design to monitor any potential Grade 3 or 4 infusion reactions that may occur as a result of coadministration of both drugs. Three subjects will be treated in each cohort. There will be no time interval restrictions for patients to begin treatment within a cohort.

If 0 to 1 of the first 3 subjects experiences a Grade 3 or 4 infusion reaction, then the cohort will be expanded to 6 subjects. If 2 of 6 subjects experience a Grade 3 or 4 infusion reaction, the cohort will be expanded to 9 subjects. If ≥ 2 of 3, ≥ 3 of 6, or ≥ 3 of 9 subjects experience Grade 3 or 4 infusion reactions, then the safety of BMS-986213 then further treatments with BMS-986213 will be held until further evaluation can be performed and randomization to the 2 coadministration arms may commence. If no more than 1 of 6 subjects, or 2 of 9, experience a Grade 3 or 4 reaction, randomization across all 3 arms will commence.

The infusion reaction observation period will be 48 hours.

Subjects will be instructed to contact the site regarding any potential infusion reaction symptoms. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the BMS Medical Monitor and reported as an SAE if it meets the criteria. Infusion reactions should be graded

according to NCI CTCAE v4.0 guidelines. Prior to allowing dosing of each subsequent cohort, sites will be contacted to confirm that there has been no report of serious reactions.

For the management of infusion reactions, please refer to the treatment guidelines outlined in Section 3.4.4.

The above enrollment plan will be executed by setting enrollment/treatment caps for each cohort in IVRS.

3.1.2.6 Part E Exposure Response Evaluation (Coadministration)

Two cohorts of melanoma subjects will be enrolled in Part E: melanoma participants who experienced disease progression on prior anti-PD-1 therapy and melanoma participants who have not received prior systemic anticancer therapy for unresectable or metastatic melanoma. Melanoma participants who experienced disease progression on prior anti-PD-1 therapy in the advanced, unresectable, or metastatic setting will only receive 480 mg BMS-986016 + 480 mg nivolumab Q4W. Melanoma participants who have not received prior systemic anticancer therapy for locally advanced, unresectable, or metastatic melanoma will be randomized to 1 of the following 2 treatment arms:

- 160 mg BMS-986016 + 480 mg nivolumab Q4W
- 480 mg BMS-986016 + 480 mg nivolumab Q4W

3.1.3 Dose-limiting Toxicities

BMS-986016 has the potential to augment the frequency and severity of previously described AEs associated with nivolumab or to produce new toxicities. For the purpose of guiding decisions regarding dose escalation in Parts A and B DLT will be determined based on the incidence, intensity, and duration of AEs that are related to study drug and that occur within 42 days (6 weeks) of initiation of study drug. The severity of AEs will be graded according to NCI CTCAE v4.0.

For the purpose of subject management, potential DLTs that occur at any time, whether during dose escalation (Parts A and B or cohort expansion Parts A1, C, and D) will result in all study drug(s) being held pending evaluation of the event's relatedness to study drug, severity, and duration, and in accordance with Section 4.3.2. Subjects must meet criteria for retreatment prior to reinitiation of study treatment (see Section 4.3.3). Any DLT that occurs after the initial 6-week DLT observation period, and after dosing in the next higher dose cohort has begun, will be accounted for and factored into the BLRM-Copula model in a post hoc manner. Additionally, as a practical matter, it should be noted that the BLRM-Copula model, based on the absence of DLTs at a preceding dose level, may dictate that an entire dose level cohort be skipped.

3.1.3.1 Rationale for 6-week DLT Period in Part B

The identification of acute DLTs that occur after administration of a study drug is critical for ensuring the safety of the patients enrolled in a clinical trial. The length of the DLT period is initially established based on the availability of preclinical data. Yet, when extensive clinical data become available, the benefit-risk evaluation used to define the appropriate DLT period must be reevaluated and should incorporate a critical analysis of all clinical and preclinical data.

Accordingly, for Part B, the DLT period will be reduced from 8 weeks to 6 weeks, effective with Revised Protocol #10, in light of the availability of extensive clinical data from ongoing clinical studies. As of the clinical cutoff date of 18-Jun-2018, treatment with relatlimab in combination with nivolumab has been administered to 876 subjects in studies CA224020 (812 subjects), CA224022 (45 subjects), and CA224034 (19 subjects). The integrated safety determination is that the AE profile of the combination of relatlimab and nivolumab is similar to nivolumab monotherapy. Additionally, a review of the 7 DLTs that have been observed in Study CA224020 to date demonstrates that the median time to onset was 4 weeks.

Effects of Prolonged DLT Period in a Population with Advanced Cancer

The target populations for Phase 1/2a oncology studies are characterized by patients with advanced stage disease. As a consequence, a relevant group of patients will progress rapidly after initiation of study drug. Across the ongoing studies CA224020 and CA224022, with BMS-986016 administered as monotherapy or in combination with nivolumab, 24% (9/38) of the subjects enrolled in dose escalation cohorts experienced disease progression between Week 4 and 8 of the DLT period, whereas only 2/38 (5%) of the subjects progressed between Week 1 and 4. It is important to note that a subject that progresses during the DLT period is no longer evaluable for the purposes of safety evaluation of the dose cohort and a new replacement subject must be enrolled in the same dose cohort in order to complete the safety evaluation for that dose cohort.

In summary, the review of the safety data from the ongoing studies strongly suggests that a 6-week DLT period will be an appropriate time frame to capture the acute, treatment-related AEs and to ensure the safety of the patients enrolled in Part B of this clinical trial. Furthermore, this DLT period revision will limit the number of patients who need to be replaced due to PD occurring between Weeks 6 and 8.

Hepatic, nonhematologic, and hematologic DLTs are defined separately as outlined below.

Hepatic DLT

Any of the following drug-related events will be considered a hepatic DLT (non-HCC subjects):

Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 8 × upper limit of normal (ULN), regardless of duration, or

ALT or AST > 5 × and ≤ 8 × ULN that fails to return to ≤Grade 1 within 2 weeks despite medical intervention, or

Total bilirubin > 5 ×ULN, or

Potential DILI event (Section 6.6)

For subjects with HCC, hepatic DLT criteria differ due to intrinsic involvement of the liver. In addition, for subjects with hepatitis B or hepatitis C, it is possible that virological breakthrough may occur, leading to temporary hepatic abnormalities. In these cases, subjects who regain virologic control may be allowed to resume study therapy after agreement between the Investigator and Sponsor.

Any of the following events will be considered a hepatic DLT for subjects with HCC:

ALT or AST > 15 x ULN, regardless of duration

ALT or AST > 10 x ULN for greater than 2 weeks

Total bilirubin > 8 x ULN regardless of duration for subjects with elevated bilirubin at study entry or > 5 x ULN for subjects with normal bilirubin at study entry

Potential DILI event for HCC (Section 6.6)

Nonhematologic DLT

Any of the following drug-related events will be considered a nonhematologic DLT:

Any ≥ Grade 2 immune-related eye pain or reduction in visual acuity that requires systemic treatment, or

Any ≥ Grade 2 eye pain or reduction in visual acuity that does not respond to topical therapy and that does not improve to Grade 1 within 2 weeks of initiation of topical therapy, or

Any ≥ Grade 3 nonhepatic or nonhematologic toxicity with the exceptions noted below.

The following Grade 3 or 4 nonhematologic events **will not** be considered DLTs:

Grade 3 electrolyte abnormality (and Grade 4 hyperglycemia) that lasts < 72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical intervention

Grade 3 or 4 increase in amylase and/or lipase that is not associated with symptoms or clinical manifestations of pancreatitis

Grade 3 nausea or vomiting that lasts < 48 hours and resolves to ≤Grade 1 either spontaneously or with conventional medical intervention

Grade 3 diarrhea that lasts < 72 hours, does not result in hospitalization, and resolves to ≤Grade 1 either spontaneously or with conventional medical intervention

Grade 3 fever that lasts < 72 hours and is not associated with hemodynamic compromise (including hypotension or clinical or laboratory evidence of end organ perfusion impairment)

Grade 3 endocrinopathy that is well controlled by hormone replacement therapy (HRT)

Grade 3 tumor flare (defined as pain, irritation, or rash that localizes to sites of known or suspected tumor)

Grade 3 fatigue for less than 7 days

Grade 3 rash meeting the following criteria: 1) improves to Grade 1 within 2 weeks, 2) does not limit self-care, and 3) is not associated with infection

Grade 3 troponin not associated with any other sign of cardiac toxicity (as determined by a cardiac evaluation)

Definition of Hematologic DLT

Any of the following drug-related events will be considered a hematologic DLT:

Grade 4 febrile neutropenia of any duration
Grade 4 neutropenia that lasts > 5 days
Grade 4 thrombocytopenia
Grade 4 anemia
Any Grade 3 thrombocytopenia associated with clinically significant bleeding
Any Grade 3 febrile neutropenia that lasts > 48 hours
Any Grade 3 hemolysis

In the event that study drug cannot be administered at a scheduled visit during the DLT evaluation interval, it must be administered as soon as possible. Subjects may be dosed no less than 12 days in the Q2W regimen and 25 days in the Q4W regimen from the previous dose and no more than 3 days from scheduled dose. If an infusion cannot be administered at a scheduled visit, it should be administered as soon as possible. Subsequent dosing visits will follow every 2 weeks or every 4 weeks after the delayed dose. A dose given more than 3 days after the intended dose date will be considered a delay. A maximum delay of 6 weeks between doses is allowed. Longer delays may be allowed following discussion with the Medical Monitor.

For Q4W dosing regimen, subjects may be dosed within a +/- 3 day window. For the purpose of making decisions on dose escalation from a safety perspective, subjects will be considered evaluable if they have received 3 out of the 4 scheduled BMS-986016 doses in Part A (or 3 out of 4 scheduled BMS-986016 and nivolumab doses in Part B Q2W dosing). Subjects will be considered evaluable if they have received 2 out of 2 scheduled BMS-986016 and nivolumab doses in Part B Q4W dosing. Unevaluable subjects may be replaced at the same dose level.

3.2 Post Study Access to Therapy

At the conclusion of the study, participants who continue to demonstrate clinical benefit (including participants remaining on study treatment and participants in rechallenge-eligible follow-up who are within 5 years from first dose) may be eligible to receive BMS-supplied study treatment for the maximum treatment duration specified in Section 3.1. Study treatment would be provided via a rollover study requiring approval by the responsible Health Authority and Ethics Committee, or, if appropriate, through another mechanism at the discretion of BMS.

3.3 Study Population

For entry into the study, the following criteria MUST be met prior to dosing on Day 1. No exceptions will be granted. Retesting of laboratory parameters and/or other assessments within any single Screening or Lead-in period will be permitted (in addition to any parameters that require a confirmatory value).

3.3.1 Inclusion Criteria

1) Signed Written Informed Consent

a) The subject must sign and date the IRB/IEC-approved written ICF prior to the performance of any study-related procedures that are not considered part of standard of care.

b) Consent for tumor biopsy samples

i) Parts A and B (Dose Escalation):

(1) During the screening period, all participants **must** have tumor tissue submitted, [redacted]. Subjects who do not meet these criteria are not eligible. However, subjects whose screening biopsy yields inadequate tissue quantity or quality will not be ineligible on this basis alone. The acquisition of existing formalin-fixed paraffin-embedded (FFPE) tumor tissue, either a block or unstained slides, for performance of correlative studies should also be collected if available. Subjects unable to provide pretreatment tumor tissue or who do not have accessible lesions are not eligible.

ii) Parts A1, C, D, and E (Cohort Expansions):

(1) During the screening period, all participants **must** have tumor tissue submitted, [redacted]. Subjects who do not meet these criteria are not eligible. However, subjects whose screening biopsy yields inadequate tissue quantity or quality will not be ineligible on this basis alone. The acquisition of existing FFPE tumor tissue, either a block or unstained slides, for performance of correlative studies should also be collected if available. Subjects unable to provide pretreatment tumor tissue or who do not have accessible lesions are not eligible.

(2) *Not applicable per Protocol Amendment 11.*

iii) If there is only 1 measurable lesion and a core-needle biopsy is done (instead of excisional), the lesion may be used as measurable lesion. If there are more than 1 measurable lesions, the lesion being biopsied should not be a target lesion.

iv) ***Not applicable per Revised Protocol 11.*** In lieu of a biopsy during screening, acceptable MANDATORY pretreatment biopsies include [redacted] or from an unresectable primary tumor lesion that has not been previously irradiated and if no intervening treatments have been administered between the time of biopsy/surgery and study entry.

[redacted]

2) Target Population

a) Subjects must have histologic or cytologic confirmation of an incurable solid malignancy that is advanced (metastatic and/or unresectable):

i) Part A: Dose Escalation – BMS-986016 Monotherapy

(1) All solid tumor histologies will be permitted except for subjects with primary CNS tumors.

(2) Only subjects without prior exposure to IO agents such as, but not limited to, anti-CTLA-4, anti–PD-1, anti–PD-L1, anti–PD-L2, anti-KIR, anti-CD137, or anti-OX40 antibodies, are allowed.

(3) Subjects must have received, and then progressed or been intolerant to, at least 1 standard treatment regimen in the advanced or metastatic setting, if such a therapy exists.

ii) Part B: Dose Escalation – BMS-986016 + nivolumab

(1) ***Not applicable as per Revised Protocol 10, see inclusion (7) and (8).*** Selected solid tumor histologies naive to IO agents such as, but not limited to, anti-CTLA-4, anti-PD-1, anti-PD-L1, anti–PD-L2, anti-KIR, anti-CD137, anti-LAG-3, or anti-OX40 antibodies, will be permitted except for subjects with primary CNS tumors. Selected tumor types (and all subtypes) include melanoma first line; RCC; NSCLC first, second, or third line; HNC (any histology); gastric (includes gastroesophageal junction) cancer; and hepatocellular, cervical, ovarian, colorectal, and bladder cancers.

(2) *Not applicable per Protocol Amendment 02.*

(3) NSCLC subjects progressing while on or after therapy with anti–PD-1 or anti–PD-L1 antibody (for Part B this does not need to be the most recent therapy).

(a) *Not applicable per Protocol Amendment 02.*

(b) Cannot have had therapy discontinued due to serious and/or life-threatening anti–PD-1 or anti–PD-L1 antibody-related toxicity (eg, DLT in prior study) per Investigator's assessment in consultation with the BMS Medical Monitor.

(c) *Not applicable per Protocol Amendment 02.*

(d) ***Not applicable as per Revised Protocol 10.*** Cannot have had prior exposure to other IOs, such as, but not limited to, anti–PD-L2, anti-KIR, anti-CD137, anti-LAG-3, or anti-OX40 antibodies. Prior anti-CTLA-4 antibody therapy is allowed.

(e) Subjects with targetable epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genetic aberrations must have previously received prior targeted therapy.

(4) Melanoma subjects whose disease is progressing while on or after receiving anti-CTLA-4 and/or anti-PD-1/anti-PD-L1 antibody therapies

(a) Anti-CTLA-4 and/or anti-PD-1 or anti-PD-L1 antibody therapies could have been received in sequential or combination regimens, as well as in combination with BRAF inhibitors, with or without MEK inhibitors.

(b) Last dose of antibody therapy must have been received ≥ 30 days of first dose of study medication.

(c) Cannot have had therapy discontinued due to serious and/or life-threatening antibody-related toxicity (eg, DLT in prior study) per Investigator's assessment in consultation with the BMS Medical Monitor.

(d) ***Not applicable as per Revised Protocol 10.*** Cannot have had prior exposure to any IOs other than anti-CTLA-4 and/or anti-PD-1/anti-PD-L1 antibody therapy. Prior IL-2 and interferon (IFN) therapy is allowed.

(5) Subjects must have received, and then progressed or been intolerant to, at least 1 standard treatment regimen or refused standard therapy in the advanced or metastatic setting, if such a therapy exists, except for NSCLC and melanoma, where treatment as first-line therapy is allowed.

(a) For first-line NSCLC subjects: The drug regimen with the highest likelihood of benefit with toxicity deemed acceptable to both the physician and the patient should be given as initial therapy for advanced lung cancer. Subjects should be offered chemotherapy if appropriate and available. Patients may refuse these standard treatments. The reason for why a subject does not receive standard first-line metastatic therapy must be documented. Subjects with targetable EGFR or ALK genetic aberrations must have previously received prior targeted therapy.

(b) For first-line melanoma subjects: The following prior adjuvant or neoadjuvant melanoma therapies are allowed if all related AEs have either returned to baseline or stabilized:

(i) Anti-PD-1 or anti-CTLA-4 therapy with at least 6 months between the last dose and date of disease recurrence.

(ii) Interferon therapy with the last dose at least 6 weeks prior to randomization.

(c) For first-line NSCLC subjects: Prior adjuvant or neoadjuvant chemotherapy, or definitive chemo/radiation, is permitted as long as the last administration of the prior regimen occurred at least 6 months prior to enrollment; while prior IO therapies are not allowed.

(6) Weight ≥ 40 kg.

(7) Selected tumor types (and all subtypes) include melanoma; RCC; NSCLC; HNC (any histology); gastric (includes gastroesophageal junction) cancer; and hepatocellular, cervical, ovarian, colorectal, and bladder cancers.

(8) Cannot have had therapy discontinued due to serious and/or life-threatening anti-PD-1 or anti-PD-L1 antibody-related toxicity.

iii) Part C: Cohort Expansion – Sequential Dosing

(1) The following groups will be enrolled:

(a) Melanoma – first line:

(i) Untreated, histologically confirmed unresectable Stage III or Stage IV melanoma, as per American Joint Committee on Cancer (AJCC) staging system.

(ii) Both BRAF V600 wild-type and mutant melanomas are allowed and mutation status must be documented.

(iii) Prior adjuvant or neoadjuvant melanoma therapy is permitted if it was completed at least 6 weeks prior to enrollment and all related AEs have either returned to baseline or stabilized. Note that adjuvant or neoadjuvant cytokine (IL-2 or IFN) therapy is allowed but other IO therapies such as, but not limited to, anti-CTLA-4, anti-PD-1, anti-PD-L1, anti–PD-L2, anti-KIR, anti-CD137, anti-LAG-3, or anti-OX40 antibodies are not allowed.

(iv) Uveal melanoma subjects are not eligible.

(b) RCC - naive to IOs

(i) Histology must have a clear-cell component.

(ii) Subjects must have received at least 1, but not more than 2, prior anti-angiogenic therapy regimens (including, but not limited to, sunitinib, sorafenib, pazopanib, axitinib, tivozanib, everolimus, temsirolimus, and bevacizumab) in the advanced or metastatic setting.

(iii) No more than 3 total previous regimens of systemic therapy are allowed, including cytokines (IL-2 or IFN), vaccine therapy, and cytotoxic chemotherapy drugs, and disease progression during or after the last treatment regimen and within 6 months before study enrollment.

(iv) Subjects cannot have had prior exposure to noncytokine IO therapies such as, but not limited to, anti-CTLA-4, anti-PD-1, anti-PD-L1, anti–PD-L2, anti-KIR, anti-CD137, anti-LAG-3, or anti-OX40 antibodies.

(c) NSCLC - naive to IOs: first, second, or third line

(i) First line:

a. Subjects with histologically confirmed Stage IIIB who have progressed following definitive concurrent chemoradiation, Stage IV, or recurrent NSCLC who are not amenable to potentially curative surgical resection or concurrent chemoradiation,[54] squamous or nonsquamous histology.

b. Prior adjuvant treatments (except IO therapies) are allowed as long as there was a 6-month interval between last adjuvant treatment dose and diagnosis of advanced disease. Prior definitive chemoradiation for locally advanced disease is also permitted as long as the last administration of chemotherapy or radiotherapy (whichever was given last) occurred at least 6 months prior to enrollment.

c. NOTE: The drug regimen with the highest likelihood of benefit with toxicity deemed acceptable to both the physician and the patient should be given as initial therapy for advanced lung cancer. Subjects should be offered chemotherapy if appropriate and available. Patients may refuse these standard chemotherapy treatments. The reason for why a subject does not receive standard first-line metastatic therapy must be documented.

d. Subjects with targetable EGFR or ALK genetic aberrations must have previously received targeted therapy.

(ii) Second or third line:

a. Subjects with histologically or cytologically documented locally advanced NSCLC who present with Stage IIIB/Stage IV or recurrent or PD following multimodality therapy (radiation therapy, surgical resection, or definitive chemoradiation therapy for locally advanced disease).

b. Subjects who will receive study therapy as second line of treatment:

Subjects must have experienced disease recurrence or progression during or after 1 prior platinum doublet-based chemotherapy regimen for advanced or metastatic disease.

First-line therapy is defined as therapy used to treat advanced disease. Each subsequent line of therapy is preceded by disease progression. A switch of an agent within a regimen in order to manage toxicity does not define the start of a new line of therapy. Subjects must have received at least 2 cycles of platinum doublet-based chemotherapy before discontinuation for toxicity.

Experimental therapies when given as separate regimen are considered as a separate line of therapy.

Maintenance therapy following platinum doublet-based chemotherapy is not considered as a separate regimen of therapy and could comprise continuation of 1 or more of the agents used in the first-line therapy regimen or switch to another non cross-resistant agent. The initiation of maintenance therapy requires the lack of PD with front-line therapy.

Treatment given for locally advanced disease is not considered as a line of therapy for advanced disease. Subjects with recurrent disease > 6 months after platinum-containing adjuvant, neoadjuvant, or definitive chemoradiation therapy given for locally advanced disease who also subsequently progressed during or after a platinum doublet-based regimen given to treat the recurrence are eligible.

Subjects who received platinum-containing adjuvant, neoadjuvant, or definitive chemoradiation therapy given for locally advanced disease and developed recurrent (local or metastatic) disease within 6 months of completing therapy are eligible.

Adjuvant or neoadjuvant platinum-doublet chemotherapy (after surgery and/or radiation therapy) followed by recurrent or metastatic disease within 6 months of completing therapy is considered as first-line therapy for advanced disease.

Subjects with targetable EGFR or ALK genetic aberrations must have previously received targeted therapy.

c. Subjects who will receive study therapy as third line of treatment must have experienced disease recurrence or progression during or after a separate EGFR or ALK tyrosine kinase inhibitor (TKI) regimen in addition to 1 prior platinum doublet-based chemotherapy regimen (regardless of order of administration).

   Subjects who received an EGFR TKI (erlotinib, gefitinib, or experimental) in addition to a platinum-based chemotherapy must have a tumor with a known activating EGFR mutation.

   Subjects with a tumor with EGFR wild-type or unknown EGFR mutation status who received an EGFR TKI after failure of a prior platinum-based chemotherapy are excluded.

   Subjects who received an ALK inhibitor (crizotinib or experimental) in addition to a platinum-based chemotherapy must have a tumor with a known ALK translocation.

(d) NSCLC subjects progressing while on or after therapy with anti–PD-1 or anti–PD-L1 antibody as most recent therapy

(i) Squamous or nonsquamous histology.

(ii) This cohort includes 2 separate subgroups: 1) primary refractory disease: defined as those subjects that progressed within the first 12 weeks of the prior anti–PD-1 or anti–PD-L1 antibody therapy and 2) relapsed disease: defined as those subjects that do not meet the criterion for primary refractory disease.

(iii) Subjects should not have discontinued antibody therapy due to serious and/or life-threatening toxicity (eg, DLT in prior study) per Investigator's assessment in consultation with the BMS Medical Monitor.

(iv) These subjects cannot have had prior exposure to any other IOs such as, but not limited to, anti–PD-L2, anti-KIR, anti-CD137, anti-LAG-3, or anti-OX40 antibodies. Prior anti-CTLA-4 antibody therapy is allowed.

(v) Subjects with targetable EGFR or ALK genetic aberrations must have previously received prior targeted therapy.

(vi) All available scans on the most recent prior anti-PD-1 containing regimen, including the baseline scan (prior to starting anti-PD-1) and scans after the last dose of anti-PD-1 but before the start of any intervening therapy may be collected and submitted to a third-party imaging vendor.

(e) HNC – naive to IOs

(i) Histology restricted to SCCHN from any of the following primary sites only: oral cavity, oropharynx, hypopharynx, and larynx.

(ii) Subjects are eligible regardless of HPV status.

(iii) Subjects must have metastatic or recurrent SCCHN that is not amenable to therapy with curative intent (surgery or radiation therapy with or without chemotherapy). Subjects who refuse potentially curative salvage surgery for recurrent disease are ineligible. Subjects must have tumor progression or recurrence after prior platinum-containing systemic therapy for recurrent or metastatic disease. In addition, subjects who have progressed within 6 months of platinum-based therapy used as part of concurrent chemoradiation (definitive or adjuvant therapy) are also eligible. Thus, for subjects where platinum-based therapy was used only in the adjuvant (ie, with radiation after surgery) or primary (ie, with radiation) setting, only patients with recurrence within 6 months of completing platinum will be eligible.

(iv) Subjects cannot have had prior exposure to IO therapies such as, but not limited to, anti-CTLA-4, anti-PD-1, anti-PD-L1, anti–PD-L2, anti-KIR, anti-CD137, anti-LAG-3, or anti-OX40 antibodies.

(f) *Not applicable per Protocol Amendment 04.*

(g) Melanoma - previously progressed on anti-PD-1/ anti-PD-L1 antibody therapy

(i) Prior anti-PD-1/anti-PD-L1 antibody alone or in any combination with anti-CTLA-4 antibody therapy, BRAF, and/or MEK inhibitors are allowed.

(ii) Subjects should not have discontinued antibody therapy due to serious and/or life-threatening toxicity (eg, DLT in prior study) per Investigator's assessment in consultation with the BMS Medical Monitor.

(iii) Subjects cannot have had prior exposure to IOs therapies including, but not limited to, anti–PD-L2, anti-KIR, anti-CD137, anti-LAG-3, or anti-OX40 antibodies. IO therapies including, but not limited to, anti-CTLA-4, anti-PD-1, anti-PD-L1 antibody therapies, or IL-2 and IFN cytokine therapies are allowed.

(iv) Prior adjuvant or neoadjuvant therapy with cytokines (IL-2 or IFN) or anti-CTLA-4 antibodies is allowed.

(v) Uveal melanoma subjects are not eligible.

(vi) All available scans on the most recent prior anti-PD-1–containing regimen, including the baseline scan (prior to starting anti-PD-1) and scans after the last dose of anti-PD-1 but before the start of any intervening therapy may be collected and submitted to BICR.

(h) Gastric adenocarcinoma (includes gastroesophageal junction) – naive to IOs

(i) HER-2(+) and HER-2(-) subjects will be allowed.

(ii) Subjects cannot have had prior exposure to IO therapies such as, but not limited to, anti-CTLA-4, anti-PD-1, anti-PD-L1, anti–PD-L2, anti-KIR, anti-CD137, anti-LAG-3, or anti-OX40 antibodies.

(i) HCC – naive to IOs

(i) Child-Pugh score of 6 points or less (ie, Child-Pugh A).

(ii) Without history of encephalopathy, clinically significant ascites (within 1 year of enrollment), or clinically significant variceal bleeding (within 6 months of enrollment).

(iii) Subjects with or without viral infection (uninfected, HCV-infected, and HBV-infected) are eligible.

(iv) Disease not amenable for management with curative intent by surgery or local therapeutic measures.

(v) Subjects with radiological diagnosis may be enrolled for screening in the study, but histological confirmation is mandatory prior to initiation of study therapy.

(vi) Subjects with chronic HBV infection must have a HBV DNA viral load < 100 IU/mL at screening. In addition, they must be on antiviral therapy per regional standard of care guidelines prior to initiation of study therapy. If not on antiviral therapy at screening, then the subjects must initiate treatment per regional standard of care guidelines at the time of consent. All subjects enrolled in the HBV cohort must continue antiviral therapy for the duration of the study. Both HBeAg positive and negative subjects will be included. Subjects with hepatitis B infection must not have coinfection with hepatitis C or hepatitis D (must obtain hepatitis D antibody testing).

(vii) Subjects cannot have had prior exposure to IO therapies such as, but not limited to, anti-CTLA-4, anti-PD-1, anti-PD-L1, anti–PD-L2, anti-KIR, anti-CD137, anti-LAG-3, or anti-OX40 antibodies.

(viii) Fibrolamellar and sarcomatoid histologies are not eligible.

(j) Bladder carcinoma – naive to IOs

(i) Histological or cytological evidence of metastatic or surgically unresectable transitional cell carcinoma of the urothelium involving the bladder, urethra, ureter, or renal pelvis.

(ii) Subjects must have metastatic or surgically unresectable (cT4b, or any N+ [N1-3], or any M-1) disease.

(iii) Visceral disease is allowed.

(iv) Subjects must have progression or recurrence after treatment: i) with at least 1 platinum-containing chemotherapy regimen for metastatic or surgically unresectable locally advanced urothelial cancer, or ii) within 12 months of peri-operative (neoadjuvant or adjuvant) treatment with a platinum agent in the setting of cystectomy for localized muscle-invasive urothelial cancer.

(v) Subjects cannot have had prior exposure to IO therapies such as, but not limited to, anti-CTLA-4, anti-PD-1, anti-PD-L1, anti–PD-L2, anti-KIR, anti-CD137, anti-LAG-3, or anti-OX40 antibodies.

(vi) No limit to the number of therapies.

(2) Prior lines of therapy (applies to all Part C subjects except those treated as first-line NSCLC and first-line melanoma): Subjects must have received, and then progressed or been intolerant to, at least 1 standard treatment regimen in the advanced or metastatic setting, if such a therapy exists or refused standard treatment (refusal must be documented). Number of maximum allowed prior systemic treatment regimens in the advanced or metastatic setting based on cohort: NSCLC progressing on prior IO = 3 lines, unless targetable EGFR or ALK genomic tumor aberrations, then 4 lines are allowed; melanoma progressing on prior IO = 3 lines, unless targetable BRAF V600 mutation, then 4 lines are allowed; gastric = no limit; HNC = 2 prior

lines; HCC = no limit. For RCC and NSCLC IO-naive cohorts, see criteria in individual cohort eligibility sections above.

iv) Part A1: Cohort Expansion – Monotherapy

(1) The following groups will be enrolled:

(a) NSCLC: Subjects whose disease progressed while on or after therapy with an approved anti–PD-1 or anti–PD-L1-containing regimen. There is no limit on other prior therapies. Subjects should have not discontinued immunotherapy due to serious and/or life-threatening toxicity (eg, DLT in prior study) per Investigator's assessment in consultation with the BMS Medical Monitor. Subjects must also have progressed on, been intolerant to, or refused at least 1 chemotherapy-containing regimen in the advanced or metastatic setting. Subjects with targetable EGFR or ALK genetic aberrations must have previously received and progressed on, or have been intolerant to, prior targeted therapy.

(b) RCC: Subjects whose disease progressed while on or after therapy with an approved anti-PD-1 or anti-PD-L1-containing regimen. There is no limit on other prior therapies. Subjects should have not discontinued immunotherapy due to serious and/or life-threatening toxicity (eg, DLT in prior study) per Investigator's assessment in consultation with the BMS Medical Monitor. Subjects must have progressed on, or been intolerant to, at least 1 prior anti-angiogenic therapy regimen (including, but not limited to, sunitinib, sorafenib, pazopanib, axitinib, tivozanib, everolimus, temsirolimus, and bevacizumab).

(2) Subjects must have received, and then progressed or been intolerant to, at least 1 standard treatment regimen or refuse standard therapy in the advanced or metastatic setting, if such a therapy exists.

v) Part D1: Melanoma Prior IO Extended Expansion - Focused Eligibility Cohort

(1) Must have measurable disease by computed tomography (CT) or magnetic resonance imaging (MRI) and documented progression while on a prior anti-PD-1-containing regimen (monotherapy or combination therapy) in the advanced unresectable or metastatic setting.

(a) Documentation should include start, stop, and progression dates of anti-PD-1 therapy (limited to nivolumab or pembrolizumab) with unequivocal progression and a progression date no more than 3 months after the last dose of anti-PD-1 therapy (limited to nivolumab or pembrolizumab).

(b) All available scans on the most recent anti-PD-1–containing regimen (limited to nivolumab or pembrolizumab), including the baseline scan (prior to starting anti-PD-1) and scans after the last dose of anti-PD-1 but before the start of any intervening therapy, will be collected and submitted to a third-party imaging vendor (see Section 5.4 and Table 5.1-1).

(c) There are no restrictions on the prior anti-PD-1 (limited to nivolumab or pembrolizumab) combination partners.

(d) Only 1 line of a prior anti-PD-1–containing regimen (limited to nivolumab or pembrolizumab) is allowed. See **2) Target Population** b) below for more detail on the definition of "a line of a prior anti-PD-1–containing regimen (limited to nivolumab or pembrolizumab)."

(e) Prior anti-LAG-3 or anti-PD-L1 therapy is not allowed.

(2) BRAF wild-type and mutant subjects are eligible.

(a) BRAF status must be known.

(b) BRAF mutant subjects must have been treated with, and progressed on, 1 prior line of a BRAF inhibitor, administered with or without a MEK inhibitor, in the advanced unresectable or metastatic setting.

(c) Only 1 line of a BRAF inhibitor, administered with or without a MEK inhibitor, in the advanced unresectable or metastatic setting is allowed.

(3) Adjuvant/neoadjuvant therapy

Adjuvant (or neoadjuvant) anti-PD-1 or anti-PD-L1 therapy is not allowed. Other adjuvant (or neoadjuvant) melanoma therapies, including anti-CTLA-4, are allowed.

(a) ***Not applicable per Revised Protocol 11.*** Anti-PD-1 or anti-CTLA-4 therapy with at least 6 months between the last dose and date of disease recurrence.

(b) ***Not applicable per Revised Protocol 11.*** Interferon therapy with the last dose at least 6 weeks prior to randomization.

(4) No limit to the number of prior therapies (except as noted above).

(5) Uveal melanoma subjects are **NOT** eligible.

(6) ECOG PS 0-1/Lansky Performance Score ≥ 80% for minors ONLY.

vi) Part D2: Melanoma Prior IO Extended Expansion – Expanded Eligibility Cohort

(1) Anti-PD-L1 therapy or combination-containing regimen can substitute for anti-PD-1 therapy (limited to nivolumab or pembrolizumab).

(2) Must have documented progression while on a prior anti-PD-1–containing regimen (monotherapy or combination therapy).

(a) Documentation on prior anti-PD-1–containing therapy (limited to nivolumab or pembrolizumab) should include start, stop, and progression dates of prior anti-PD-1 therapy with unequivocal progression and a progression date no more than 3 months after the last dose of anti-PD-1 therapy.

(b) All available scans on the most recent prior anti-PD-1–containing regimen (limited to nivolumab or pembrolizumab), including the baseline scan (prior to starting anti-PD-1) and scans after the last dose of anti-PD-1 but before the start of any intervening therapy, will be collected and submitted to a central imaging vendor (see Section 5.4 and Table 5.1-1).

(c) Patients with prior adjuvant or neoadjuvant anti-PD-1 therapy are allowed as long as 1 of the 2 conditions is met: 1) progression occurred during or within 6 months of the last dose of adjuvant anti-PD-1 therapy, or 2) there has been subsequent progression on additional anti-PD-1 therapy in the metastatic setting.

(i) ***Not applicable per Revised Protocol 11.*** Anti-PD-1 or anti-CTLA-4 therapy with at least 6 months between the last dose and date of disease recurrence.

(ii) ***Not applicable per Revised Protocol 11.*** Interferon therapy with the last dose at least 6 weeks prior to randomization.

(d) Multiple prior lines of anti-PD-1–containing regimens are allowed.

(3) BRAF wild-type and mutant subjects are eligible.

(a) BRAF status must be known.

(b) Multiple prior lines of BRAF inhibitor administered with or without a MEK inhibitor are allowed.

(4) No limit to the number of prior therapies.

(5) Uveal melanoma subjects are **NOT** eligible.

(6) ECOG PS 0-2/Lansky Performance Score ≥ 60% for minors ONLY.

(7) Subject does not qualify for Part D1.

vii) Part E: Exposure Response Evaluation in Melanoma Participants

(1) **Melanoma participants who experienced disease progression on prior anti-PD-1 therapy:** Must have measurable disease by CT or MRI and documented progression while on a prior anti-PD-1–containing regimen (monotherapy or combination therapy) in the advanced unresectable or metastatic setting.

(a) Documentation should include start, stop, and progression dates of anti-PD-1 therapy (limited to nivolumab or pembrolizumab) with unequivocal progression and a progression date no more than 3 months after the last dose of anti-PD-1 therapy (limited to nivolumab or pembrolizumab).

(b) All available scans on the most recent anti-PD-1–containing regimen (limited to nivolumab or pembrolizumab), including the baseline scan (prior to starting anti-PD-1) and scans after the last dose of anti-PD-1 but before the start of any

intervening therapy, will be collected and submitted to a third-party imaging vendor (see Section 5.4 and Table 5.1-1).

(c) There are no restrictions on the prior anti-PD-1 (limited to nivolumab or pembrolizumab) combination partners.

(d) Only 1 line of a prior, anti-PD-1–containing regimen (limited to nivolumab or pembrolizumab) is allowed. See **2) Target Population** b) below for more detail on the definition of "a line of a prior anti-PD-1–containing regimen (limited to nivolumab or pembrolizumab)."

(e) Prior anti-LAG-3 or anti-PD-L1 therapy is not allowed.

(f) BRAF wild-type and mutant subjects are eligible.

(i) BRAF status must be known.

(ii) BRAF mutant subjects must have been treated with, and progressed on, 1 prior line of a BRAF inhibitor, administered with or without a MEK inhibitor, in the advanced unresectable or metastatic setting.

(iii) Only 1 line of a BRAF inhibitor, administered with or without a MEK inhibitor, in the advanced unresectable or metastatic setting is allowed.

(g) Adjuvant/neoadjuvant therapy

(i) ***Not applicable per Revised Protocol 11.*** Anti-PD-1 or anti-CTLA-4 therapy with at least 6 months between the last dose and date of disease recurrence.

(ii) ***Not applicable per Revised Protocol 11.*** Interferon therapy with the last dose at least 6 weeks prior to randomization.

(iii) Adjuvant (or neoadjuvant) anti-PD-1 or anti-PD-L1 therapy is not allowed. Other adjuvant (or neoadjuvant) melanoma therapies, including anti-CTLA-4, are allowed.

(h) No limit to the number of prior therapies (except as noted above).

(i) Uveal melanoma subjects are **NOT** eligible.

(j) ECOG PS 0-1/Lansky Performance Score ≥ 80% for minors ONLY.

(2) **Melanoma participants who have not received prior systemic anticancer therapy for unresectable or metastatic melanoma:**

(a) Participants must have an ECOG PS ≤ 1/Lansky Performance Score Ꞑ 80% for minors (aged 12 to 17 years) ONLY (for details, see Appendix 3).

(b) Participants must have histologically confirmed Stage III (unresectable) or Stage IV melanoma, per the AJCC staging system.

(c) Participants must not have had prior systemic anticancer therapy for unresectable or metastatic melanoma.

(d) The following prior adjuvant or neoadjuvant melanoma therapies are allowed if all related AEs have either returned to baseline or stabilized:

(i) Anti-PD-1 or anti-CTLA-4 therapy with at least 6 months between the last dose and date of recurrence.

(ii) Interferon therapy with the last dose at least 6 weeks prior to randomization

(iii) BRAF- or MEK-inhibitor–containing regimens with at least 6 months between the last dose and date of recurrence.

(e) Participants must have measurable disease by CT or MRI per RECIST v1.1 criteria (for details, see Appendix 2).

(f) Participants must have known BRAF V600 mutation status or consent to BRAF V600 mutation testing per local institutional standards during the screening period.

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

(h) Uveal melanoma subjects are **NOT** eligible.

b) In subjects with prior treatment regimens, the following are not considered separate lines of treatment: 1) addition of a compound to an ongoing regimen, 2) restarting the same regimen after a drug holiday, or 3) switching from IV to oral therapy. In addition, 4) a switch between nivolumab and pembrolizumab within a regimen in order to manage toxicity, or for reason of patient convenience, institutional practice standards, or insurance coverage does <u>not</u> define the start of a new line of therapy. A consult with the Medical Monitor on individual cases is highly recommended where there is uncertainty. Maintenance therapy is not considered as a separate regimen of therapy and could comprise continuation of 1 or more of the agents used in the effective treatment regimen or switch to another non cross-resistant agent. The initiation of maintenance therapy requires the lack of PD with the effective treatment regimen.

c) Presence of at least 1 lesion with measurable disease as defined by RECIST v1.1 criteria for response assessment. Subjects with lesions in a previously irradiated field as the sole site of measurable disease will be permitted to enroll provided that the lesion(s) have demonstrated clear progression prior to the time of informed consent and can be measured accurately.

d) ECOG PS 0 or 1; Lansky Performance Score ≥ 80%. For RCC subjects ONLY: Karnofsky Performance Score (KPS) ≥ 80%. Note: Exception Part D2 ECOG PS 0 to 2; Lansky Performance Score ≥ 60% (Appendix 3).

e) Life expectancy of ≥ 12 weeks at the time of informed consent per Investigator assessment.

f) Adequate organ function as defined by the following:

i) White blood cells ≥ 2000/μL (stable and off any growth factor within 4 weeks of first study drug administration)

ii) Neutrophils ≥ 1500/μL (stable and off any growth factor within 4 weeks of first study drug administration)

iii) Platelets ≥ 100 (≥ 60 for HCC) × 10^3/μL (transfusion to achieve this level is not permitted within 2 weeks of first study drug administration)

iv) Hemoglobin ≥ 8.5 g/dL (transfusion to achieve this level is not permitted within 2 weeks of first study drug administration)

v) Creatinine < 1.5 × ULN or creatinine clearance ≥ 40 mL/min (Cockcroft-Gault formula)

vi) ALT and AST ≤ 3 × ULN (≤ 5 × ULN for HCC)

vii) Lipase and amylase < 1.5 × ULN

viii) Total bilirubin ≤ 1.5 × ULN (except subjects with Gilbert's Syndrome, who must have normal direct bilirubin) [3 mg/dL for HCC]

ix) Normal thyroid function or stable on hormone supplementation per Investigator assessment

x) Albumin ≥ 2.8 g/dl

xi) ***Not applicable per Revised Protocol 08***. See exclusion 2o.

g) Ability to comply with treatment, PK, and pharmacodynamic sample collection and required study follow-up.

h) Subject re-enrollment: This study permits the re-enrollment of a subject who has discontinued the study as a pretreatment failure (ie, subject has not been randomized/has not been treated). If re-enrolled, the subject must be reconsented.

i) Left ventricular ejection fraction (LVEF) assessment with documented LVEF ≥ 50% by either transthoracic echocardiogram (TTE) or multigated acquisition scan (MUGA) (TTE preferred test) within 6 months from first study drug administration.

3) Age and Reproductive Status

a) For Parts A, B, C, D, and E males and females, ≥ 18 years at the time of informed consent. Additionally, for Parts C (melanoma only), D, and E, males and females ≥ 12 years at the time of informed consent if local regulations and/or institutional policies allow for participants < 18 years of age (pediatric population). If pediatric population is not allowed to participate, then ≥ 18 years applies.

b) **Not applicable as per Protocol Amendment 14**: Women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception for the duration of treatment with BMS-986016 plus 5 half-lives of BMS-986016 (135 days) plus 30 days

(duration of ovulatory cycle) for a total of 165 days (24 weeks) after completion of treatment.

c) **As per Protocol Amendment 14:** Women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception for the duration of treatment with nivolumab and relatlimab plus 5 half-lives of study treatment for a total of 5 months post-treatment completion and agree not to donate eggs (ova, oocytes) for the purpose of reproduction for the same time period. Investigators shall counsel WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% per year when used consistently and correctly (see Appendix 1).

d) Women of childbearing potential must have a negative serum or urine pregnancy test (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [hCG]) within 24 hours prior to the start of study drug.

e) Women must not be breastfeeding.

f) **Not applicable as per Protocol Amendment 14:** Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with BMS-986016 plus 5 half-lives of BMS-986016 (135 days) plus 90 days (duration of sperm turnover) for a total of 225 days (33 weeks) after completion of treatment. This criterion applies to azoospermic males as well. In addition, male participants must be willing to refrain from sperm donation during this time.

    a. Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% per year when used consistently and correctly.

    b. At a minimum, subjects must agree to the use of 2 methods of contraception, with one method being highly effective and the other being either highly effective or less effective as listed in Appendix 1.

g) **Note as of Protocol Amendment 14:** No contraception requirements for nivolumab and relatlimab are necessary for male participants. Therefore, pregnancy reporting from female partners of childbearing potential is not required.

h) WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However, WOCBP who abstain from heterosexual activity on a continuous basis must still undergo pregnancy testing as described in this protocol.

3.3.2 Exclusion Criteria

1) Target Disease Exceptions

a) Subjects with known or suspected CNS metastases or with the CNS as the only site of active disease are excluded with the following exceptions:

    i) Subjects with controlled brain metastases will be allowed to enroll. Controlled brain metastases are defined as those with no radiographic progression for at least 4 weeks

after radiation and/or surgical treatment at the time of consent. Subjects must have been off of steroids for at least 2 weeks prior to informed consent and have no new or progressive neurological signs and symptoms.

ii) Subjects with signs or symptoms of brain metastases are not eligible unless brain metastases are ruled out by CT or MRI.

b) ***Not applicable as per Revised Protocol 09.*** Participation in any prior clinical study with nivolumab, including subjects in comparator arms, in which OS is listed as the primary or coprimary endpoint and which has not completed analysis based on the primary endpoint.

2) Medical History and Concurrent Diseases

a) 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

b) Subjects with an active, known or suspected autoimmune disease. Subjects with type I diabetes mellitus, hypothyroidism only requiring HRT, 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.

c) A known or underlying medical condition that, in the opinion of the Investigator or Sponsor, could make the administration of study drug hazardous to the subject or could adversely affect the ability of the subject to comply with or tolerate study.

d) Requirement for daily supplemental oxygen.

e) Uncontrolled or significant cardiovascular disease including, but not limited to, any of the following:

i) Myocardial infarction (MI) or stroke/transient ischemic attack within the 6 months prior to consent

ii) Uncontrolled angina within the 3 months prior to consent

iii) Any history of clinically significant arrhythmias (such as poorly controlled atrial fibrillation, ventricular tachycardia, ventricular fibrillation, or torsades de pointes)

iv) QTc prolongation > 480 msec

v) History of other clinically significant cardiovascular disease (ie, cardiomyopathy, congestive heart failure with New York Heart Association functional classification III-IV, pericarditis, significant pericardial effusion, significant coronary stent occlusion, poorly controlled venous thrombosis, etc)

vi) Cardiovascular disease–related requirement for daily supplemental oxygen

vii) History of 2 or more MIs OR 2 or more coronary revascularization procedures (regardless of the number of stent placements during each procedure)

viii) Subjects with history of myocarditis, regardless of etiology

f) A confirmed history of encephalitis, meningitis, or uncontrolled seizures in the year prior to informed consent.

g) Positive blood screen for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). NOTE: Testing for HIV must be performed at sites where mandated locally.

h) Any positive test result for hepatitis B virus (HBV) or hepatitis C virus (HCV) indicating presence of virus, eg, hepatitis B surface antigen (HBsAg; Australia antigen) positive or hepatitis C antibody positive (except if HCV-RNA negative) (does not apply to HCC subjects)

i) Not applicable per Revised Protocol 08.

ii) Not applicable per Revised Protocol 08.

iii) Not applicable per Revised Protocol 08.

i) Evidence of active infection that requires systemic antibacterial, antiviral, or antifungal therapy ≤ 7 days prior to initiation of study drug therapy

j) Any other significant acute or chronic medical illness

k) Subjects who are unable to undergo venipuncture and/or tolerate venous access

l) Any other sound medical, psychiatric, and/or social reason as determined by the Investigator

m) Any of the following procedures or medications:

i) Within 2 weeks prior to time of study treatment:

(1) Systemic or topical corticosteroids at immunosuppressive doses (> 10 mg/day of prednisone or equivalent). Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

(2) Palliative radiation or gamma knife radiosurgery

(3) *Not applicable per Protocol Amendment 02.*

ii) Within 4 weeks prior to study drug administration:

(1) Any cytotoxic drug. Exposure to any noncytotoxic drug within 4 weeks or 5 half-lives (whichever is shorter) is prohibited. If 5 half-lives is shorter than 4 weeks, agreement with Sponsor/Medical Monitor is mandatory.

(2) *Not applicable per Protocol Amendment 05.*

(3) Receipt of a live/attenuated vaccine within 30 days of first treatment

(4) Allergen hyposensitization therapy

(5) Growth factors, eg, granulocyte-colony stimulating factor, granulocyte macrophage-colony stimulating factor, erythropoietin

(6) Major surgery

(7) *Not applicable per Protocol Amendment 11.*

iii) Not applicable per Protocol Amendment 04.

n) Subjects with history of life-threatening toxicity related to prior immune therapy (eg, anti-CTLA-4 or anti-PD-1/PD-L1 treatment or any other antibody or drug specifically targeting T cell costimulation or immune checkpoint pathways) except those that are unlikely to reoccur with standard countermeasures (eg, HRT after endocrinopathy)

o) Troponin T (TnT) or I (TnI) > 2 × institutional ULN. Troponin levels between > 1 to 2 x ULN will be permitted if a repeat assessment remains ≤ 2 x ULN and subject undergoes a cardiac evaluation.

p) Prior treatment with LAG-3 targeted agents

q) ***Not applicable as per Revised Protocol 09.*** Adolescents weighing < 30 kg

3) Allergies and Adverse Drug Reaction

a) History of allergy to anti–PD-1 or anti–PD-L1 antibody therapy or to other mAbs or related compounds or to any of their components (eg, history of severe hypersensitivity reactions to drugs formulated with polysorbate 80)

b) History of allergy or hypersensitivity to study drug components

4) Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated

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

c) Inability to comply with restrictions and prohibited activities and treatments as listed in Section 3.4

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

3.3.3 Women of Childbearing Potential

Women of childbearing potential are defined as any female who have experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 in the absence of other biological or physiological causes. In addition, females under the age of 55 must have a documented serum follicle-stimulating hormone (FSH) level > 40 mIU/mL to confirm menopause.

Females treated with HRT are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgment in checking serum FSH levels. If the serum FSH level is > 40 mIU/mL at any time during the washout period, the woman can be considered postmenopausal.

1 week minimum for vaginal hormonal products (rings, creams, gels)

4 week minimum for transdermal products

8 week minimum for oral products

Other parenteral products may require washout periods as long as 6 months.

3.4 Concomitant Treatments

3.4.1 Prohibited and/or Restricted Treatments

The following medications are prohibited during the study:

Immunosuppressive agents unless they are utilized to treat an AE or as specified in Sections 3.4.3 and 3.4.4

Concurrent administration of any anticancer therapies (investigational or approved) in the Treatment period, with the exception of subjects in Clinical Follow-up period as well as the Survival period of the study.

Use of growth factors should be discussed with BMS Medical Monitor.

Use of allergen hyposensitization therapy.

Palliative radiotherapy is permitted only under certain conditions as described in Section 3.4.3.

3.4.2 Other Restrictions and Precautions

Any live/attenuated vaccine (eg, varicella zoster; yellow fever; rotavirus; oral polio; and measles, mumps, rubella [MMR]) during treatment and until 100 days post last dose. Inactivated influenza vaccination will be permitted on study without restriction.

It is the local imaging facility's responsibility to determine, based on subject attributes (eg, allergy history, diabetic history, and renal status), the appropriate imaging modality and contrast regimen for each subject. Imaging contraindications and contrast risks should be considered in this assessment. Subjects with renal insufficiency should be assessed as to whether or not they should receive contrast and, if so, what type and dose of contrast is appropriate. Specific to MRI, subjects with severe renal insufficiency (ie, estimated glomerular filtration rate < 30 mL/min/1.73 m^2) are at increased risk of nephrogenic systemic fibrosis. Magnetic resonance imaging contrast should not be given to this subject population. In addition, subjects are excluded from MRI if they have tattoos, metallic implants, pacemakers, etc.

The ultimate decision to perform MRI in an individual subject in this study rests with the site radiologist, the Investigator, and the standard set by the local Ethics Committee.

3.4.3 Permitted Therapy

Subjects are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Immunosuppressive agents and the use of systemic corticosteroids are permitted in the context of treating AEs, prophylaxis prior to a diagnostic procedure (eg, contrast MRI/CT scans), or as specified in Section 3.4.4. A brief course of corticosteroids for prophylaxis (eg, contrast dye allergy) is permitted after discussion with the BMS Medical Monitor.

Subjects may continue to receive HRT.

For subjects who need to undergo elective surgery (not tumor related) during the study, it is recommended to hold study drug(s) for at least 2 weeks before and 2 weeks after surgery or until the subject recovers from the procedure, whichever is longer. Prior to resuming study drug treatment, surgically related AEs should resolve to ≤ Grade 1 or baseline, and subjects must meet relevant eligibility criteria as determined by the BMS Medical Monitor in discussion with the Investigator. The BMS Medical Monitor must be consulted prior to reinitiating treatment in a subject with a dosing interruption lasting > 6 weeks after the last dose.

Non-live COVID-19 vaccination is considered a simple concomitant medication within the study. However, the efficacy and safety of non-live vaccines (including non-live COVID-19 vaccines) in participants receiving BMS-986016 in combination with nivolumab is unknown.

COVID-19 vaccines that are NOT live are allowed and should be handled in the same manner as other vaccines. Administration may occur during the study, including during the administration of the BMS study treatment and after the last administration of the BMS study treatment.

3.4.3.1 Palliative Radiotherapy

Palliative radiotherapy and supportive care for disease-related symptoms may be offered to all subjects on the trial; however, Investigators should consult with the BMS Medical Monitor prior to initiating palliative radiotherapy in subjects who have not yet completed the DLT evaluation interval (Parts A and B).

The potential for overlapping toxicities with radiotherapy and BMS-986016 ± nivolumab is currently not known. Therefore, palliative radiotherapy is not recommended while receiving any of these drugs, alone or in combination. If palliative radiotherapy in short courses and for isolated fields is required to control symptoms not clearly related to disease progression, then drug administration should be withheld, if possible, for at least 1 week before radiation and for at least 1 week after its completion. Subjects should be closely monitored for any potential toxicity during and after receiving radiotherapy. Prior to resuming study drug treatment, radiotherapy-related AEs should resolve to ≤ Grade 1 or baseline and subjects must meet relevant eligibility criteria as determined by the BMS Medical Monitor in discussion with the Investigator. The BMS Medical Monitor must be consulted prior to reinitiating treatment in a subject with a dosing interruption lasting > 6 weeks after the last dose.

Details of palliative radiotherapy should be documented in the source records and electronic case report form (eCRF). Details in the source records should include dates of treatment, anatomical site, dose administered, fractionation schedule, and AEs. Symptoms requiring palliative radiotherapy should be evaluated for objective evidence of disease progression. Subjects receiving palliative radiation of target lesions will have the evaluation of ORR just prior to radiotherapy, but such subjects will no longer be evaluable for determination of response subsequent to the date palliative radiotherapy occurs.

3.4.4 Treatment of BMS-986016, Nivolumab-related Infusion Reactions

Since all study treatments contain only human immunoglobulin protein sequences, they are unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the BMS Medical Monitor and reported as an SAE if it meets the criteria. Infusion reactions should be graded according to NCI CTCAE v4.0 guidelines.

If a subject has an infusion reaction with nivolumab, the BMS-986016 infusion can be given (without prophylactic medications) if the infusion reaction resolves within 3 hours. For scheduling purposes after a nivolumab infusion reaction, the BMS-986016 infusion may be given within the next 2 days. Prophylactic preinfusion medications should be given prior to all subsequent nivolumab infusions.

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

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

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

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

Stop the infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur, then no further study drug will be administered at that visit.

For future infusions, the following prophylactic premedications are recommended:

Diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg should be administered at least 30 minutes before study drug infusions. If necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent) may be used.

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

Immediately discontinue infusion of study drug. Begin an IV infusion of normal saline and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the Investigator is comfortable that the symptoms will not recur. All study drug(s) will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery of the symptoms.

In case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine or corticosteroids).

Please refer to Appendix 4 for a complete list of the AE management algorithms.

3.5 Discontinuation of Subjects From Treatment

Subjects MUST discontinue investigational product (and noninvestigational product at the discretion of the Investigator) for any of the following reasons:

Subject's request to stop study treatment

Pregnancy

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

Inability to comply with protocol requirements

- Progressive disease (see also Section 4.3.4 for details regarding continuing treatment beyond initial assessment of PD per RECIST)

Clinical deterioration as assessed by the Investigator

Adverse event meeting discontinuation criteria (Section 4.3.5)

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

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

3.6 Post Treatment Study Follow-up

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

3.6.1 Withdrawal of Consent

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

3.6.2 Lost to Follow-up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of 3 documented phone calls, faxes, or emails, as well as lack of response by subject to 1 registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death.

If Investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the subject's ICF, then the Investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining the subject'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 subject remains lost to follow-up, then the last known alive date as determined by the Investigator should be reported and documented in the subject's medical records.

4 TREATMENTS

All protocol-specified investigational and noninvestigational products are considered study drug.

4.1 Study Treatments

Product description and storage information is described in Table 4.1-1. Preparation and administration instructions will be provided separately via site training materials.

For study drugs not provided by BMS and obtained commercially by the site, storage should be in accordance with the package insert, SmPC, or similar documentation.

Table 4.1-1: Product Description and Dosage Form

Product Description and Dosage Form	Potency	Primary Packaging (Volume)/Label Type	Secondary Packaging (Qty)/Label Type	Appearance	Storage Conditions (per Label)
BMS-986016-01[a] Relatlimab Injection, 100 mg/vial or 80 mg/vial	10 mg/mL	10 mL vial/open label or 8 mL vial/open label	4 vials/carton/open label	A clear to slightly opalescent, colorless to pale yellow liquid. May contain particles	Store refrigerated, 2-8°C (36-46 °F) Protect from light Protect from freezing
BMS-936558-01[b] Nivolumab Injection, 100 mg/vial (10 mg/mL)	10 mg/mL	10 mL vial/open label	4 or 5 vials/carton/open label	Clear to opalescent, colorless to pale yellow liquid. May contain particles	Store refrigerated, 2-8°C (36-46°F) Protect from light Protect from freezing
BMS-986213[c] (Relatlimab 80 mg/ Nivolumab 240 mg vial) (16 mg/mL)	16 mg/mL	20 mL vial/open label	2 vials/carton	Colorless to pale yellow liquid, clear to slightly opalescent, light (few) particulates (consistent in appearance to protein particulates) may be present.	Refer to the label on container and/or pharmacy manual

[a] Designated as BMS-986016 in the protocol.

[b] Nivolumab; designated as BMS-936558 in the protocol.

[c] Designated as BMS-986213 in the protocol.

4.1.1 Investigational Product

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

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

In this protocol, investigational products are BMS-986016, BMS-936558 (nivolumab), and BMS-986213 (relatlimab/nivolumab). BMS-986213 is a FDC drug product and contains relatlimab and nivolumab at a protein-mass ratio of 1:3 in a single vial.

4.1.2 Noninvestigational Product

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

In this protocol, noninvestigational product(s) is/are: not applicable for this study.

4.1.3 Handling and Dispensing

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

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

For noninvestigational product, if marketed product is utilized, it should be stored in accordance with the package insert, SmPC, or similar.

In Part B Q2W dose escalation, nivolumab will be administered first over approximately 60 minutes, followed by approximately 60 minutes infusion of BMS-986016 within 15 to 30 minutes after completion of the nivolumab infusion. In Part B, for doses of BMS-986016 960 mg + 480 mg nivolumab Q4W and higher doses, BMS-986016 infusion should be administered no sooner than 30 minutes following completion of nivolumab infusion. The nivolumab infusion will be administered over approximately 30 minutes in Part B Q4W and all Part C cohorts. In Part D, BMS-986016 and nivolumab will be coadministered in a single IV bag over approximately 60 minutes and BMS-986213 (FDC) will be administered over approximately 60 minutes. In Part E, BMS-986016 and nivolumab will be coadministered in a single IV bag over approximately

60 minutes Q4W. Further details regarding preparation and administration will be provided separately in site/pharmacy training materials.

4.2 Method of Assigning Subject Identification

This is an open-label study. All subjects must be assigned a subject number upon providing signed written informed consent. The investigative site will call into the enrollment option of the IVRS designated by BMS for assignment of a [redacted]-digit subject number that will be unique across all sites. Enrolled subjects, including those not dosed, will be assigned sequential subject numbers starting with [redacted] The patient identification number (PID) will ultimately comprise the site number and subject number. For example, if the first subject is enrolled at site 3, they will have a PID of [redacted]. Specific instructions for using IVRS will be provided to the investigational sites in a separate document.

Once it is determined that the subject meets the eligibility criteria, the investigative site will call the IVRS within 3 days prior to first study drug administration for the subject to be either:

Assigned to a part (Parts A and B) and dose cohort in the dose escalation portion of the study

Assigned to an expansion cohort in the cohort expansion portion (Parts A1 and C) of the study

Assigned to Part D1 or Part D2 based on eligibility criteria.

- Part D1: randomized to either Arm 1, 2, or 3

Assigned to Part E based on eligibility criteria, including status of prior anti-PD-1 therapy (melanoma participants who experienced disease progression on prior anti-PD-1 therapy and melanoma participants who have not received prior systemic anticancer therapy for unresectable or metastatic melanoma). Melanoma participants who experienced disease progression on prior anti-PD-1 therapy will be allocated to a single treatment arm, and melanoma participants who have not received prior systemic anticancer therapy for unresectable or metastatic melanoma will be randomized to 1 of 2 treatment cohorts.

During dose escalation, all subjects will be assigned to Part A until the decision is made to escalate to the third dose cohort. Subsequently, treatment in Part B will be initiated, and escalation in the 2 parts will occur in parallel. Treatment assignments for subjects eligible for both Part A and Part B will alternate between the 2 parts, with consecutively treated subjects assigned to different parts through IVRS whenever possible. If there are no openings available in the part to which the subject would be assigned by this algorithm, then the subject will be assigned to the next open part/cohort.

During dose escalation (Parts A and B), subjects who are not evaluable for DLT determination may be replaced. Replacement subjects will be assigned to the same part (Part A or Part B) and dose but will be assigned a new subject number.

Treatment assignments for subjects eligible for both Part A1 and Part C will alternate between the 2 parts, with consecutively treated subjects assigned to different parts through IVRS whenever possible. If there are no openings available in the part to which the subject would be assigned by this algorithm, then the subject will be assigned to the next open part/cohort.

Prior to Revised Protocol 09, Part D1 subjects are being enrolled only into single arm BMS-986016 80 mg + nivolumab 240 mg Q2W. Subsequent to activation of this amendment, and until the enrollment to Part D1 arm BMS-986016 80 mg + nivolumab 240 mg Q2W is completed, subjects in Part D1 will be randomized 1:1:1 across the 3 arms: Part D1 BMS-986016 80 mg + nivolumab 240 mg Q2W (Arm 1), Part D1 BMS-986016 160 mg + nivolumab 480 mg Q4W coadministration (Arm 2), Part D1 BMS-986016 160 mg/nivolumab 480 mg Q4W FDC (Arm 3). Once enrollment to Part D1 arm BMS-986016 80 mg + nivolumab 240 mg Q2W is completed, subjects will be randomized 1:1 to the 2 remaining arms. If enrollment to Q4W arms is completed prior to arm BMS-986016 80 mg + nivolumab 240 mg Q2W, then enrollment to arm BMS-986016 80 mg + nivolumab 240 mg Q2W will be completed as a single arm.

4.3 Selection and Timing of Dose for Each Subject

4.3.1 Guidelines for Dose Modification

4.3.1.1 Intrasubject Dose Escalation

Intrasubject dose escalation of BMS-986016, BMS-986213, or nivolumab (BMS-936558) is not permitted in this study.

4.3.1.2 Dose Reductions

With the possible exception of subjects being treated at a dose level that is subsequently deemed to exceed the MTD, intrasubject dose reduction of BMS-986016, BMS-986213, or nivolumab (BMS-936558) is not permitted.

4.3.2 Dose Delay Criteria

In some cases, the natural history of select AEs associated with immunotherapy can differ from and be more severe than AEs caused by other therapeutic classes. Early recognition and management may mitigate severe toxicity.

Guidance for Investigators is provided in the current BMS-986016 and BMS-936558 (nivolumab) IBs.[11,29] Additionally, management algorithms have been developed to assist Investigators with select toxicities and can be found in the current BMS-936558 (nivolumab) IB; toxicities for which management algorithms have been developed include:

Pulmonary
Gastrointestinal
Hepatic
Endocrine
Renal
Dermatologic
Neurologic (see Table 5.1-2 “Neurological Exam” for criteria for protocol-required neurologic exams)
Cardiac

Subjects who experience the following must have all study drug(s) held:

Potential DLTs (per definition, are related to study drug) until DLT relatedness is defined

Select drug-related AEs and drug-related laboratory abnormalities:

- ≥ Grade 1 pneumonitis
- ≥ Grade 1 myocarditis (see Appendix 4)
- All troponin T or I elevations require a dose delay to allow for prompt cardiac and safety evaluation.
- ≥ Single grade increase shift from baseline (at least to Grade 2) of AST, ALT, and/or total bilirubin
- ≥ Grade 2 creatinine
- ≥ Grade 2 diarrhea or colitis
- ≥ Grade 2 neurological AE
- Grade 4 amylase and/or lipase abnormalities regardless of symptoms or clinical manifestations

AE, laboratory abnormality, or concurrent illness that, in the judgment of the Investigator, warrants delaying the dose of study drug.

Subjects may be dosed no less than 12 days in Q2W regimen and 25 days in Q4W from the previous dose and no more than 3 days from scheduled dose. If an infusion cannot be administered at a scheduled visit, it should be administered as soon as possible. Subsequent dosing visits will follow every 2 weeks or every 4 weeks after the delayed dose. A dose given more than 3 days after the intended dose date will be considered a delay. A maximum delay of 6 weeks between doses is allowed. Longer delays may be allowed following discussion with the Medical Monitor. Subjects who meet criteria listed in Section 4.3.5 are required to permanently discontinue all study drug(s). All other subjects will be permitted to resume therapy with study drug(s) at the same dose level(s) following resolution of the AE as described in Section 4.3.3.

4.3.3 Criteria to Resume Treatment After Dose Delay

Subjects will be permitted to resume therapy at the same dose level(s) following resolution of the AE to ≤Grade 1 or to baseline within 6 weeks after last dose, with the exception of subjects who meet criteria for permanent discontinuation as specified in Section 4.3.5. Subjects who meet criteria for permanent discontinuation should receive no further study therapy. The following exceptions apply:

If the toxicity resolves to ≤Grade 1 or baseline > 6 weeks after last dose but the subject does not otherwise meet the criteria for permanent discontinuation (see Section 4.3.5) and the Investigator believes that the subject is deriving clinical benefit, then the subject may be eligible to resume the study drug(s) following the approval of the BMS Medical Monitor.

Subjects with a Grade 4 drug-related amylase and/or lipase increase that is not associated with symptoms or clinical manifestations of pancreatitis can be restarted on therapy once the levels have recovered to Grade 3 or less, and after consultation with the BMS Medical Monitor.

Subjects with baseline Grade 1 AST, ALT, or total bilirubin who require dose delays for reasons other than a drug-related hepatic event may resume treatment in the presence of Grade 2 AST, ALT, or total bilirubin.

Subjects who require dose delays for drug-related elevations in AST, ALT, or total bilirubin may resume treatment when these values have returned to their baseline CTCAE Grade or normal, provided the criteria for permanent discontinuation are not met.

Subjects may resume treatment in the presence of Grade 2 fatigue.

Drug-related endocrinopathies adequately controlled with only physiologic HRT may resume treatment.

Troponin T or I elevations will require the participant to undergo a cardiac and safety evaluation. Following this evaluation, determination of further treatment will be based on the discussion with the BMS Medical Monitor or designee.

4.3.4 Treatment Beyond Disease Progression

Accumulating evidence indicates a minority of participants treated with immunotherapy may derive clinical benefit despite initial evidence of PD.

Participants treated with nivolumab and BMS-986016 or BMS-986213 will be permitted to continue treatment beyond initial RECIST v1.1–defined PD, 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)

Subjects 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 follow-up scan should be performed at the next scheduled imaging evaluation 8 weeks later (but no sooner than 4 weeks) 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 treatment with nivolumab and BMS-986016 or BMS-986213.

If the investigator feels that the subject continues to achieve clinical benefit by continuing treatment beyond progression, the subject should remain on the trial and continue to receive monitoring according to the Schedule of Activities (Table 5.1-2).

For the subjects 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. Study treatment should be discontinued permanently upon documentation of further progression.

New lesions are considered measureable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes that must have a short axis of at least 15 mm). Any new lesion considered nonmeasureable at the time of initial progression may become measureable and therefore included in the tumor burden if the longest diameter increases to at least 10 mm (except for pathological lymph nodes that 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 that become measurable, these new lesions must demonstrate an absolute increase of at least 5 mm.

4.3.5 Guidelines for Permanent Discontinuation

Subjects meeting any of the following criteria will be required to permanently discontinue all study drug(s) (BMS-986016 in Part A and Part A1; BMS-986016 and nivolumab [BMS-936558] or BMS-986213 in Parts B, C, D, and E):

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 retreatment period OR requires systemic treatment

Any ≥ Grade 3 nonskin, drug-related AE lasting > 7 days or recurs, with the following exceptions for laboratory abnormalities, drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, infusion reactions, and endocrinopathies

Any ≥ Grade 3 drug-related myocarditis, uveitis, pneumonitis, bronchospasm, or hypersensitivity reaction of any duration requires discontinuation.

Any ≥ Grade 3 infusion reaction that does not return to Grade 1 in 6 hours or less requires discontinuation.

Any ≥ Grade 3 drug-related endocrinopathies adequately controlled with only physiologic HRT do not require discontinuation.

Any ≥ Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:

- Any ≥ Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation.
- AST, ALT, or bilirubin abnormalities that meet DLT criteria (Section 3.1.2.6) (In most cases of AST or ALT elevation meeting DLT criteria, study drugs will be permanently discontinued. If the Investigator determines a possible favorable benefit-risk ratio that warrants continuation of study drugs, a discussion between the Investigator and the BMS Medical Monitor/designee must occur.)
- Elevated troponin that meets DLT criteria (Section 3.1.2.6)

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
- Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis
- Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
- Grade 4 drug-related endocrinopathy AEs, such as adrenal insufficiency, adrenocorticotropic hormone deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic HRT (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS Medical Monitor.

Any event that leads to delay in dosing lasting > 6 weeks from the previous dose requires discontinuation, with the following exceptions:

- Dosing delays to allow for prolonged steroid tapers to manage drug-related AEs are allowed. Prior to reinitiating treatment in a subject with a dosing delay lasting > 6 weeks from the previous dose, the BMS Medical Monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.
- Dosing delays lasting > 6 weeks from the previous dose that occur for nondrug-related reasons may be allowed if approved by the BMS Medical Monitor. Prior to reinitiating treatment in a subject with a dosing delay lasting > 6 weeks, the BMS Medical Monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.

Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing.

The consideration to reinitiate study therapy in selected cases at any time point after discontinuation could be made on a case-by-case basis after considering the overall benefit-risk profile and in consultation between the Investigator and the study Sponsor. The selected subjects will need to meet eligibility criteria. The original dose and schedule and protocol rules would apply accordingly (Section 3.1.2.5).

4.4 Blinding/Unblinding

Data emerging from this exploratory study may be necessary to inform timely decisions for adjusting procedures in subsequent portions of the study, including early termination of the study. Additionally, treatment assignments may facilitate optimization of the bioanalytical analysis of samples.

Designated staff of the Sponsor can access Interactive Response Technology (IRT) treatment codes prior to the formal locking of the study database. This access to the treatment codes will not impact the data integrity of the study.

4.5 Treatment Compliance

Study drug will be administered in the clinical facility by trained medical personnel. Treatment compliance will be monitored by drug accountability, as well as by recording BMS-986016, BMS-986213, and nivolumab (BMS-936558) administration in subjects' medical records and CRFs.

4.6 Destruction and Return of Study Drug

4.6.1 Destruction of Study Drug

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

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

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

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

On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.

Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's standard operating procedures and a copy provided to BMS upon request.

Records are maintained that allow for traceability of each container, including the date disposed, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor, must be documented.

Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

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

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

4.6.2 Return of Study Drug

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

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

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Study assessments and procedures are presented in Table 5.1-1, Table 5.1-2, and Table 5.1-3.

Additional measures, including nonstudy required laboratory tests, should be performed as clinically indicated or to comply with local regulations. Laboratory toxicities (eg, suspected drug induced liver enzyme evaluations) will be monitored during the follow-up phase via on-site/local labs until all study drug-related toxicities resolve, return to baseline, or are deemed irreversible.

If a participant shows pulmonary-related signs (hypoxia, fever) or symptoms (eg. dyspnea, cough, fever) consistent with possible pulmonary adverse events, the participant should be immediately evaluated to rule out pulmonary toxicity, according to the suspected pulmonary toxicity management algorithm in the BMS-936558 (nivolumab) Investigator Brochure.

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

Table 5.1-1: Screening Procedural Outline (CA224020)

Procedure	Screening Visit (Day -28 to -1)	Day -14 to -1 Visit	Day -3 to -1 Visit	Notes
Eligibility Assessments				
Informed consent	X See Notes			A subject is considered enrolled only when an IRB/IEC-approved ICF is signed and dated. Obtain subject number from IVRS. [redacted]
Inclusion/exclusion criteria	X			
Medical history	X			May include more detailed medical history of risk factors for potential events such as pulmonary-related events. Include any toxicities or allergy related to previous treatments. Include any prior PD-L1 results available.
Submission of pretreatment tumor tissue	X See Notes and Table 5.7-5			For all subjects: See Laboratory Manual for delivery and processing indications. Tumor tissue to be sent to central lab after performing specified tests locally within approximately 1 week of C1D1 (see "Laboratory tests" in this table below). **During the screening period, all participants must have tumor tissue submitted,** [redacted]. If a screening biopsy is required, participants must have a lesion that can be biopsied at an acceptable clinical risk as judged by the investigator. Tissue may be from a core, punch, or excisional biopsy or surgical specimen. Sufficient quantities must be available: a block or a minimum of 20 slides is required.
Safety Assessments				
Physical examination (PE)	X			If the screening PE is performed within 1 day of dosing on Cycle 1 Day 1, then a single exam may count as both the screening and predose evaluation.
Performance status	X			ECOG PS/KPS for RCC subjects ONLY/Lansky for minors ONLY (Appendix 3)

Table 5.1-1: Screening Procedural Outline (CA224020)

Procedure	Screening Visit (Day -28 to -1)	Day -14 to -1 Visit	Day -3 to -1 Visit	Notes
Physical measurements	X			Includes height, weight
Vital signs	X See Notes			Includes body temperature, seated blood pressure, and heart rate. Blood pressure and heart rate should be measured after the subject has been seated quietly for at least 5 minutes.
Oxygen saturation	X See Notes			Collected at rest and after mild exertion via pulse oximetry to establish baseline. If subject has oxygen saturation ≤ 90%, consult BMS Medical Monitor prior to enrollment.
Electrocardiogram (ECG)	X			12-lead ECG
Chest radiograph	X			Posterior-anterior and lateral chest x-ray to establish baseline (preferred)
Echocardiogram	X See Note			LVEF assessment with documented LVEF ≥ 50% by either TTE or MUGA (TTE preferred test) within 6 months from first study drug administration

Table 5.1-1: Screening Procedural Outline (CA224020)

Procedure	Screening Visit (Day -28 to -1)	Day -14 to -1 Visit	Day -3 to -1 Visit	Notes
Laboratory tests	X See Notes			Blood and Urine Tests: To include hematology, serum chemistry, endocrine panel, serology, urinalysis, [redacted] See Section 5.3.1 for panel requirements. (Subjects with controlled hyperthyroidism must be negative for thyroglobulin and thyroid peroxidase antibodies and thyroid-stimulating immunoglobulin.) (Subjects with type 2 diabetes must have HbA1c to establish baseline.) If tests are performed within 3 days of dosing on C1D1, then C1D1 laboratories are not required. Tests on Tumor Tissue (see Section 5.3.1): • For all subjects in Parts A, B, C, D, and E: Subjects with applicable tumor types must provide results of previous gene mutation testing. For colorectal cancer, EGFR, K-RAS, and microsatellite instability (MSI) mutation status; for gastric cancer, presence of EBV and human epidermal growth factor receptor 2 (HER-2); for melanoma, BRAF mutation status; and for NSCLC, ALK, K-RAS and EGFR mutation status; otherwise, these tests will be performed locally. Test(s) will be requested at baseline, but subjects can proceed to treatment prior to receipt of results. • Subjects in Part C with head and neck tumors: Subjects must be tested for HPV status by p16 IHC and/or HPV in situ hybridization (ISH). If testing has not been previously performed, testing must be performed locally to confirm HPV status. • Not required for subjects in cohorts for crossover and rechallenge. As of Protocol Amendment 14, rechallenge is not permitted.
Pregnancy test (WOCBP)			X See Notes	Pregnancy test should be performed in all WOCBP prior to first study drug administration. Serum or urine pregnancy test (minimum sensitivity of urine pregnancy test of 25 IU/L of either total hCG or the beta fraction). If performed within 24 hours of dosing on C1D1, then C1D1 pregnancy test is not required.
Follicle-stimulating hormone (FSH)	X See Notes			If needed to document postmenopausal status as defined in Section 3.3.3 Not required at crossover or rechallenge. As of Protocol Amendment 14, rechallenge is not permitted.

Table 5.1-1: Screening Procedural Outline (CA224020)

Procedure	Screening Visit (Day -28 to -1)	Day -14 to -1 Visit	Day -3 to -1 Visit	Notes
Concomitant medications		X		Collected during the 2-week period prior to Cycle 1 Day 1
Assessment of signs and symptoms		X		Collected during the 2-week period prior to Cycle 1 Day 1
Adverse Event Reporting				
Monitor for serious adverse events	X			All SAEs must be collected from the date of subject's written consent.
Efficacy Assessments				
Diagnostic Imaging	X See Notes			CT with contrast is the preferred modality (CT chest without contrast or MRI if CT is not feasible or appropriate given location of the disease). Assessment should include the chest/abdomen/pelvis at a minimum and should include other anatomic regions as indicated based on the subject's tumor type and/or disease history. Imaging scans must be de-identified and archived in their native Digital Imaging and Communications in Medicine (DICOM) format as part of the subject study file.
Prior Diagnostic Imaging	X See Notes			For Part D and Part E melanoma: All available scans on the most recent prior anti-PD-1–containing regimen, including the baseline scan (prior to starting anti-PD-1) and scans after the last dose of anti-PD-1 but before the start of any intervening therapy, will be collected and submitted to a central imaging vendor. At minimum the following time points are to be submitted: 1) pretreatment scan; 2) nadir scan (if applicable); 3) scan documenting progression (does not need to be submitted if it has already been submitted as the baseline scan for the trial); 4) scan confirming progression (if applicable, it must be at least 4 weeks after the scan documenting progression and without intervening therapy and does not need to be submitted if it has already been submitted as the baseline scan for the trial); 5) Treatment beyond progression scan (if applicable, as this is the last scan on treatment if the subject was treated beyond a progression confirmation scan and does not need to be submitted if it has already been submitted as the baseline scan for the trial).

Table 5.1-1: Screening Procedural Outline (CA224020)

Procedure	Screening Visit (Day -28 to -1)	Day -14 to -1 Visit	Day -3 to -1 Visit	Notes
Brain imaging	X See Notes			Applicable Subjects: Brain imaging (MRI) for subjects with history or symptoms of brain metastases who have not had brain imaging within 30 days of anticipated first study drug administration. MRI of the brain should have been be done for all subjects treated on study as first-line NSCLC or first-line melanoma as part of their initial evaluation of advanced disease, and if not, it should be done during screening.
Bone Scan	X See Notes			As clinically indicated (ie, subjects with history or symptoms of bone metastases), but bone scans will not be considered a modality for assessment for measurable disease.

Table 5.1-2: On-treatment Procedural Outline for Q2W and Q4W BMS-986016/Nivolumab Treatment Regimens Parts A Through E

Procedure	Treatment Cycles					Notes
	Day 1	**Day 15**	**Day 29**	**Day 43**	**Day 50-56[a]**	
Visit Window for Q2W	± 2 days	± 2 days	± 2 days	± 2 days		
Visit Window for Q4W	± 3 days	± 3 days	± 3 days	± 3 days		
IVRS Assignment						
IVRS assignment	X See Notes					Cycle 1 only Once subject eligibility has been confirmed, IVRS assignment can be performed within 3 days prior to first study drug administration. (Discuss with Sponsor if institutional policies and procedures require additional lead time.) For all subsequent treatment visits, IVRS assignment can be performed within applicable visit window.
Safety Assessments	**All assessments are to be performed/results are to be reviewed <u>PRIOR</u> to study drug dosing unless otherwise specified.** *Note: For Part D, D1, D2, and participants in Part E receiving doses of relatlimab/nivolumab 160mg/480mg Q4W: Study visits will occur Q2W (Day 1, 15, 29, 43) to assess safety for the first cycle of treatment, and thereafter visits will only be on Day 1 and Day 29 of each subsequent cycle.*					
Clinical Observation	See notes					All participants should be clinically evaluated for any immune-mediated events. Evaluations should occur every week (± 1 day) up to and including Week 8. Participants with any clinical symptoms, in particular fatigue, should immediately be evaluated.
Physical examination (PE)[b]	X See Notes	X See Notes	X See Notes	X See Notes		Perform PE within 2 days of dosing for each cycle. On subsequent treatment visits in each cycle, perform a symptom-directed PE.

Table 5.1-2: On-treatment Procedural Outline for Q2W and Q4W BMS-986016/Nivolumab Treatment Regimens Parts A Through E

Procedure	Treatment Cycles					Notes
	Day 1	Day 15	Day 29	Day 43	Day 50-56[a]	
Visit Window for Q2W	± 2 days	± 2 days	± 2 days	± 2 days		
Visit Window for Q4W	± 3 days	± 3 days	± 3 days	± 3 days		
						[redacted]
Neurological exam (NE)	See Notes					Subjects in Part B, Part C, Part D, and Part E: Obtain neurological exam (performed by a neurologist) in subjects who experience a study drug related ≥ Grade 2 neurological AE.
Performance status	X	X	X	X		ECOG PS/KPS for RCC subjects ONLY/Lansky for minors ONLY (Appendix 3).
Weight	X	X	X	X		

Table 5.1-2: On-treatment Procedural Outline for Q2W and Q4W BMS-986016/Nivolumab Treatment Regimens Parts A Through E

Procedure	Treatment Cycles					Notes
	Day 1	Day 15	Day 29	Day 43	Day 50-56[a]	
Visit Window for Q2W	± 2 days	± 2 days	± 2 days	± 2 days		
Visit Window for Q4W	± 3 days	± 3 days	± 3 days	± 3 days		
Vital signs	X See Notes	X See Notes	X See Notes	X See Notes		Includes temperature, seated blood pressure, and heart rate. Blood pressure and heart rate should be measured after the subject has been seated quietly for at least 5 minutes. On Cycle 1 Day 1, vital signs will be obtained before the infusion and then every 15 minutes (± 5 minutes) until 60 minutes (120 minutes for subjects in the first dose cohort of Part B) after the completion of the infusion(s). Vital signs on subsequent treatment visits will be collected before the infusion and then every 30 minutes (± 10 minutes until 60 minutes following completion of the infusion(s). If any vital sign is abnormal (based upon clinician assessment) at the final check, the subject must be observed further for a period of time, as clinically indicated.
12-lead electrocardiogram (ECG)	X See Notes	X See Notes	X See Notes	X See Notes		Subjects enrolled in Parts A and B: • Cycle 1 Day 1 and Cycle 3 Day 1: 12-lead ECG collected per Holter monitor. Monitoring to begin prior to dosing and to continue through the collection of the 4-hour postdose BMS-986016 PK sample. • 12-lead ECG to be performed within 2 days of dosing for ALL cycles using site's own ECG machine; results to be assessed prior to dosing. For Cycle 1

Table 5.1-2: On-treatment Procedural Outline for Q2W and Q4W BMS-986016/Nivolumab Treatment Regimens Parts A Through E

Procedure	Treatment Cycles					Notes
	Day 1	Day 15	Day 29	Day 43	Day 50-56[a]	
Visit Window for Q2W	± 2 days	± 2 days	± 2 days	± 2 days		
Visit Window for Q4W	± 3 days	± 3 days	± 3 days	± 3 days		
						only, 12-lead ECG is also to be performed predose on Day 15, Day 29, and Day 43. Subjects enrolled in Part A1, Part C, Part D, and Part E: • 12-lead ECG to be performed within 2 days of Day 1 dose for all cycles using site's own ECG machine; results to be assessed prior to dosing. For Cycle 1 only, 12-lead ECG is also to be performed predose on Day 15, Day 29, and Day 43. Subjects enrolled in cohorts for rechallenge or crossover: • 12-lead ECG to be performed within 2 days of dosing on Day 1 of all cycles using site's own ECG machine; results to be assessed prior to dosing. • As of Protocol Amendment 14, rechallenge is not permitted.
Chest radiograph						As clinically indicated
Oxygen saturation	X See Notes	X See Notes	X See Notes	X See Notes		Collected at rest and after mild to moderate exertion via pulse oximetry. Oxygen levels will be used in combination with clinical signs and symptoms and radiographic images to evaluate pulmonary/respiratory status. Changes in O2 levels will not be used in isolation to document or diagnose pulmonary toxicity.
Laboratory tests	X See Notes	X See Notes	X See Notes	X See Notes		Labs are performed locally and may be collected within 3 days prior to dosing. To include serum chemistry, hematology, urinalysis, [redacted]; see Section 5.3.1 for panel requirements. All laboratory results should be checked prior to dosing.

Table 5.1-2: On-treatment Procedural Outline for Q2W and Q4W BMS-986016/Nivolumab Treatment Regimens Parts A Through E

Procedure	Treatment Cycles					Notes
	Day 1	Day 15	Day 29	Day 43	Day 50-56[a]	
Visit Window for Q2W	± 2 days	± 2 days	± 2 days	± 2 days		
Visit Window for Q4W	± 3 days	± 3 days	± 3 days	± 3 days		
						In asymptomatic participants, these laboratory tests can be performed locally, but treating investigator must be notified on the same day.
Endocrine panel	X See Notes					Labs are performed locally and may be collected within 3 days prior to dosing. See Section 5.3.1 for panel requirements. Results must be reviewed by the Investigator or appropriate designee within 2 days following dose administration.
[redacted]	See Notes **C2 Day 1 ONLY**	X See Notes	X See Notes	X See Notes		Labs are performed locally only for **Cycle 1 Day 15, 29, and 43 and Cycle 2 Day 1** and may be collected within 3 days prior to dosing. [redacted] Section 5.3.1 for requirements.
Serologic tumor markers	X See Notes					Labs performed locally for subjects with colorectal, gastric, germ cell, HCC, ovarian, or prostate cancer. See Section 5.3.1.
Pregnancy test (WOCBP)	X		X			A pregnancy test must be performed within 24 hours prior to administration of study drug.

Table 5.1-2: On-treatment Procedural Outline for Q2W and Q4W BMS-986016/Nivolumab Treatment Regimens Parts A Through E

Procedure	Treatment Cycles					Notes
	Day 1	Day 15	Day 29	Day 43	Day 50-56[a]	
Visit Window for Q2W	± 2 days	± 2 days	± 2 days	± 2 days		
Visit Window for Q4W	± 3 days	± 3 days	± 3 days	± 3 days		
	See Notes		See Notes			Serum or urine pregnancy test may be performed (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG). If results are positive, hold all study drug and perform confirmatory testing. If pregnancy is confirmed, permanently discontinue all study drug and immediately notify Sponsor per Section 6.4.
Assess adequate contraceptive use	X See Notes		X See Notes			For WOCBP: Assess for continued use of acceptable methods of contraception; see Appendix 1. **As of Protocol Amendment 14**, no contraception requirements for relatlimab and nivolumab are necessary for male participants.
Adverse Event and ConMed Assessment						
Monitor for nonserious adverse events	X	X	X	X		
Monitor for serious adverse events	X	X	X	X		
ConMed assessment	X	X	X	X		
Sample Collection						
Pharmacokinetic (PK) assessments	See Section 5.5 and Table 5.5.1-1 and Table 5.5.1-2 for Q2W dosing See Table 5.5.1-3 for Q4W dosing Part B and Part C (Bladder Cohort), Table 5.5.1-4/Table 5.5.1-5 for Part D and Part E					Performed in all subjects

Table 5.1-2: On-treatment Procedural Outline for Q2W and Q4W BMS-986016/Nivolumab Treatment Regimens Parts A Through E

Procedure	Treatment Cycles					Notes
	Day 1	Day 15	Day 29	Day 43	Day 50-56[a]	
Visit Window for Q2W	± 2 days	± 2 days	± 2 days	± 2 days		
Visit Window for Q4W	± 3 days	± 3 days	± 3 days	± 3 days		
Immunogenicity assessments	See Section 5.5 and Table 5.5.1-1 and Table 5.5.1-2 See Table 5.5.1-3 for Q4W dosing Part B and Part C (Bladder Cohort), Table 5.5.1-4/Table 5.5.1-5 for Part D and Part E					Performed in all subjects
Biomarker assessments	See Section 5.7 and Table 5.7-1, Table 5.7-2, Table 5.7-3, and Table 5.7-4 See Notes					**Subjects in Part A and B:** Performed in all subjects enrolled at each dose level. See Laboratory Manual for delivery and processing indications. **Subjects in Part C:** [redacted]. See Laboratory Manual for delivery and processing indications. **Subjects in Part A1:** Mandatory in all subjects of each cohort for US IION sites. See Laboratory Manual for delivery and processing indications. **Subjects in Part D and E:** Biomarker collections are required for all subjects. Refer to footnotes for Table 5.7-3 and Table 5.7-4 for details.

Table 5.1-2: On-treatment Procedural Outline for Q2W and Q4W BMS-986016/Nivolumab Treatment Regimens Parts A Through E

Procedure	Treatment Cycles					Notes
	Day 1	Day 15	Day 29	Day 43	Day 50-56[a]	
Visit Window for Q2W	± 2 days	± 2 days	± 2 days	± 2 days		
Visit Window for Q4W	± 3 days	± 3 days	± 3 days	± 3 days		
On-treatment tumor biopsy			X See Notes and Table 5.7-5			[redacted]
OPTIONAL Postprogression (PD) tumor biopsy	See Notes See Table 5.7-5					OPTIONAL tumor biopsy for any subject; obtained upon confirmation of PD. See Laboratory Manual for delivery and processing indications.
Efficacy Assessments						
Diagnostic imaging					X See Notes	Every 8 weeks by methods used at baseline, until disease progression or discontinuation of study treatment. Imaging scans must be de-identified and archived in their native DICOM format as part of the subject study file.
Brain imaging					X See Notes	Subjects with known CNS disease must have imaging assessments at least every 12 weeks.
Bone scan					X See Notes	As clinically indicated
Response assessment					X See Notes	Assessed by RECIST v1.1; see Appendix 2. Assessment must be performed prior to initiating the next cycle of treatment.

Table 5.1-2: On-treatment Procedural Outline for Q2W and Q4W BMS-986016/Nivolumab Treatment Regimens Parts A Through E

Procedure	Treatment Cycles					Notes
	Day 1	Day 15	Day 29	Day 43	Day 50-56[a]	
Visit Window for Q2W	± 2 days	± 2 days	± 2 days	± 2 days		
Visit Window for Q4W	± 3 days	± 3 days	± 3 days	± 3 days		
Study Drug Administration	Details regarding preparation and administration are provided in site training materials.[c]					
Parts A, A1, B, and C: BMS-986016 administration	X	X	X	X		Use vials assigned per IVRS: approximately 60-minute infusion.
Parts B and C Q2W: Nivolumab (BMS-936558) administration	X See Notes	X See Notes	X See Notes	X See Notes		Use vials assigned per IVRS. Nivolumab is administered ONLY for those subjects enrolled in Part B and Part C. Combination therapy with nivolumab and BMS-986016 will be administered as sequential infusions (Parts B and C). In Part C, nivolumab infusion will be administered over approximately 30 minutes.
Parts B and C Q4W: Nivolumab BMS-936558 and BMS-986016 administration	X See Notes		X See Notes			Combination therapy with nivolumab and BMS-986016 will be administered as sequential infusions. The nivolumab infusion will be administered over approximately 30 minutes and BMS-986016 over approximately 60 minutes. Study visits will occur Q2W (Day 1, 15, 29, 43) to assess safety for the **first 3 cycles of treatment**, and thereafter visits will only be on Day 1 and Day 29 of each subsequent cycle for Part B subjects. For Part C, study visits will occur Q2W (Day 1, 15, 29, 43) to assess safety for the **first cycle of treatment**, and thereafter visits will only be on Day 1 and Day 29 of each subsequent cycle.
Part D1 Q2W: Nivolumab BMS-936558 and BMS-986016 coadministration	X See Notes	X See Notes	X See Notes	X See Notes		Combination therapy with nivolumab and BMS-986016 will be coadministered in a single IV bag over approximately 60 minutes.

Table 5.1-2: On-treatment Procedural Outline for Q2W and Q4W BMS-986016/Nivolumab Treatment Regimens Parts A Through E

Procedure	Treatment Cycles					Notes
	Day 1	Day 15	Day 29	Day 43	Day 50-56[a]	
Visit Window for Q2W	± 2 days	± 2 days	± 2 days	± 2 days		
Visit Window for Q4W	± 3 days	± 3 days	± 3 days	± 3 days		
Parts D1 and D2 Q4W: Nivolumab BMS-936558 and BMS-986016 coadministration	X See Notes		X See Notes			Combination therapy with nivolumab and BMS-986016 will be coadministered in a single IV bag over approximately 60 minutes. Study visits will occur Q2W (Day 1, 15, 29, 43) to assess safety for the first cycle of treatment, and thereafter visits will only be on Day 1 and Day 29 of each subsequent cycle.
Part D1 Q4W: BMS-986213 FDC	X See Notes		X See Notes			FDC treatment will be administered over approximately 60 minutes. Study visits will occur Q2W (Day 1, 15, 29, 43) to assess safety for the first cycle of treatment, and thereafter visits will only be on Day 1 and Day 29 of each subsequent cycle.
Part E Q4W: Nivolumab (BMS-936558) and BMS-986016 coadministration	X See Notes		X See Notes			Combination therapy with nivolumab and BMS-986016 will be coadministered in a single IV bag over approximately 60 minutes. Study visits will occur Q2W (Day 1, 15, 29, 43) to assess safety for the first cycle of treatment, and thereafter visits will only be on Day 1 and Day 29 of each subsequent cycle.

[a] This visit is not a clinic visit. The purpose of this visit is for diagnostic imaging and subsequent evaluation of results by the Investigator (response assessment). Diagnostic imaging should occur during Day 50-56, and response assessment must be completed prior to initiating the next cycle of treatment.

[b] [redacted]

[c] Study drug may continue to be administered for applicable patients past 5 years from first dose. The original dose, schedule, and protocol rules would apply.

Table 5.1-3: Follow-up Procedural Outline Parts A Through E

Procedure	Clinical Follow-up			Survival Follow-up	Notes
	FU 1 30 days[a] (± 5 days)	**FU 2 60 days[a] (± 5 days)**	**FU 3 135 days[a] (± 5 days)**	**Begins After Completion of Clinical Follow-up Every 12 wks (± 2 wks) up to 5 yrs after FIRST dose of study drug**	
Safety Assessments					
Physical examination (PE)	X	X	X		
Performance status	X	X	X		ECOG PS/KPS for RCC subjects ONLY/Lansky for minors ONLY (Appendix 3)
Weight	X	X	X		
Vital signs	X See Notes	X See Notes	X See Notes		Includes body temperature, seated blood pressure, and heart rate. Blood pressure and heart rate should be measured after the subject has been seated quietly for at least 5 minutes.
12-lead electrocardiogram (ECG)	X See Notes				Subjects enrolled in Parts A and B: • 12-lead ECG collected per Holter monitor, as well as an additional 12-lead ECG using site's own ECG machine Subjects enrolled in Parts C, D, and E: • 12-lead ECG using site's own ECG machine

Table 5.1-3: Follow-up Procedural Outline Parts A Through E

Procedure	Clinical Follow-up			Survival Follow-up	Notes
	FU 1 30 days[a] (± 5 days)	**FU 2 60 days[a] (± 5 days)**	**FU 3 135 days[a] (± 5 days)**	**Begins After Completion of Clinical Follow-up Every 12 wks (± 2 wks) up to 5 yrs after FIRST dose of study drug**	
Oxygen saturation	X See Notes	X See Notes	X See Notes		Collected at rest and after mild to moderate exertion via pulse oximetry. Oxygen levels will be used in combination with clinical signs and symptoms and radiographic images to evaluate pulmonary/respiratory status. Changes in O2 levels will not be used in isolation to document or diagnose pulmonary toxicity.
Laboratory tests	X See Notes		X See Notes		To include serum chemistry, hematology, endocrine panel, and urinalysis; see Section 5.3.1 for panel requirements.
Serologic tumor markers	X See Notes				Labs performed locally for subjects with colorectal, gastric, germ cell, HCC, ovarian, or prostate cancer. See Section 5.3.1.
Pregnancy test (WOCBP)	X See Notes	X See Notes	X See Notes		Serum or urine pregnancy test may be performed (clinic urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG). Home pregnancy testing required on FU Days 90, 120, 150, and 165. If positive, perform confirmatory testing. If pregnancy is confirmed, immediately notify Sponsor per Section 6.4.

Table 5.1-3: Follow-up Procedural Outline Parts A Through E

Procedure	Clinical Follow-up			Survival Follow-up	Notes
	FU 1 30 days[a] (± 5 days)	**FU 2 60 days[a] (± 5 days)**	**FU 3 135 days[a] (± 5 days)**	**Begins After Completion of Clinical Follow-up Every 12 wks (± 2 wks) up to 5 yrs after FIRST dose of study drug**	
Assess adequate contraceptive use	X See Notes	X See Notes	X See Notes		For WOCBP: Assess for continued use of acceptable methods of contraception; see Appendix 1.
Adverse Event and Concomitant Medications Assessment					
Monitor for nonserious adverse events	X See Notes	X See Notes	X See Notes		Nonserious AEs will be collected starting with the first dose of study medication and through 135 days after discontinuation of dosing.
Monitor for serious adverse events	X See Notes	X See Notes	X See Notes		All SAEs must be collected starting at the time a subject signs an ICF and through 135 days after discontinuation of dosing.
Concomitant Medications assessment	X	X	X		
Sample Collection					
Pharmacokinetic (PK) assessments			X See Notes		See Table 5.5.1-1 and Table 5.5.1-2 for Q2W. See Table 5.5.1-3 for Q4W; see Table 5.5.1-4/Table 5.5.1-5 for Part D and Part E.

Table 5.1-3: Follow-up Procedural Outline Parts A Through E

Procedure	Clinical Follow-up			Survival Follow-up	Notes
	FU 1 30 days[a] (± 5 days)	**FU 2 60 days[a] (± 5 days)**	**FU 3 135 days[a] (± 5 days)**	**Begins After Completion of Clinical Follow-up Every 12 wks (± 2 wks) up to 5 yrs after FIRST dose of study drug**	
Immunogenicity (ADA) assessments			X See Notes		See Table 5.5.1-1 and Table 5.5.1-2 for Q2W. See Table 5.5.1-3 for Q4W; see Table 5.5.1-4/Table 5.5.1-5 for Part D and Part E.
Efficacy Assessments					
Diagnostic imaging	X See Notes			X See Notes	Diagnostic imaging required by method used at baseline; an unconfirmed PR, unconfirmed CR, or unconfirmed PD must be confirmed ≥ 4 weeks after initial assessment. Q12W diagnostic imaging must be performed in subjects who discontinue study treatment, at Investigator's discretion, with CR, PR, or SD by RECIST v1.1, until disease progression. Images will be acquired until withdrawal of consent, death, or initiation of another anticancer treatment.
Response assessment	X See Notes				Assessed by RECIST v1.1; see Appendix 2.

Table 5.1-3: Follow-up Procedural Outline Parts A Through E

Procedure	Clinical Follow-up			Survival Follow-up	Notes
	FU 1 30 days[a] (± 5 days)	**FU 2 60 days[a] (± 5 days)**	**FU 3 135 days[a] (± 5 days)**	**Begins After Completion of Clinical Follow-up Every 12 wks (± 2 wks) up to 5 yrs after FIRST dose of study drug**	
Survival Status					
Assessment of subject survival status				X See Notes	Subject status will be assessed by either a clinic visit or telephone contact. The nature and start dates of any new anticancer therapies during this period will be recorded.

a After last dose of study drug.

5.2 Study Materials

The following materials will be provided at study start:

NCI CTCAE v4.0

BMS-986016, BMS-986213, and BMS-936558 IBs

Pharmacy binder

Laboratory manuals for collection and handling of blood (including PK, immunogenicity, and biomarkers) and tissue specimens

Holter monitor, associated supplies, and manual

IVRS manual

Enrollment worksheets

Serious Adverse Event forms

Pregnancy Surveillance forms

5.3 Safety Assessments

Adverse events will be assessed continuously during the study and for 135 days after the last treatment. Adverse events will be evaluated according to the NCI CTCAE v4.0 and should be followed per requirements in Sections 6.1.1 and 6.2.1. Adverse events will be coded using the most current version of MedDRA and reviewed for potential significance and importance.

Protocol-specified assessments are described in Table 5.1-1 (Screening Procedural Outline), Table 5.1-2 (On-treatment Procedural Outline), and Table 5.1-3 (Follow-up Procedural Outline).

5.3.1 Laboratory Test Assessments

A local laboratory will perform the analyses and will provide reference ranges for these tests. Investigators must document their review of each laboratory safety report.

Clinical laboratories will be assessed at the time points indicated in Table 5.1-1 (Screening Procedural Outline), Table 5.1-2 (On-treatment Procedural Outline), and Table 5.1-3 (Follow-up Procedural Outline).

At screening, sites should collect samples during the timeframe indicated in Table 5.1-1 and ensure that results required for eligibility are verified prior to registration. During treatment, unless otherwise indicated in Table 5.1-2, results of clinical laboratory tests must be reviewed prior to dosing.

The following clinical laboratory tests will be performed:

Hematology
Hemoglobin
Hematocrit
Total leukocyte count, including differential
Platelet count

Serum Chemistry

Aspartate aminotransferase (AST)
Alanine aminotransferase (ALT)
Total bilirubin
Alkaline phosphatase
Lactate dehydrogenase (LDH)
Creatinine
Creatinine clearance[a] (screening only)
Blood urea nitrogen (BUN)
Glucose
Amylase
HbA1c (obtain during screening to establish baseline in subjects with type 2 diabetes, then as clinically indicated)
Lipase
C-reactive protein (CRP)
Albumin
Sodium
Potassium
Chloride
Bicarbonate
Calcium
Magnesium
Phosphorus

[a] Cockcroft-Gault formula

Endocrine Panel

Thyroid-stimulating hormone (TSH) with reflex to free triiodothyronine (T3) and free thyroxine (T4) as applicable

Subjects with controlled hyperthyroidism must be negative for thyroglobulin and thyroid peroxidase antibodies and thyroid stimulating (receptor) immunoglobulin (screening only).

Urinalysis

Protein
Glucose
Blood
Leukocyte esterase/leukocyte count

Microscopic examination of the sediment if blood, protein, or leukocyte esterase are positive on the dipstick

Serology (screening only)

Hepatitis B surface antigen (HBsAg, Australia antigen) and/or hepatitis B core antigen
Hepatitis D antibody (for hepatitis B infected HCC subjects only)
Test for quantitative hepatitis B viral load (by polymerase chain reaction [PCR]) (for HCC subjects only)
Test for quantitative hepatitis C viral load (by PCR)
HIV-1, -2 antibody

[redacted]

For those subjects receiving on-going treatment with BMS-986016 and nivolumab, [redacted] elevations will require the subject to undergo a cardiac evaluation. Following this evaluation, determination of further treatment will be based on the discussion with the BMS Medical Monitor or designee.

Reproductive Analyses

Pregnancy test: serum or urine (minimum sensitivity of urine pregnancy test of 25 IU/L of either total human chorionic gonadotropin (hCG) or the beta fraction)

Home pregnancy test kits

Follicle-stimulating hormone (FSH; if needed to document postmenopausal status as defined in Section 3.3.3)

Other Analyses

Various serologic tumor markers, gene mutation status, and additional analyses are required dependent upon the subject's tumor type as listed in Table 5.3.1-1. With the exception of the serologic tumor markers, the assessments do not need to be performed if the lab results from previous testing are available to be submitted to the Sponsor.

Table 5.3.1-1: Biomarkers by Tumor Type: All Cohorts Except for Subjects Crossing Over or Rechallenged

Tumor Type	Matrix	Lab Test	Assessment	Time point
Colorectal	Blood	Serologic Tumor Marker	CEA[a]	Multiple
	Tumor Tissue	Gene Mutation Status	EGFR[b] K-RAS MSI[c]	Screening
Gastric	Blood	Serologic Tumor Marker	CEA[a]	Multiple
	Tumor Tissue	Gene Amplification Status	HER-2[d]	Screening
	Tumor Tissue	Real Time qPCR[e] and/or EBER ISH[i] (ICH also allowed but not preferred)	EBV[f]	Screening
Germ Cell	Blood	Serologic Tumor Marker	βhCG[g] AFP[h]	Multiple
HNC	Tumor Tissue	p16 IHC and/or HPV ISH[i]	HPV[j]	Screening
HCC	Blood	Quantitative PCR (qPCR)	HBV or HCV viral load[n]	Multiple
	Blood	Serologic Tumor Marker	AFP[h]	Multiple
Melanoma	Tumor Tissue	Gene Mutation Status	BRAF	Screening

Table 5.3.1-1: Biomarkers by Tumor Type: All Cohorts Except for Subjects Crossing Over or Rechallenged

Tumor Type	Matrix	Lab Test	Assessment	Time point
NSCLC	Tumor Tissue	Gene Mutation Status	ALK[k] K-RAS EGFR[b]	Screening
Ovarian	Blood	Serologic Tumor Marker	CA125[l]	Multiple
Prostate	Blood	Serologic Tumor Marker	PSA[m]	Multiple

[a] CEA: carcinoembryonic antigen.

[b] EGFR: epidermal growth factor receptor.

[c] MSI: microsatellite instability.

[d] HER-2: human epidermal growth factor receptor 2 amplification status via IHC and/or ISH.

[e] Real-time qPCR: real-time quantitative polymerase chain reaction for BamH1-A Reading Frame-1 (BARF1) gene.

[f] EBV: Epstein-Barr virus.

[g] βhCG: beta-human chorionic gonadotropin.

[h] AFP: alpha-fetoprotein.

[i] ISH: in situ hybridization.

[j] HPV: human papilloma virus.

[k] ALK: anaplastic lymphoma kinase.

[l] CA125: cancer antigen 125.

[m] PSA: prostate-specific antigen.

[n] HBV/HCV: Hepatitis B virus or hepatitis C virus load, depending on the underlying infection, if any.

Note: As of Protocol Amendment 14, rechallenge is not permitted.

Additional measures including nonstudy-required laboratory tests should be performed as clinically indicated.

Results of all laboratory tests required by this protocol must be provided to BMS, either recorded on the laboratory pages of the CRF or by another mechanism as agreed upon between the Investigator and BMS (eg, provided electronically). If the units of a test result differ from those printed on the CRF, the recorded laboratory values must specify the correct units. Any abnormal laboratory test result considered clinically significant by the Investigator must be recorded on the appropriate AE page of the CRF (see Section 6.3).

5.4 Efficacy Assessments

5.4.1 Imaging Assessment for the Study

As described in Section 5.1, images will be collected during study treatment and acquired until withdrawal of consent, death, or initiation of another anticancer treatment.

Images will be submitted to an imaging central lab. Sites should be trained prior to scanning the first study participant. Image acquisition guidelines and submission process will be outlined in the protocol. Imaging manual will be provided by the core lab.

Contrast-enhanced CT scans acquired on dedicated CT equipment is preferred for this study. CT scans with contrast of the chest, abdomen, and pelvis is to be performed for tumor assessments. CT scans should be acquired with 5-mm slices with no intervening gap (contiguous). Should a subject have a contraindication for CT IV contrast, a noncontrast CT of the chest and a contrast-enhanced MRI of the abdomen and pelvis may be obtained. MRIs should be acquired with slice thickness of 5 mm with no gap (contiguous). Every attempt should be made to image each subject using an identical acquisition protocol on the same scanner for all imaging time points.

MRI of brain is required at screening only for subjects with a history of brain metastasis or as clinically indicated. MRI brain scans at least every 12 weeks during on-study treatment and follow-up periods are required only if there is a prior history of lesions or if there are new signs and symptoms that suggest CNS involvement, if applicable

Bone scans can be used to evaluate metastatic disease, if applicable.

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 Investigator as per standard medical/clinical judgment.

Tumor assessments at other time points may be performed, if clinically indicated, and should be submitted to the central imaging vendor as soon as possible. Unscheduled CT/MRI should be submitted to central imaging vendor. X-rays and bone scans that clearly demonstrate interval progression of disease, eg, most commonly as unequivocal lesions that are unmistakably new since the prior CT/MRI, should be submitted to central imaging vendor. Otherwise, they do not need to be submitted centrally.

Any additional imaging that may demonstrate tumor response or progression (including scans performed at unscheduled time points and/or at an outside institution) should be collected for RECIST v1.1 tumor assessment and submitted to the BICR.

5.4.2 Efficacy Assessment for the Study

Efficacy will be evaluated in Parts A and B (dose escalation) as well as in Parts A1, C, and D (cohort expansion) and Part E. Changes in tumor measurements and tumor response at the time of each assessment will be determined by the Investigator based on RECIST v1.1 (see Appendix 2).[55] In addition, the longest diameter of any new measureable lesions will be captured at each time point.

In Part C melanoma prior IO and NSCLC prior IO, and Part D and Part E subjects, all available scans on the most recent prior anti-PD-1-containing regimen, including the baseline scan (prior to starting anti-PD-1) and scans after the last dose of anti-PD-1 but before the start of any intervening therapy, will be collected and submitted to a central imaging vendor. At minimum, the following time points are to be submitted: 1) pretreatment scan; 2) nadir scan (if applicable); 3) scan documenting progression (does not need to be submitted if it has already been submitted as the

baseline scan for the trial); 4) scan confirming progression (if applicable, it must be at least 4 weeks after the scan documenting progression and without intervening therapy and does not need to be submitted if it has already been submitted as the baseline scan for the trial); and 5) treatment beyond progression scan (if applicable, as this is the last scan on treatment if the subject was treated beyond a progression confirmation scan and does not need to be submitted if it has already been submitted as the baseline scan for the trial).

The baseline assessment during the screening period requires chest CT and CT or MRI scans of the abdomen, pelvis, and other anatomic regions as indicated by individual subject's tumor type and/or disease history. Subsequent time points require scans of the chest, abdomen, and pelvis, as well as other anatomic regions that were scanned at baseline based on the individual subject's tumor type and/or disease history. Scans of the brain are otherwise required as clinically indicated.

Individual subject's best overall response (BOR) will be determined as appropriate.

Tumor status will be assessed at baseline during treatment (every 8 weeks regardless of dose delays) during the Treatment period. Tumor assessments will continue every 12 weeks during the Clinical Follow-up and Survival periods until disease progression in subjects who discontinue study treatment, at the Investigator's discretion, with CR, PR, or SD by RECIST v1.1. CT and MRI scans will be read and assessed locally per RECIST v1.1. All imaging scans must be de-identified and archived in their native DICOM format as part of the subject's study file. At the Sponsor's discretion, scans may be collected centrally to be reviewed by independent radiologists.

Efficacy assessment of subjects who have been rechallenged after achieving a response or SD will be conducted in a separate analysis. Scans for participants who are rechallenged should be performed as per the on-treatment schedule in Table 5.1-2 and submitted to the central imaging vendor for collection. However, the BOR in the first treatment may be considered in the study analysis. Subjects who cross over from BMS-986016 monotherapy (Part A1) to combination therapy are not to be included in the analysis of any expansion cohorts with combination therapy. **As of Protocol Amendment 14, rechallenge is not permitted.**

5.4.3 Primary Efficacy Assessment

The BOR based on BICR assessment using RECIST v1.1 will be the primary assessment, where applicable, in selected cohorts in Parts C, D, and E.

5.4.4 Secondary Efficacy Assessments

The BOR will be assessed by investigator using RECIST v1.1. OS in Part D1 will also be assessed as a secondary efficacy measure.

5.4.5 Exploratory Efficacy Assessments

OS will be assessed as an exploratory efficacy measure in parts other than Part D1.

5.5 Pharmacokinetic Assessments

Serum samples for BMS-986016 and nivolumab (BMS-936558) PK and ADA assessments will be collected for all subjects.

5.5.1 Pharmacokinetics: Collection and Processing

A detailed schedule of PK and ADA evaluations is provided in Table 5.5.1-1 and Table 5.5.1-2 for Q2W dosing and in Table 5.5.1-3, Table 5.5.1-4, and Table 5.5.1-5 for Parts B and C (bladder cohort) for Q4W dosing and for Part D and Rechallenge (**As of Protocol Amendment 14, rechallenge is not permitted**) and Part E. All time points are relative to the start of BMS-986016 study drug administration except for Part D, which is from the start of the coadministration of nivolumab and BMS-986016 or BMS-986213 infusion. Predose samples should be taken within 30 minutes before the start of dose administration. End-of-infusion samples should be taken just prior to the end of infusion (preferably within 2 minutes). Further details of sample collection, processing, and shipment will be provided in the laboratory procedures manual. On-treatment PK samples are intended to be drawn relative to actual dosing days; if a dose occurs on a different day within the cycle due to delays or minor schedule adjustments, PK samples should be adjusted accordingly. **As per Protocol Amendment 14**: PK sample collection upon the occurrence of a ≥ Grade 3 AE is not required.

Table 5.5.1-1: PK and ADA Sampling Schedule for BMS-986016 and Nivolumab for Dose Escalation Parts A and B Q2W Dosing and Expansion Parts A1 and C (Approximately the First 6 Subjects in Each Cohort Only)

Study Day of Sample Collection	Event (Relative to BMS-986016)	Time (Relative to Start of BMS-986016 Infusion) Hour:Min	BMS-986016 PK Sample (All Subjects)	Nivolumab PK Sample (All Subjects Except Part A and A1)	BMS-986016 ADA Sample (All Subjects)	Nivolumab ADA Sample (All Subjects Except Part A and A1)
Cycle 1						
1	Predose[a]	00:00	X	X	X	X
1	EOI [b]	01:00 [b]	X	X		
1		04:00	X			
2		24:00	X			
5[c]		96:00	X			
8[d]		168:00	X			
15	Predose[a]	00:00	X	X	X	X
29	Predose[a]	00:00	X	X	X	X
43	Predose[a]	00:00	X	X	X	X
Cycle 2						
1	Predose[a]	00:00	X	X	X	X
1	EOI[b]	01:00 [b]	X	X		

Table 5.5.1-1: PK and ADA Sampling Schedule for BMS-986016 and Nivolumab for Dose Escalation Parts A and B Q2W Dosing and Expansion Parts A1 and C (Approximately the First 6 Subjects in Each Cohort Only)

Study Day of Sample Collection	Event (Relative to BMS-986016)	Time (Relative to Start of BMS-986016 Infusion) Hour:Min	BMS-986016 PK Sample (All Subjects)	Nivolumab PK Sample (All Subjects Except Part A and A1)	BMS-986016 ADA Sample (All Subjects)	Nivolumab ADA Sample (All Subjects Except Part A and A1)
15	Predose[a]	00:00	X	X		
Cycle 3						
1	Predose[a]	00:00	X	X	X	X
1	EOI[b]	01:00 [b]	X	X		
1		04:00	X			
2		24:00	X			
5 [c]		96:00	X			
8 [d]		168:00	X			
15	Predose[a]	00:00	X	X		
Alternate Treatment Cycles (Starting from Cycle 5 to treatment discontinuation or maximum of 24 months of treatment, whichever comes first)						
1	Predose[a]	00:00	X	X	X	X
End of Treatment and Follow-up Period						
135 Day FU[e]			X	X	X	X

[a] Predose: All predose samples for nivolumab and BMS-986016 should be taken prior to the start of nivolumab infusion.

[b] EOI: End of Infusion. EOI samples for both nivolumab and BMS-986016 should be collected after the end of the BMS-986016 infusion. This sample should be taken immediately prior to stopping the infusion (preferably within 2 minutes prior to EOI). If the EOI is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.

[c] Day 5 sample may be taken during Days 3-5 of a cycle.

[d] Day 8 sample may be taken during Days 7-9 of a cycle.

[e] FU: Follow-up.

Table 5.5.1-2: PK and ADA Sampling Schedule for BMS-986016 and Nivolumab for Dose Expansion Part C Q2W Dosing (After First 6 Subjects) and for Cohort with Crossover or Rechallenge

Study Day of Sample Collection	Event (Relative to BMS-986016)	Time (Relative to Start of BMS-986016 Infusion) Hour:Min	BMS-986016 PK Sample (All Subjects)	Nivolumab PK Sample (All Subjects Except Part A1)	BMS-986016 ADA Sample (All Subjects)	Nivolumab ADA Sample (All Subjects Except Part A1)
Cycle 1						
1	Predose[a]	00:00	X	X	X	X
1	EOI[b]	01:00 [b]	X	X		
15	Predose[a]	00:00	X	X	X	X
29	Predose[a]	00:00	X	X	X	X
43	Predose[a]	00:00	X	X		
Cycle 2						
1	Predose[a]	00:00	X	X	X	X
1	EOI[b]	01:00 [b]	X	X		
Cycle 3						
1	Predose[a]	00:00	X	X	X	X
1	EOI[b]	01:00[b]	X	X		
Alternate Treatment Cycles (Starting From Cycle 5 to treatment discontinuation or maximum of 24 months of treatment, whichever comes first)						
1	Predose[a]	00:00	X	X	X	X
End of Treatment and Follow-up Period						
135 Day FU[c]			X	X	X	X

[a] Predose: All predose samples for nivolumab and BMS-986016 should be taken prior to the start of nivolumab infusion.

[b] EOI: End of Infusion. EOI samples for both nivolumab and BMS-986016 should be collected after the end of the BMS-986016 infusion. This sample should be taken immediately prior to stopping the infusion (preferably within 2 minutes prior to EOI). If the EOI is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.

[c] FU: Follow-up.

Note: As of Protocol Amendment 14, rechallenge is not permitted.

.

Table 5.5.1-3: PK and ADA Sampling Schedule for BMS-986016 and Nivolumab for Dose Escalation Parts B and C (Bladder Cohort Approximately First 6 Subjects) with Q4W Regimen

Study Day of Sample Collection	Event (Relative to BMS-986016)	Time (Relative to Start of BMS-986016 Infusion) Hour:Min	BMS-986016 PK Sample	Nivolumab PK Sample	BMS-986016 ADA Sample	Nivolumab ADA Sample
Cycle 1						
1	Predose[a]	00:00	X	X	X	X
1	EOI [b]	01:00 [b]	X	X		
1		04:00	X			
2		24:00	X			
5 [c]		96:00	X			
8 [d]		168:00	X			
15		336:00	X			
29	Predose[a]	00:00	X	X	X	X
Cycle 2						
1	Predose[a]	00:00	X	X	X	X
1	EOI[b]	01:00 [b]	X	X		
29	Predose[a]	00:00	X	X		
Cycle 3						
1	Predose[a]	00:00	X	X	X	X
1	EOI [b]	01:00 [b]	X	X		
1		04:00	X			
2		24:00	X			
5 [c]		96:00	X			
8 [d]		168:00	X			
15 [e]		336:00	X			
29	Predose[a]	00:00	X	X		
Alternate Treatment Cycles (Starting From Cycle 5 to treatment discontinuation or maximum of 24 months of treatment, whichever comes first)						
1	Predose[a]	00:00	X	X	X	X

Table 5.5.1-3: PK and ADA Sampling Schedule for BMS-986016 and Nivolumab for Dose Escalation Parts B and C (Bladder Cohort Approximately First 6 Subjects) with Q4W Regimen

Study Day of Sample Collection	Event (Relative to BMS-986016)	Time (Relative to Start of BMS-986016 Infusion) Hour:Min	BMS-986016 PK Sample	Nivolumab PK Sample	BMS-986016 ADA Sample	Nivolumab ADA Sample
End of Treatment and Follow-up Period						
135 Day FU[f]			X	X	X	X

[a] Predose: All predose samples for nivolumab and BMS-986016 should be taken prior to the start of nivolumab infusion.

[b] EOI: End of Infusion. EOI samples for both nivolumab and BMS-986016 should be collected after the end of the BMS-986016 infusion. This sample should be taken immediately prior to stopping the infusion (preferably within 2 minutes prior to EOI). If the EOI is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.

[c] Day 5 sample may be taken during Days 3-5 of a cycle.

[d] Day 8 sample may be taken during Days 7-9 of a cycle.

[e] Day 15 sample may be taken during Days 14-16 of a cycle.

[f] FU: Follow-up.

Table 5.5.1-4: PK and ADA Sampling Schedule for BMS-986016 and Nivolumab for Dose Expansion Part C Bladder Cohort (After Approximately First 6 Subjects), Part D1 Arm 1, Part D1 (Arm 2 and Arm 3, After First 12 Subjects), Part D2, Part E, and Rechallenge

Study Day of Sample Collection	Event (Relative to BMS-986016)	Time (Relative to Start of BMS-986016 +Nivolumab Coadministration) OR BMS-986213 Infusion Hour:Min	BMS-986016 PK Sample	Nivolumab PK Sample	BMS-986016 ADA Sample	Nivolumab ADA Sample
Cycle 1						
1	Predose[a]	00:00	X	X	X	X
1	EOI[b]	01:00[b]	X	X		
29	Predose[a]	00:00	X	X	X	X
Cycle 2						
1	Predose[a]	00:00	X	X	X	X
Cycle 3						
1	Predose[a]	00:00	X	X	X	X
1	EOI[b]	01:00[b]	X	X		
Alternate Treatment Cycles (Starting From Cycle 5 to treatment discontinuation or maximum of 24 months of treatment, whichever comes first)						
1	Predose[a]	00:00	X	X	X	X
End of Treatment and Follow-up Period						
135 Day FU[c]			X	X	X	X

[a] Predose: All predose samples for nivolumab and BMS-986016 should be taken prior to the start of the coadministration of nivolumab and BMS-986016 infusion.

[b] EOI: end of infusion. EOI samples for both nivolumab and BMS-986016 should be collected after the end of the coadministration or BMS-986213 infusion. This sample should be taken immediately prior to stopping the infusion (preferably within 2 minutes prior to EOI). If the EOI is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.

[c] FU: Follow-up.

Note: As of Protocol Amendment 14, rechallenge is not permitted.

Table 5.5.1-5: PK and ADA Sampling Schedule for BMS-986016 and Nivolumab for Part D1 (Arm 2 and 3, First 12 Subjects)

Study Day of Sample Collection	Event (Relative to BMS-986016)	Time (Relative to Start of BMS-986016 + Nivolumab Coadministration OR BMS-986213 Infusion) Hour:Min	BMS-986016 PK Sample	Nivolumab PK Sample	BMS-986016 ADA Sample	Nivolumab ADA Sample
Cycle 1						
1	Predose[a]	00:00	X	X	X	X
1	EOI[b]	01:00[b]	X	X		
1		04:00	X			
8[c]		168:00	X			
15[d]		336:00	X			
29	Predose[a]	00:00	X	X	X	X
Cycle 2						
1	Predose[a]	00:00	X	X	X	X
Cycle 3						
1	Predose[a]	00:00	X	X	X	X
1	EOI[b]	01:00[b]	X	X		
Alternate Treatment Cycles (Starting From Cycle 5 to treatment discontinuation or maximum of 24 months of treatment, whichever comes first)						
1	Predose[a]	00:00	X	X	X	X
End of Treatment and Follow-up Period						
135 Day FU[e]			X	X	X	X

[a] Predose: All predose samples for nivolumab and BMS-986016 should be taken prior to the start of the coadministration of nivolumab and BMS-986016 infusion.

[b] EOI: End of Infusion. EOI samples for both nivolumab and BMS-986016 should be collected after the end of the coadministration or BMS-986213 infusion. This sample should be taken immediately prior to stopping the infusion (preferably within 2 minutes prior to EOI). If the EOI is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.

[c] Day 8 sample may be taken during Days 7-9 of a cycle.

[d] Day 15 samples may be taken during Days 14-16 of a cycle.

[e] FU: Follow-up.

5.5.2 Pharmacokinetic Sample Analyses

The serum samples will be analyzed for BMS-986016 and nivolumab by a validated immunoassay. In addition, selected serum samples may be analyzed by an exploratory orthogonal method (eg, liquid chromatography–mass spectrometry [LC-MS]/MS) that measures total BMS-986016 and/or nivolumab, but the generated data will not be reported. Only results generated from the validated immunoassay method will be reported. Potential results generated from any orthogonal method are intended as informational for technology exploration purposes and will not be reported.

5.6 Biomarker Assessments

Not applicable.

5.7 Exploratory Biomarker Assessments

[redacted] Detailed schedules of pharmacodynamic evaluations are provided in Table 5.7-1 and Table 5.7-2. For Parts D and E, sample collection will be per Table 5.7-3 and Table 5.7-4, respectively. Details regarding the tumor tissues requirements for subjects in all parts of the study are provided in Table 5.7-5. Details regarding the biomarkers to be analyzed are provided in the sections that follow.

Further details of blood collection and processing will be provided to the site in the procedure manual.

Table 5.7-1: Part A and B (Dose Escalation): Biomarker Sampling Schedule (for All Subjects in Each Dose Level Either Q2W or Q4W Dosing)

Collection Timing	Serum	[redacted]	Tumor	[redacted]
Study Day	**Soluble Biomarkers Serum Biomarkers**		**Fresh Tumor Biopsy[b]**	
Screening			X[b]	
Day 1	X			
Day 5[c]	X			
Day 8[d]	X			
Day 15[e]	X			
Day 29	X		X[b]	
Day 43[e]	X			
Cycle 2				
Day 1	X			
Upon Progression				
Upon progression[f]	X		X	
Upon Drug-related AE				
Upon occurrence of ≥ Grade 3 drug-related AE	X			

[redacted]

[b] During the screening period, all participants must have tumor tissue submitted, [redacted]. An on-treatment (predose Days 23-31) biopsy is optional but encouraged.

[c] Day 5 visit can occur on Day 3 or Day 4.

[d] Day 8 visit can occur on Day 7 or Day 9.

[e] For Q4W dosing, Day 15 and Day 43 samples are not predose.

[f] Optional: to be collected upon confirmation of PD.

[redacted]

Note: All samples are to be drawn predose.

Table 5.7-2: Parts A1 and C (Cohort Expansion) and Cohorts for Crossover or Rechallenge: Biomarker Sampling

Collection Timing	Serum	[redacted]	Tumor	[redacted]
Study Day	**Soluble Biomarkers (Serum Biomarkers)[b]**		**"Fresh" Tumor Biopsy[d]**	
Screening			X[d]	
Cycle 1				
Day 1	X			
Day 5[e]	X			
Day 8[f]	X			
Day 15	X			
Day 29	X		X[d]	
Cycles 2, 3, 5, 7, 9, and 11				
Day 1	X			
Upon Progression				
Upon progression[g]	X		X	
Upon Drug-related AE				
Upon occurrence of ≥ Grade 3 drug-related AE	X			

[redacted].

[redacted]

[d] During the screening period, all participants must have tumor tissue submitted, [redacted]. For other sites, on-treatment biopsy is optional but encouraged.

[e] Day 5 visit can occur on Day 3 or Day 4.

[f] Day 8 visit can occur on Day 7 or Day 9.

[g] Optional: to be collected upon confirmation of PD.

[redacted]

NOTE: All samples are to be drawn predose. As of Protocol Amendment 14, rechallenge is not permitted.

Table 5.7-3: Biomarker Sampling for Part D Melanoma Prior IO Extended Expansion and Rechallenge

Collection Timing	Serum	[redacted]	Tumor[b]	[redacted]
Study Day	**Soluble Biomarkers (Serum Biomarkers)**		**Fresh Tumor Biopsy**	
Screening			X[b]	
Cycle 1				
Day 1	X			
Day 15	X			
Day 29	X		X[b]	
Day 43	X			
Cycle 2 and Alternate Treatment Cycles (Starting From Cycle 3 to treatment discontinuation or maximum of 24 months of treatment)				
Day 1	X	[redacted]		
Upon Progression				
Upon progression[d]	X			
Upon Drug-related AE				
Upon occurrence of ≥ Grade 3 drug-related AE	X			

[redacted]

b During the screening period, all participants must have tumor tissue submitted, [redacted]. Tumor tissue should be sent to central laboratory within 1 week from Cycle 1 Day 1 (see Table 5.7-5 for details). On-treatment (predose Days 23-31) biopsy is optional.

[redacted]

d Optional: to be collected upon confirmation of PD.

[redacted]

NOTE: All samples to be drawn predose. As of Protocol Amendment 14, rechallenge is not permitted.

Table 5.7-4: Biomarker Sampling for Part E Exposure/Response Expansion Q4W Dosing and Rechallenge

Collection	**Serum**	[redacted]	**Tumor[b]**	[redacted]
Study Day	**Soluble Biomarkers (Serum Biomarkers)**		**Fresh Tumor Biopsy**	
Screening			X (fresh or archived)	
Cycle 1				
Day 1	X			
Day 15	X			
Day 29	X		X	
Day 43	X			
Cycle 2 and Alternate Treatment Cycles (Starting From Cycle 3 to treatment discontinuation or maximum of 24 months of treatment)				
Day 1	X	[redacted]		
Upon Progression				
Upon progression[d]	X			
Upon Drug-related AE				
Upon occurrence of ≥ Grade 3 drug-related AE	X			

[redacted]

[b] During the screening period, all participants must have tumor tissue submitted, [redacted]. On-treatment (predose Days 23-31) biopsy is encouraged but optional.

[redacted]

[d] Optional: to be collected upon confirmation of PD.

[redacted]

Note: As of Protocol Amendment 14, rechallenge is not permitted.

Table 5.7-5: Tumor Tissue Requirements

Study Part	Parts A and B (Dose Escalation)	Parts A1 and C (Cohort Expansion) and D and E
Subjects	ALL Subjects	
Type of Specimen Baseline	During the screening period, all participants **must** have tumor tissue submitted, [redacted]	
On-treatment	Optional "fresh" biopsy predose at Day 23-31 of first cycle	MANDATORY [redacted]
Upon Progression	Optional "fresh" biopsy upon confirmation of PD	

5.7.1 Soluble Biomarkers (Serum Biomarkers)

Pretreatment and on-treatment serum levels of chemokines, cytokines, and tumor-associated soluble proteins will be assessed by techniques that may include, but are not limited to, ELISA or multiplex assays. Analyses may include markers of inflammation, immune activation, host tumor growth factors, and tumor-derived proteins, including sLAG-3.

5.7.2 Antitumor Antibodies (Serum Biomarkers)

Treatment with BMS-986016 and nivolumab may result in the generation of novel, or an increase in existing, antibodies to tumor-associated antigens. An assessment of antibodies to a panel of > 8000 proteins will be performed using pretreatment and on-treatment serum in multiplex and ELISA. These data will be used in a subset of subjects to explore whether antitumor antibodies are associated with clinical response and safety parameters, as well as to inform pharmacodynamics of drug administration.

[redacted]

[redacted]

5.7.9 Tumor Biopsy Analysis

Tumor biopsy specimens will be obtained from consenting participants prior to treatment to characterize immune cell populations and expression of selected tumor markers. [redacted]

[redacted] must be available for submission prior to randomization. Tumor tissue will be collected from all subjects. Immunohistochemistry will be used to assess the number and composition of immune infiltrates in order to define the immune cell subsets present within tumor tissue before and potentially after exposure to BMS-986016 and nivolumab. [redacted]

5.7.10 Tumor-based Biomarker Measures

[redacted]

The Investigator, in consultation with the radiology staff, must determine the degree of risk associated with the procedure and find it acceptable. Biopsies may be done with local anesthesia or conscious sedation. Institutional guidelines for the safe performance of biopsies should be followed. Excisional biopsies may be performed to obtain tumor biopsy samples. Invasive procedures that require general anesthesia should not be performed to obtain a biopsy specimen. However, if a surgical procedure is performed for a clinical indication, excess tumor tissue may be used for research purposes with the consent of the subject.

5.7.11 Additional Research Collection

This protocol will include residual sample storage for additional research.

For All US Sites:

Additional research participation is required for all investigational sites in the US.

For Non-US Sites:

Additional research is optional for all study participants, except where retention and/or collection is prohibited by local laws or regulations, ethics committees, or institutional requirements.

This collection for additional research is intended to expand the translational research and development capability at BMS and will support as yet undefined research aims that will advance

our understanding of disease and options for treatment. It may also be used to support health authority requests for analysis and advancement of pharmacodiagnostic development to better target drugs to the right patients. This may also include genetic/genomic exploration aimed at exploring disease pathways, progression and response to treatment, etc.

Sample Collection and Storage

All requests for access to samples or data for additional research will be vetted through a diverse committee of the study Sponsor's senior leaders in Research and Development (or Designee) to ensure the research supports appropriate and well-defined scientific research activities.

Residual samples from tumor biopsies and biomarker collections (Table 5.7.11-1) will also be retained for additional research purposes.

Samples kept for future research will be stored at the BMS Biorepository in [redacted] or an independent, BMS-approved storage vendor.

The manager of these samples will ensure they are properly used throughout their usable life and will destroy the samples at the end of the scheduled storage period, no longer than 15 years after the end of the study or the maximum allowed by applicable law.

Transfers of samples by research Sponsor to third parties will be subject to the recipient's agreement to establish similar storage procedures.

Samples will be stored in a coded fashion, and no researcher will have access to the key. The key is securely held by the Investigator at the clinical site, so there is no direct ability for a researcher to connect a sample to a specific individual.

Further details of sample collection and processing will be provided to the site in the procedure manual.

Table 5.7.11-1: Residual Sample Retention for Additional Research Schedule

Sample Type	Time Points for Which Residual Samples Will Be Retained
Tumor biopsy	All
Biomarker blood collections	All

5.8 Outcomes Research Assessments

Not applicable.

5.9 Other Assessments

5.9.1 Immunogenicity Assessments

Serum samples collected at time points identified in Table 5.5.1-1 and Table 5.5.1-2 for Q2W dosing, Table 5.5.1-3 for Q4W dosing, and Table 5.5.1-4 and Table 5.5.1-5 for Part D and Part E will be analyzed by a validated immunogenicity assay. Selected serum samples may be analyzed by an exploratory orthogonal method that measures anti-BMS-986016 or anti-nivolumab.

Potential results generated from any orthogonal method are intended as informational for technology exploration purposes and will not be reported.

In addition, ad hoc serum samples designated for PK or biomarker assessments may also be used for immunogenicity analysis if required (eg, insufficient volume for complete immunogenicity assessment or to follow up on suspected immunogenicity-related AE).

5.10 Results of Central Assessments

The effect of BMS-986016 on QTc interval when administered alone or in combination with nivolumab will be evaluated by a central reader using ECG data collected via Holter monitors supplied by a core laboratory; these results will be summarized at the end of the study. For the purposes of monitoring subject safety, Investigators will review 12-lead ECGs per the protocol-specified schedule (see Table 5.1-2) using their site's standard ECG machines.

6 ADVERSE EVENTS

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

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 preexisting 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).

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 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 the 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.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject.

Care should be taken not to introduce bias when collecting AEs and/or SAEs. Inquiry about specific AEs should be guided by clinical judgment in the context of known AEs, when appropriate for the program or protocol.

Definition of SAE:

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

6.1 Serious Adverse Events

A ***SAE*** is any untoward medical occurrence that at any dose:

Results in death

Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)

Requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)

Results in persistent or significant disability/incapacity

Is a congenital anomaly/birth defect

Is an important medical event (defined as a medical event[s] that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization. Potential DILI is also considered an important medical event (see Section 6.6 for the definition of potential DILI).

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

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

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

NOTE:

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

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

Immune-mediated AEs (IMAEs) are AEs consistent with an immune-mediated mechanism or immune-mediated component for which noninflammatory etiologies (eg, infection or tumor progression) have been ruled out. IMAEs can include events with an alternate etiology that were exacerbated by the induction of autoimmunity. Information supporting the assessment will be collected on the subject's case report form.

6.1.1 Serious Adverse Event Collection and Reporting

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 135 days of discontinuation of dosing. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

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

A SAE Report Form should be completed for any event where doubt exists regarding its seriousness.

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

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS (or designee) immediately within 24 hours. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). The required method of SAE data reporting collection is through the eCRF. The paper SAE/Pregnancy Surveillance Forms are only intended as a back-up option when the eCRF system is unavailable/not functioning. In this case, the paper forms are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

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

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

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

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

All SAEs should be followed to resolution or stabilization.

6.2 Nonserious Adverse Events

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

6.2.1 Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug and continue for 135 days after discontinuation of dosing.

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

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

6.3 Laboratory Test Result Abnormalities

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

Any laboratory test result that is clinically significant or meets the definition of an SAE

Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted

Any laboratory test result abnormality that required the subject to receive specific corrective therapy

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

6.4 Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 5 half-lives plus 30 days 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 and in accordance with SAE reporting procedures described in Section 6.1.1.

In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety). If the Investigator determines a possible favorable benefit-risk ratio that warrants continuation of study treatment or reinitiation of study treatment, a discussion between the Investigator and the BMS Medical Monitor/designee must occur. If, for whatever reason, pregnancy has ended, confirmed by negative serum pregnancy test, treatment may be resumed (at least 3 weeks and not greater than 6 weeks after the pregnancy has ended), following approvals of participant/Sponsor/IRB/IEC, as applicable.

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

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

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

6.5 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. See Section 6 for reporting of overdose.

6.6 Potential Drug-induced Liver Injury

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

Potential DILI is defined as:

1. Aminotransaminase (AT) (ALT or AST) elevation > 3 times ULN
   AND
2. Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),
   AND
3. No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, tumor progression; acute viral hepatitis; cholestasis; preexisting hepatic disease; or the administration of other drug(s), herbal medications, and substances known to be hepatotoxic.

Given the organ-specific nature of HCC, the definition of potential DILI is defined differently specifically for HCC subjects. The rationale for HCC-specific DILI language as follows: 1) standardization of the DILI definition so that a unified approach is taken across the BMS HCC program; 2) concern that the previous language may not be sensitive to capture all potential cases given the lack of a requirement for a concomitant elevation in transaminases and bilirubin and the significant increase in total bilirubin regardless of baseline value; and 3) alignment with the daclatasvir direct-acting antiviral agent (DAA) program, which has criteria that have been developed after consultation with Health Authorities for subjects with chronic HCV infection with underlying liver disease and therefore consistent with the patient population in this study.

Therefore, potential DILI for HCC subjects is defined as:

1. AT (ALT or AST) elevation > 10 times ULN
   AND
2. Total bilirubin > 2 times ULN or baseline value (if elevated bilirubin at study entry)

AND

3. No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, tumor progression; acute viral hepatitis; cholestasis; preexisting hepatic disease; or the administration of other drug(s), herbal medications, and substances known to be hepatotoxic.

This change in potential DILI definition is not anticipated to pose any risk for subjects since management of hepatic events will follow pre-established algorithms that are not impacted by the DILI definition and include dose delay and/or discontinuation as well as intervention with immunosuppressants.

6.7 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, ECG, radiologic exams, or any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or SAE, as appropriate, and reported accordingly.

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

7.1 Data Monitoring Committee

A data monitoring committee (DMC) will be established to provide oversight of safety and to provide advice to the sponsor regarding actions the committee deems necessary for the continuing protection of participants. The DMC will be charged with assessing such actions in light of an acceptable benefit-risk profile for BMS-986016. The DMC will act in an advisory capacity to BMS and will monitor participant safety and evaluate the available efficacy data for the study. The oncology therapeutic area of BMS has primary responsibility for design and conduct of the study. The DMC will meet as outlined in the DMC charter or as needed on an ad hoc basis. Information regarding DMC membership, responsibilities, and procedures are detailed in the DMC charter. The DMC will be informed should a safety signal emerge and may convene an ad hoc meeting on its own initiative. When required, adjudicated events will be submitted to the DMC and Health Authorities for review. The DMC will review all available data (safety and efficacy) at each meeting. At the conclusion of each DMC meeting, the committee will provide the Sponsor with a recommendation to continue, modify, or terminate the study protocol based upon their review. Ultimately, decisions regarding the study protocol will be made by the Sponsor in conjunction with feedback from Investigators and the DMC.

7.2 Blinded Independent Central Review Committee

A BICR committee may be used in selected disease cohorts in Part C, Part D, and Part E.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

8.1.1 Dose Escalation (Parts A and B)

Sample size at each dose depends on observed toxicity and cannot be precisely determined. Parts A and B will have 3 to 9 (15 in BLRM-Copula in Part B) subjects in each cohort.

In the Part B dose escalation using BLRM-Copula, the sample size at each dose depends on observed toxicity and posterior inference. Initially, approximately 3 subjects will be treated at the starting dose level (using the new BLRM-Copula design) of BMS-986016 in combination with nivolumab. Due to the potential for early discontinuation, an additional subject(s) may be enrolled to ensure approximately 3 evaluable subjects at each dose level.

Cohort tolerability assessment and subsequent dose recommendation will occur when 2 evaluable subjects within a set have completed the DLT evaluation period. If the potential DLT occurring in any third evaluable subject regarding the specific dose level does not influence the dose recommendation by BLRM-Copula, the BLRM-Copula recommended next dose level may proceed without waiting for the third subject to complete the corresponding DLT observation period, after discussion and agreement between Sponsor and Investigators. Continuous reassessment of dose recommendation by BLRM-Copula in the combination phase will be carried out at each dose level.

During dose escalation, BLRM could recommend escalating to the next dose or skipping an entire dose level altogether. In that case, a new cohort of approximately 3 subjects will be treated at the recommended new dose. BLRM could also recommend staying at the same dose level, in which case an additional increments of approximately 3 subjects will be treated at that dose. At least 6 DLT-evaluable subjects will be treated in the selected dose cohort(s) chosen for expansion. Up to 15 subjects may be treated at any dose level for further evaluation of safety and pharmacodynamic/PK parameters as required.

8.1.2 Cohort Expansion Monotherapy (Part A1)

A sample size of 6 subjects per cohort allows for estimation of the proportion of subjects with objective response (ie, BOR of CR + PR) within a cohort such that the maximum distance between the estimated rate and either limit of the exact 2-sided 95% Clopper-Pearson confidence interval (CI) is 47.5%.

A sample size of 12 subjects per cohort allows for estimation of the proportion of subjects with objective response (ie, BOR of CR + PR) within a cohort such that the maximum distance between the estimated rate and either limit of the exact 2-sided 95% Clopper-Pearson CI is 32.2%

8.1.3 Cohort Expansion (Part C)

The objective of this expansion in combination with nivolumab is to support further clinical testing by demonstrating adequate safety and tolerability as well as favorable benefit-risk by assessing preliminary efficacy measured by ORR and other clinically relevant efficacy measures such as

DOR and DCR. However, the sample size is strictly based on efficacy, specifically based on the target ORR relative to historic ORR.

Disease- and prior IO therapy–restricted cohorts will be investigated in the Part C cohort expansion: NSCLC progressed on IO therapy; melanoma progressed on anti-PD-1/anti-PD-L1; RCC naive to IO therapy; NSCLC naive to IO therapy; melanoma first line; SCCHN naive to IO therapy; bladder naive to IO therapy; gastric cancer naive to IO therapy; and HCC naive to IO therapy. The NSCLC progressing on IO therapy cohort will be analyzed as a whole and as 2 separate subgroups, refractory and relapsed, as defined in Section 3.3.1. All disease cohorts will be handled independently, and there will be no multiplicity adjustment.

A multistage design will be used as a guide for each expansion cohort in order to decide whether the treatment of BMS-986016 in combination with nivolumab warrants more extensive development. At first, a 2-stage design[57,58] with a reasonable false positive rate (eg, < 10%) and false negative rate (eg, < 10%) will be used for decision making based on assumptions of true (target) and historic/standard-of-care response rate for each cohort. The assumed historic and target response rates may change over time and may need to be adjusted by the time of response data from this study are available. Using a 2-stage design provides an option to stop early for futility as well as a signal of preliminary antitumor activity for strong-go early on. Enrollment may continue into stage 2 while the planned number of subjects for Stage 1 are followed for efficacy evaluable tumor assessments. There will be no stopping of a disease cohort for efficacy, although early plan for the next stage of clinical development may be initiated.

The ORRs considered to be of clinical value for further expansion of selected populations, sample size, and operational characteristics of using a 2-stage design, as an example, are provided in Table 8.1.3-1, although this is not used for statistical hypothesis testing.

Table 8.1.3-1: Example of a 2-stage Design Characteristics

Cohort	Historic/ Target Rate (%)	Stage	Cum. Sample Size	Conclude Futility if R[a]	Conclude Efficacy if R	PET[b] or Futility (%)	PEE[c] or Efficacy (%)
Gastric IO naive	10/30	1	15	≤ 1	≥ 4	55	70
		2	26	≤ 5	≥ 6		
HCC IO naive							
Melanoma progressed on anti-PD-1/PD-L1							
RCC IO naive	25/50	1	11	≤ 2	≥ 6	46	50
		2	26	≤ 9	≥ 10		
NSCLC IO refractory	5/20	1	12	0	≥ 3	54	44
		2	37	≤ 3	≥ 4		
NSCLC IO relapsed							
NSCLC	20/45	1	14	≤ 3	≥ 7	70	45

Table 8.1.3-1: Example of a 2-stage Design Characteristics

Cohort	Historic/ Target Rate (%)	Stage	Cum. Sample Size	Conclude Futility if R[a]	Conclude Efficacy if R	PET[b] or Futility (%)	PEE[c] or Efficacy (%)
1/2L, IO naive		2	25	≤ 7	≥ 8		
Melanoma 1L	40/65	1 2	13 28	≤ 5 ≤ 14	≥ 10 ≥ 15	57	28
SCCHN IO naive	20/40	1 2	20 36	≤ 4 ≤ 10	≥ 8 ≥ 11	63	58
Bladder IO naive							

[a] R is the cumulative number of responses at the end of stage.

[b] PET: probability of early termination.

[c] PEE: probability of early expansion.

Once there is preliminary evidence of the treatment effect that may represent substantial improvement over available therapies, sufficient additional subjects will be treated to demonstrate a substantial and clinically meaningful effect in ORR that is supported by duration of the effect. The total sample size at this stage will be determined based on the ability to produce a CI, which would exclude an ORR of the historic response, and to provide sufficient information for a reliable understanding of the safety profile. With 90 to 120 subjects in total, this design yields a less than 5% 2-sided type I error rate and at least 80% power depending on tumor type with specified historic/standard of care and target rates. Table 8.1.3-2 summarizes the 95% exact CI for various observed ORRs with sample sizes of 90, 100, and 120.

Guided by Table 8.1.3-1 initially, approximately 11 RCC subjects, for example, will be treated in Stage 1. Assuming the true response rate is 50% when treated with BMS-986016 in combination with nivolumab, if there are 6 or more responses in 11 subjects, it may be decided to expand further up to approximately 90 subjects in total after careful evaluation of all available data, including DOR and safety profile. The probability of early decision to expand further for efficacy is approximately 50% if, in fact, the treatment is efficacious. If there are 2 or fewer responses in 11 treated subjects, the cohort may be stopped for futility. The probability of early stopping for futility is approximately 46% if, in fact, the treatment is inefficacious, eg, 25%. If there are 3 to 5 responses, an additional 15 subjects may be treated to collect more data. At the end of Stage 2, if there are 10 or more responses, an additional 64 subjects may be treated up to a total of 90 subjects. Table 8.1.3-2 shows that at observed ORR ≥ 36%, the lower bound of the 95% CI excludes 25% with a sample size of 90.

Table 8.1.3-2: Observed ORR with Exact 95% CI

Sample Size	Number of Responses	ORR	95% Exact CI
90	18	20%	[12.3%, 29.8%]
	27	30%	[20.8%, 40.6%]
	32	36%	[25.7%, 46.4%]
	37	41%	[30.8%, 52.0%]
	46	51%	[40.4%, 61.8%]
100	20	20%	[12.7%, 29.2%]
	30	30%	[21.2%, 40.0%]
	35	35%	[25.7%, 45.2%]
	40	40%	[30.3%, 50.3%]
	50	50%	[39.8%, 60.2%]
120	24	20%	[13.3%, 28.3%]
	36	30%	[22.0%, 39.0%]
	42	35%	[26.5%, 44.2%]
	48	40%	[31.2%, 49.3%]
	60	50%	[40.7%, 59.3%]

8.1.4 Melanoma Prior IO Extended Expansion (Part D)

The objective of this expansion in melanoma subjects whose disease is progressing while receiving anti-PD-1 (anti-PD-L1 allowed in Part D2) antibody therapies is to assess safety and tolerability of more convenient dosing regimen (ie, coadministration and Q4W dosing interval) and demonstrate preliminary clinical evidence of the treatment effect measured by ORR, as determined by BICR, that may represent substantial improvement over available therapies in subjects with LAG-3 expression (Part D1).

8.1.4.1 Melanoma Prior IO Extended Expansion (Part D1-Q2W)

Data from Part C melanoma subjects who progressed while receiving anti-PD-1 antibody therapies demonstrated a preliminary evidence that subjects with LAG-3 expression are more likely to respond to treatment of BMS-986016 in combination with nivolumab. The marker prevalence using the initial 1% cut (ie, LAG-3 expression ≥ 1%) is estimated to be approximately 60% in this patient population.

In order to establish safety and tolerability of a more convenient dosing regimen and further characterize an enriched responder population, approximately a total of 150 subjects who meet the eligibility criteria for Part D1 will be treated with BMS-986016 80 mg + nivolumab 240 mg Q2W coadministered. A sample size of 150 is expected to provide approximately 90 subjects with LAG-3 expression using the initial cutoff of 1% and provide reasonable precision to examine the enrichment of patient population with LAG-3 expression.

Since the optimal marker cutpoint is not well known prior to the study, several different cutoffs may be explored, and, depending on the prevalence of the marker-positive using these cutoffs, the

initial total sample size may be modified in order to have an adequate precision for demonstrating preliminary clinical evidence of the treatment effect in the marker-positive population (ie, approximately 90 subjects). Although evaluation of the cutpoint will be based on the ORR, the decision of the cutpoint will be based on the totality of the efficacy data, including DOR and DCR.

Additionally, in an effort to explore an enriched patient population in advanced melanoma subjects who progressed while on anti-PD-1 antibody therapies in Part D1, other potential predictive markers such as BRAF mutation status may be explored. Approximately 60 subjects among the 90 subjects with LAG-3 expression in Part D1 are expected to be BRAF wild-type.

For the purpose of demonstrating preliminary clinical evidence of the treatment effect, the primary efficacy population will be subjects with LAG-3 expression who progressed while on anti-PD-1 antibody therapies and receive BMS-986016 80 mg + nivolumab 240 mg Q2W in Part D1. A portion of subjects in Part C who meet the eligibility criteria of Part D1 will be included in a sensitivity analysis to further strengthen the evidence.

The sample size of 90 subjects with LAG-3 expression was determined based on the ability to produce a CI, which would exclude an ORR of the historic response, and to provide sufficient information for a reliable understanding of the safety profile.

There is no standard of care for advanced melanoma patients who have progressed during prior anti-PD-1 therapy; thus, the demonstration of effective and tolerable therapy in these patients remains a large unmet need. The only published or reported studies in this clinical setting employ anti-CTLA-4 therapy, namely ipilimumab, and they are small retrospective or exploratory ad hoc analyses. The patient population characteristics and results of ipilimumab monotherapy in these studies are listed in Table 8.1.4.1-1 below. There have been no prospective studies defining the benefit of anti-CTLA-4 therapy after progression during anti-PD1 therapy.

Table 8.1.4.1-1: Ipilimumab After Prior Anti-PD-1 Therapy

Study Population	ORR/CI/DOR	Toxicity	Source
Retrospective: Sequential treatment of anti-PD-1 (all progressed on clinical trials) then ipilimumab. 10% BRAF mutant. 42% with PD as BOR to prior anti-PD-1. 10% prior ipilimumab (response not reported).	10% (4/40 PRs) No CI reported DOR not reported	55% received all 4 doses of ipilimumab 35% had Grade 3 to 5 irAE;1 drug-related death due to pneumonitis	Bowyer et al 10.1038/bjc.2016.107
Retrospective: Documented progression on prior anti-PD-1 as per RECIST v1.1 (details not provided). 15% BRAF mutant. 51% with PD as BOR to prior anti-PD-1. 26% prior ipilimumab (response not reported).	16% (7/43 PRs) No CI reported DOR not reported Median DoDC 7 months 95% CI (2.8-22.8) months	53% received all 4 doses of ipilimumab (33% did not due to toxicity) Rates of irAEs were not reported	Zimmer et al 10.1016/j.ejca.2017.01.009
Exploratory post-hoc analysis of patients who received ipilimumab sequentially after pembrolizumab	13% (3 CRs and 10 PRs out of 97 patients) No CI reported	Not reported	Long et al KEYNOTE-006 presentation at

Table 8.1.4.1-1: Ipilimumab After Prior Anti-PD-1 Therapy

Study Population	ORR/CI/DOR	Toxicity	Source
(91% with documented progression). Data from subsequent therapies case report forms. 16% BRAF mutant. 62% with PD as BOR to prior anti-PD1.	DOR not reported		Society for Melanoma Research November 6-9, 2016
All treated subjects - nivolumab crossover to ipilimumab (the subjects randomized to nivolumab who received ipilimumab as subsequent therapy). 56% with PD as BOR to prior anti-PD-1.	10% (7/68 PRs) 95% CI (4.2%, 20.1%) DOR not reported	Not reported	CA209066 study Unpublished analysis

Combined analyses employing a standard response evaluable population definition across the multiple small studies of ipilimumab monotherapy in the setting of prior anti-PD-1 therapy reveal an approximate 12% ORR. Durability of these responses are poorly documented.

In heavily pretreated patients where clinical benefit is observed in only a subset of the population, safety is a significant concern. The reported rates of Grade 3 (or greater) TRAEs of approximately 35% from single-agent ipilimumab after anti-PD-1 therapy limits the overall utility of this approach.[59]

The majority of our patient population (approximately 60%) have also been previously treated with anti-CTLA-4 therapy. There are no reported effective therapies in this setting. In addition, antitumor responses with continued anti-PD-1 therapy after initial progression on anti-PD-1 therapy is relatively rare, with estimates of incidence of approximately 5%.[60] Thus, given a population in which all have progressed during prior anti-PD-1 therapy, and the majority have received prior anti-CTLA-4 therapy as well, it is reasonable to target an ORR that excludes 10% as a lower bound within a 95% CI.

Table 8.1.4.1-2: Observed ORR with Exact 95% CI for Cohort D

Sample Size	Number of Responses	ORR	95% Exact CI
60	12	20%	[10.8%, 32.3%]
	15	25%	[14.7%, 37.9%]
	18	30%	[18.9%, 43.2%]
90	16	18%	[10.5%, 27.3%]
	18	20%	[12.3%, 29.8%]
	20	22%	[14.1%, 32.2%]
120	20	17%	[10.5%, 24.6%]
	24	20%	[13.3%, 28.3%]
	27	23%	[15.4%, 31.0%]

Table 8.1.4.1-2: Observed ORR with Exact 95% CI for Cohort D

Sample Size	Number of Responses	ORR	95% Exact CI
150	24	16%	[10.5%, 22.9%]
	27	18%	[12.2%, 25.1%]
	30	20%	[13.9%, 27.3%]
220	26	12%	[7.9%, 16.8%]
	29	13%	[9.0%, 18.4%]
	32	15%	[10.2%, 19.9%]

8.1.4.2 Melanoma Prior IO Focused Eligibility Expansion (Part D1-Q4W)

The coprimary objective in Part D1-Q4W is to evaluate the difference in safety between coadministration relative to FDC as measured by the incidence of AEs in the Broad Scope MedDRA Anaphylactic Reaction SMQ occurring within 2 days after dosing during the combination and to confirm with Q4W dosing of BMS-986016 160 mg in combination with nivolumab 480 mg the safety of the BMS-986016 80 mg in combination with nivolumab 240 mg Q2W in advanced melanoma subjects who progressed while on anti-PD-1 antibody therapies (see Appendix 5).

Prior to Revised Protocol 09, subjects are being enrolled into a single arm: Part D1 BMS-986016 80 mg + nivolumab 240 mg Q2W. Subsequent to this amendment, and until the enrollment to Part D1 BMS-986016 80 mg + nivolumab 240 mg Q2W is completed, subjects in Part D1 will be randomized 1:1:1 to Part D1 BMS-986016 80 mg + nivolumab 240 mg Q2W, Part D1 BMS-986016 160 mg + nivolumab 480 mg Q4W coadministration, and Part D1 BMS-986213 (relatlimab 160 mg/nivolumab 480 mg) Q4W arms. Once enrollment to Part D1 BMS-986016 80 mg + nivolumab 240 mg Q2W is completed, subjects will be randomized 1:1 to Part D1 BMS-986016 160 mg + nivolumab 480 mg Q4W coadministration and Part D1 BMS-986213 (relatlimab 160 mg/nivolumab 480 mg) Q4W arms. If enrollment to Q4W arms is completed prior to arm BMS-986016 80 mg + nivolumab 240 mg Q2W, then enrollment to arm BMS-986016 80 mg + nivolumab 240 mg Q2W will be completed as a single arm.

Approximately 150 subjects will be randomized to the 2 treatment arms Part D1 BMS-986016 160 mg + nivolumab 480 mg Q4W coadministration and Part D1 BMS-986213 (relatlimab 160 mg/nivolumab 480 mg) Q4W. This number of treated subjects was chosen to achieve a sufficient level of precision for a descriptive analysis to estimate the difference in rates of AEs in the Broad Scope MedDRA Anaphylactic Reaction SMQ between the 2 treatment arms. Seventy-five (75) treated subjects per arm will allow estimation of the rate difference within 95% confidence limits of ±15% or less and will be supplemented by a qualitative clinical assessment of the type and severity of events to evaluate benefit-risk (see Appendix 5).

From the Q2W expansion cohorts in Part C of the current study, AEs in the Broad Scope MedDRA Anaphylactic Reaction SMQ with onset within 2 days after sequential dosing of nivolumab 240 mg combined with BMS-986016 80 mg were reported in 14% of treated subjects. In Part D1-Q4W, if

the observed rate of these events is equal to 14% among 75 treated subjects in each arm, then the 95% CI for the difference in rates between arms will be (-11.1%, 11.1%) (see Appendix 5).

Table 8.1.4.2-1 shows the precision that the sample size of 75 treated subjects per arm in Part D1-Q4W and 150 treated subjects each in Part D1-Q2W and Part D1-Q4W dosing will provide for estimating rates and rate differences between the treatment arms under different assumed observed rates. Enrollment and randomization across treatment arms Part D1 BMS-986016 160 mg + nivolumab 480 mg Q4W coadministration and Part D1 BMS-986016 160 mg + nivolumab 480 mg Q4W FDC may continue until the following criteria are met: 90 efficacy-evaluable LAG-3-positive subjects have been treated, 60 efficacy-evaluable LAG-3-positive and BRAF wild-type subjects have been treated, and 60 efficacy-evaluable LAG-3–positive and ipilimumab pretreated subjects have been treated.

Table 8.1.4.2-1: 95% CI for Rate Differences When Observed in 75 Subjects per Arm and 150 Subjects per Dosing Regimen

75 Subjects per Arm		
Coadministration Arm	**Fixed Dose Combination Arm**	**Rate Difference (95% CI)**
14%	14%	0% (-11.1%, 11.1%)
14%	12%	2% (-8.8%, 12.8%)
16%	14%	2% (-9.4%, 13.4%)
18%	16%	2% (-10%, 14%)
20%	18%	2% (-10.6%, 14.6%)
150 Subjects Each in Part D1-Q4W and Part D1-Q2W		
Q2W	**Q4W**	**Rate Difference (95% CI)**
14%	14%	0% (-7.9%, 7.9%)
14%	12%	2% (-5.6%, 9.6%)
16%	14%	2% (-6.1%, 10.1%)
18%	16%	2% (-6.5%, 10.5%)
20%	18%	2% (-6.9%, 10.9%)

Also, with 75 subjects per arm, there is a 99% probability that the 95% CI for the geometric mean ratio of Cmax of FDC to coadministration is wholly contained within [0.8, 1.25]. log(Cmax) is assumed to follow a normal distribution and, with intrasubject coefficients of variation, is assumed to be no greater than 30%.

8.1.4.3 Melanoma Prior IO Expanded Eligibility Expansion (Part D2)

Part D2 will have an expanded eligibility criteria with 2 cohorts in sequence: 160 mg BMS-986016 with 480 mg nivolumab Q4W and 240 mg BMS-986016 with 480 mg nivolumab Q4W. Subjects in Part D2 on average will have a worse performance status and be more heavily treated. Approximately 30 subjects will be initially treated with 160 mg BMS-986016 with 480 mg

nivolumab Q4W. Once this dose level is deemed safe, approximately up to 220 additional subjects will be treated with either 160 mg BMS-986016 with 480 mg or 240 mg BMS-986016 with 480 mg nivolumab Q4W to establish safety and efficacy in this broader group of melanoma patients. With 30 subjects, there is approximately 96% chance to observe at least 1 occurrence of any AE that would occur with a 10% incidence in the population from which the sample is drawn. With 250 subjects, there is approximately 92% chance to observe at least 1 occurrence of any AE that would occur with a 1% incidence in the population from which the sample is drawn. Safety and efficacy data will be collected as in the other cohorts, and the data will be used as supportive evidence of safety and efficacy of the combination therapy.

8.1.5 Exposure/Response Expansion Q4W Dosing (Part E)

In Part E, 2 disease cohorts will be investigated: melanoma participants who experienced disease progression on prior anti-PD-1 therapy in the advanced, unresectable, or metastatic setting and melanoma participants who have not received prior systemic anticancer therapy for unresectable or metastatic melanoma. The objective of this expansion is to support further clinical testing at higher dose of relatlimab in combination with nivolumab by demonstrating adequate safety and tolerability as well as favorable benefit-risk by assessing preliminary efficacy measured by ORR and other clinically relevant efficacy measures such as DOR and DCR. However, the sample size is based on efficacy, specifically on the target ORR relative to the ORR observed at the lower dose of relatlimab in combination with nivolumab. Both disease cohorts will be handled independently, and there will be no multiplicity adjustment. The sample size of the melanoma cohort of participants who experienced disease progression on prior anti-PD-1 therapy is based on the comparison of the ORR of subjects who receive 480 mg BMS-986016 + 480 mg nivolumab Q4W vs the benchmark (ie, historical control) observed ORR of subjects who received 80 mg BMS-986016 + 240 mg nivolumab Q2W in this study. A sample size of 75 subjects who experienced disease progression on prior anti-PD-1 therapy will provide approximately 85% power for testing the ORR difference with a 2-sided alpha of 0.1, assuming ORR of 25% and 10% in the 480 mg BMS-986016 + 480 mg nivolumab Q4W arm and in the historical control arm, respectively.

The sample size of the cohort of participants who have not received prior systemic anticancer therapy for advanced, unresectable, or metastatic melanoma is based on the comparison of the ORR of subjects who receive 480 mg BMS-986016 + 480 mg nivolumab Q4W vs the ORR of subjects who receive 160 mg BMS-986016 + 480 mg nivolumab Q4W. A sample size of 150 subjects who have not received prior systemic anticancer therapy for unresectable or metastatic melanoma randomized in a 1:1 ratio in 2 arms will provide approximately 81% power for testing the ORR difference with a 2-sided alpha of 0.1, assuming ORR of 67% and 47% in the 480 mg BMS-986016 + 480 mg nivolumab Q4W arm and in the 160 mg BMS-986016 + 480 mg nivolumab Q4W arm, respectively.

8.2 Populations for Analyses

All Enrolled Subjects Analysis Set: This analysis set contains all subjects (including screen failures) who signed an ICF for the study.

All Treated Subjects Analysis set: This analysis set includes all subjects who receive either drug.

Response-evaluable Subjects: This analysis set includes all subjects who receive either study drug, have a baseline tumor assessment with measurable disease, and 1 of the following: 1) at least 1 evaluable on-treatment tumor assessment, 2) clinical progression, or 3) death prior to the first on-treatment tumor evaluation.

Enriched Subjects: This analysis set includes all treated subjects with LAG-3 expression.

BMS-986016 Pharmacokinetic Analysis Set: This analysis set includes all subjects who receive BMS-986016 and have at least 1 valid PK parameter to be included in statistical analyses of BMS-986016 PK data.

BMS-986016 Immunogenicity Analysis Set: This analysis set includes all subjects who receive BMS-986016 and have baseline and at least 1 postbaseline preinfusion BMS-986016 immunogenicity assessment.

Nivolumab Immunogenicity Analysis Set: This analysis set includes all subjects who receive nivolumab and have baseline and at least 1 postbaseline preinfusion nivolumab immunogenicity assessment.

Pharmacodynamic Analysis Set: This analysis set includes all treated subjects for whom pharmacodynamic measurements are available at baseline and at least 1 other time point.

8.3 Endpoints

8.3.1 Primary Endpoints

The primary endpoint of this Phase 1/2a study is safety as measured by the rate of AEs, SAEs, AEs leading to discontinuation of treatment, deaths, and laboratory abnormalities assessed during treatment and for up to 135 days of follow-up. All subjects who receive at least 1 dose of BMS-986016 or nivolumab will be analyzed for safety.

The coprimary endpoints in Part C are ORR, DCR, and DOR based on BICR assessments using RECIST v1.1, where applicable, in selected disease cohorts.

The coprimary endpoint in Part D1-Q2W is ORR, as determined by BICR using RECIST v1.1, in advanced melanoma subjects with LAG-3 expression who progressed while on anti-PD-1 antibody therapies.

- ORR is defined as the total number of subjects whose BOR is either CR or PR divided by the total number of treated subjects in the population of interest.

  Best overall response per RECIST v1.1 is defined as the best response designation recorded between the date of first dose and the date of first objectively documented progression per RECIST v1.1 or the date of subsequent therapy, whichever occurs first. CR or PR determinations included in the BOR assessment must be confirmed by a second scan no less than 4 weeks after the criteria for response are first met. For subjects who continue treatment beyond progression per RECIST v1.1 or begin subsequent therapy, the BOR should be determined based on response designations recorded up to the time of the initial progression or subsequent therapy, whichever occurs first. For subjects without documented progression or subsequent therapy, all available response designations should contribute to the BOR assessment.

- DCR is defined as the total number of subjects whose BOR is either CR, PR, or SD for at least 12 weeks divided by the total number of treated subjects in the population of interest.

DOR computed only for subjects with a BOR of CR or PR is defined as the number of days between the date of first response and the date of first objectively documented disease progression based on the criteria (RECIST v1.1) or death, whichever occurs first. For those subjects who neither progress nor die, the duration of objective response will be censored at the same time they will be censored for the primary definition of PFS (see Section 8.3.2.2).

The primary endpoint in Part D1-Q4W of the study is the incidence of AEs in the Broad Scope MedDRA Anaphylactic Reaction SMQ occurring within 2 days after dosing. This incidence rate is defined as number of subjects who experienced at least 1 AE in the Broad Scope MedDRA Anaphylactic Reaction SMQ with onset on the day of or within 2 days after any study therapy infusion divided by number of treated subjects. The terms included in the MedDRA Anaphylactic Reaction SMQ based on the most current MedDRA version will be listed in the statistical analysis plan (see Appendix 5).

8.3.2 Secondary Endpoints

8.3.2.1 Pharmacokinetics

The PK of BMS-986016 administered both alone and in combination with nivolumab will be assessed as a secondary objective using the following endpoints derived from serum concentration vs time data in Cycle 1 and Cycle 3:

Cmax	Maximum observed serum concentration
Tmax	Time of maximum observed serum concentration
Ctrough	Trough observed serum concentration
Ctau	Concentration at the end of a dosing interval (eg, concentration at 336 hours)
Css,avg	Average concentration over a dosing interval ([AUC(TAU)/tau]
AUC(TAU)	Area under the concentration-time curve in 1 dosing interval
CLT	Total body clearance
T-HALFeff_AUC	Effective elimination half-life that explains the degree of AUC accumulation observed
T-HALFeff_Cmax	Effective elimination half-life that explains the degree of Cmax accumulation observed
AI_AUC	Accumulation index; ration of AUC(TAU) at steady state to AUC(TAU) after the first dose
AI_Cmax	Cmax accumulation index; ratio of Cmax at steady state to Cmax after the first dose
AI_Ctau	Ctau accumulation index; ratio of Ctau at steady state to Ctau after the first dose
DF	Degree of fluctuation or fluctuation index ([Cmax - Ctau]/Css,avg)

Individual subject PK parameter values will be derived by noncompartmental methods by a validated PK analysis program. Actual times will be used for the analyses.

In Part D1-Q4W, PK of nivolumab and BMS-986016 coadministered will be assessed and compared to that of FDC of BMS-986016 and nivolumab. PK will be measured using serum concentration-time data. PK of nivolumab and BMS-986016 in Part D1-Q4W and Part D1-Q2W will also be assessed.

8.3.2.2 Efficacy

The BOR, ORR, DCR, DOR, and PFS rates at prespecified time points (eg, 24 weeks) based on Investigator assessment using RECIST v1.1 will be the secondary efficacy endpoints. The efficacy endpoints based on BICR assessment, where applicable (ie, not designated as the primary), will also be the secondary efficacy endpoints.

BOR, ORR, DCR, and DOR were defined under the primary endpoints. Progression Free Survival is defined as the time from first dose to the date of first objectively documented progression, per RECIST v1.1, or death due to any cause, whichever occurs first. Clinical deterioration in the absence of objectively documented progression per RECIST v1.1 is not considered progression for the purpose of determining PFS. Subjects who die without a reported progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment. Subjects who did not have any on study tumor assessments and did not die will be censored on the date of first dose. Subjects who started any subsequent anticancer therapy, including tumor-directed radiotherapy and tumor-directed surgery, without a prior reported progression will be censored at the last evaluable tumor assessment prior to initiation of the subsequent anticancer therapy. The PFS rate at time T is defined as the probability that a subject has not progressed and is alive at time T following first dose.

Landmark 1-year and 2-year OS rates will be assessed as secondary efficacy endpoints in Part D.

8.3.2.3 Immunogenicity

Incidence of ADA to either BMS-986016 or nivolumab will be assessed during treatment and for up to 135 days after their last treatment in post-treatment follow-up or for a maximum of up to 24 months of treatment, whichever comes first. A baseline ADA-positive subject is defined as a subject with positive seroconversion detected in the last sample before initiation of treatment. An ADA-positive subject is a subject with at least 1 ADA-positive sample relative to baseline after initiation of the treatment.

8.3.2.4 Centrally Read ECGs (Parts A and B)

In Part A and Part B, QTc will be assessed by a central reader at follow-up Visit 1, and on Day 1 of Cycle 1 and Cycle 3 (predose and 4-hour postdose time points). These assessments will be used to address the secondary objective of assessing the effect of BMS-986016 administered alone and in combination with nivolumab on QTc.

ECGs assessed locally by the Investigator are also collected at the start of each cycle. QTc will be calculated by the Sponsor for these ECGs. However, results will be summarized separately and are not considered part of the secondary objective.

8.3.2.5 Safety

8.3.2.5.1 Part D1-Q4W

The secondary endpoint in Part D1-Q4W is the incidence of AEs in the Narrow Scope MedDRA Anaphylactic Reaction SMQ occurring within 2 days after any study therapy infusion. This incidence rate will be defined similarly to the primary safety endpoint for this part of the study except that the event rate will be based on terms within the Narrow Scope SMQ rather than the Broad Scope.

The second secondary endpoint in Part D1-Q4W is the incidence of events within the hypersensitivity/infusion reaction select AE category occurring within 2 days after any study therapy infusion. The select AEs consist of a list of preferred terms (PTs) defined by the Sponsor and represent AEs with a potential immune-mediated etiology. The MedDRA PTs to be included in the hypersensitivity/infusion reaction select AE category will be updated with each new version of MedDRA prior to database lock. The list that is the most current at the time of analysis will be used. The incidence rate of hypersensitivity/infusion reaction select AEs will be defined similarly to the primary endpoint except that the event rate will be based on terms from the hypersensitivity/infusion reaction select AE category rather than the Broad Scope MedDRA Anaphylactic Reaction SMQ.

The drug-related and all-causality Grade 3 - 5 AE rate is defined as number of subjects who experienced at least 1 AE of Grade 3 or higher, or at least 1 AE of Grade 3 or higher judged to be related to study drug by the Investigator, and with onset on or after the first dose of study treatment and within 30 days of the last dose of study treatment divided by number of treated subjects.

8.3.3 Exploratory Endpoints

8.3.3.1 Biomarkers

Biomarker endpoints from peripheral blood will generally be measured at multiple time points and evaluated as both predictive and pharmacodynamic markers in the context of the exploratory biomarker objectives. These may include measures such as levels and change from baseline in levels of the following at each scheduled time point:

- Serum soluble factors

[redacted]

Biomarker endpoints from tumor biopsies will be explored predominantly in an effort to identify baseline markers predictive of efficacy since they are only measured at baseline for most subjects. For the subset of subjects who have both pretreatment and on-treatment biopsies, pharmacodynamic associations may be explored. Endpoints may include measures such as pretreatment levels and change in levels observed on-treatment of:

Appropriate functional transformation of these exploratory measures will be applied as necessary. Measures not available at the time of the clinical study report may be summarized in a separate report.

8.3.3.2 Pharmacokinetics

Nivolumab concentration-time data at scheduled trough (Ctrough) and end-of-infusion time points will be evaluated as an exploratory endpoint. Measurements will be collected on treatment (up to 12 cycles) and for up to 135 days during the post-treatment follow-up or for a maximum of up to 24 months of treatment, whichever comes first.

8.3.3.3 Efficacy

The BOR, ORR, DCR, DOR, and PFS rates at prespecified time points will be explored by iRECIST assessments based on BICR. Landmark 1-year and 2-year OS rates will be assessed as exploratory efficacy endpoints in the study (except for Part D).

8.4 Analyses

Unless otherwise specified, data from Part A (monotherapy dose escalation) and Part A1 (monotherapy dose expansion) will be presented separately from data collected in Part B, Part C (sequential combination therapy), and Part D (coadministration). Safety data from dose escalation phases will be summarized by dose, dosing regimen, and across all doses and dosing regimens. Safety data from dose expansion phases will be summarized for each disease cohort, overall by dose and dosing regimen, and across doses and dosing regimens, as appropriate. Efficacy data from dose expansion phases will be summarized for each disease cohort by dose and across doses. Efficacy data from dose escalation phases will be summarized by dose and listed by tumor type.

Descriptive statistics will include the number of observations and percentage in each category for categorical variables. For continuous variables, the number of observations, mean, median, standard deviation, minimum, and maximum will be presented unless otherwise specified. All available data will be included in-subject listings.

8.4.1 Demographics and Baseline Characteristics

Frequency distributions of gender, race, ethnicity, and other categorical baseline characteristics will be tabulated. Baseline body mass index (BMI) will be derived from measurements of baseline body weight and height. Summary statistics for age, body weight, height, and BMI will be

tabulated. Baseline disease characteristics will be summarized for expansion cohorts for different disease cohorts separately, as appropriate.

8.4.2 Efficacy Analyses

Individual BOR, DOR, and PFS will be determined based on RECIST v1.1 criteria for the primary and secondary analyses. iRECIST will be used as an exploratory analysis in Parts C and D. BOR outcomes will be summarized using frequency tables together with 2-sided 95% CIs. Time to event distribution (eg, PFS and DOR) will be estimated using the Kaplan-Meier method. When appropriate, the median along with 95% CI will be provided using Brookmeyer and Crowley methodology (using log-log transformation for constructing the CIs). Rates at fixed time points (eg, PFS rate 24 weeks) will be derived from the Kaplan-Meier estimate, and corresponding CI will be derived based on Greenwood formula. CIs for binomial proportions will be derived using the Clopper-Pearson method. OS data will be analysed similarly to PFS data analysis.

For the purpose of demonstrating preliminary clinical evidence of the treatment effect in advanced melanoma subjects who progressed while on receiving anti-PD-1 antibody therapies, the primary efficacy population will be subjects with LAG-3 expression who progressed while on anti-PD-1 antibody therapies in Part D1-Q2W. A portion of subjects in Part C who meet the eligibility criteria of Part D1 will be included in the sensitivity analysis to further strengthen the evidence. Efficacy analysis will also be performed for subjects with a lack of LAG-3 expression, and also for all treated subjects regardless of LAG-3 expression to support the treatment effect of the combination therapy.

Initial cutpoint for the purpose of exploring an enriched population is LAG-3 expression ≥ 1%. However, as the optimal marker cutpoint is not well known prior to the study, several different cutoffs may be explored other than the initial cutpoint of 1% by examining receiver operating characteristics curves using the ORR, although the decision of the cutpoint will be based on the totality of the efficacy data, including DOR and DCR. Details of methodology will be described in the statistical analysis plan prior to any data exploration in Part D.

In an effort to explore an enriched patient population in advanced melanoma subjects who progressed while on anti-PD-1 antibody therapies in Part D1, other potential predictive markers such as BRAF mutation status may be explored.

Subsequently, efficacy analysis for Part D1-Q4W will be done similarly to that for Part D1-Q2W. If the outcome of BOR in the Part D1-Q4W is deemed similar to that of the Part D1-Q2W, data from both Part D1-Q2W and Part D1-Q4W may be combined to strengthen the evidence.

Efficacy analysis for Part D2 will be done similarly to that for Part D1.

8.4.3 Safety Analyses

All subjects who receive study drug therapy will be evaluated for safety endpoints. All recorded AEs will be coded according to the most current version of MedDRA and will be graded using the NCI CTCAE v4.0. AEs will be listed and subjects with AEs will be summarized based on the event with worst CTCAE grade by system organ class (SOC) and PT, counting once at the PT term level and once at the SOC level, for each dose, dosing regimen, and overall. The incidence of AEs

in the Broad and Narrow Scope MedDRA Anaphylactic Reaction SMQ and select AEs in hypersensitivity/infusion reaction category occurring within 2 days after dosing by treatment arm, the difference in rates between arms, and the corresponding 95% CIs will be reported descriptively. The CIs for the rate estimates will be based on the Clopper-Pearson method. Vital signs and clinical laboratory test results will be listed and summarized by treatment. In addition, the worst grade of a laboratory measure observed on-study by the baseline grade (per CTCAE v4.0) will also be generated for selected laboratory tests. Any significant physical examination findings and results of clinical laboratory tests will be listed. ECG results will be evaluated by the Investigator, and abnormalities, if present, will be listed. In Parts A and B, ECG will be assessed by a central reader at specific time points. All ECG data analyses, including summaries of each ECG parameter, frequency distributions of subjects' maximum values/changes, and scatter plots, will be performed following the current practice of ECG data analysis. Concentration-response analysis may be performed using mixed-effect model, if appropriate. The details of ECG data analysis will be provided in the statistical analysis plan.

8.4.4 Pharmacokinetic Analyses

Pharmacokinetic parameters for BMS-986016 will be calculated using noncompartmental analyses. Summary statistics will be tabulated for the PK parameters of BMS-986016 by dose and study day/cycle. To describe the association of these parameters with dose of BMS-986016, scatter plots of Cmax and AUC(TAU) vs dose may be provided for each day/cycle measured. Dose proportionality of BMS-986016 when administered alone or coadministered with nivolumab may also be assessed based on a power model. Trough concentrations of BMS-986016 will be plotted vs study day and cycle. Nivolumab end-of-infusion and trough (Ctrough) concentrations will be tabulated using summary statistics. These data may also be pooled with other datasets for population PK analysis, which will be presented in a separate report. In Part D1-Q4W, PK comparisons will be summarized using descriptive summary statistics, and the point estimate and CI of geometric mean ratios of Cmax and AUC(TAU) will be presented to compare nivolumab and BMS-986016 administered as FDC to that of coadministered nivolumab and BMS-986016. PK parameters will also be summarized using descriptive summary statistics for nivolumab and BMS-986016 administered in Part D1-Q2W and Part D1-Q4W dosing.

8.4.5 Biomarker Analyses

Not applicable.

8.4.6 Exploratory Biomarker Analyses

Pharmacodynamic effect in subjects who undergo biopsy will be assessed using summary statistics and plots. [redacted]

[redacted]

8.4.7 Outcomes Research Analyses

Not applicable.

8.4.8 Other Analyses

8.4.8.1 Immunogenicity Analyses

A listing will be provided for all available immunogenicity data. A baseline ADA-positive subject is defined as a subject with positive seroconversion detected in the last sample before initiation of treatment. An ADA-positive subject is a subject with at least 1 ADA-positive sample relative to baseline after initiation of the treatment. For each drug, frequency distribution of baseline ADA-positive subjects and ADA-positive subjects after initiation of the treatment will be summarized. To examine the potential relationship between immunogenicity and safety, a table summarizing the frequency and type of AEs of special interest may be explored by immunogenicity status. In addition, potential relationships between immunogenicity and efficacy and/or PK may also be explored.

8.5 Interim Analyses

Data emerging from this study may be needed for timely decisions about adjustments to procedures in subsequent parts of the study. Therefore, data may be reviewed prior to the final lock of the study database. Additional interim analyses may also be performed for administrative purposes or publications. No formal inferences requiring adjustment to the statistical significance level will be performed.

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

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

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

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

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

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

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

9.1.2 Monitoring

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

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

The Investigator must notify BMS promptly of any inspections scheduled by Regulatory Authorities and promptly forward copies of inspection reports to BMS.

9.1.3 Investigational Site Training

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

9.2 Records

9.2.1 Records Retention

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

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

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

9.2.2 Study Drug Records

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

Amount received and placed in storage area

Amount currently in storage area

Label identification number or batch number

Amount dispensed to and returned by each subject, including unique subject identifiers

Amount transferred to another area/site for dispensing or storage

Nonstudy disposition (eg, lost, wasted)

Amount destroyed at study site, if applicable

Amount returned to BMS

Retain samples for bioavailability/bioequivalence, if applicable

Dates and initials of person responsible for investigational product dispensing/accountability, as per the Delegation of Authority Form

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

9.2.3 Case Report Forms

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

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

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

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

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

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

9.3 Clinical Study Report and Publications

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

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

Subject recruitment (eg, among the top quartile of enrollers)
Involvement in trial design
Other criteria (as determined by the study team)

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

10 GLOSSARY OF TERMS

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

11 LIST OF ABBREVIATIONS

Term	Definition
ADA	antidrug antibody
AE	adverse event
AFP	alpha-fetoprotein
AI	accumulation index
AI_AUC	AUC accumulation index; ratio of AUC(TAU) at steady state to AUC(TAU) after the first dose
AI_Cmax	Cmax accumulation index; ratio of Cmax at steady state to Cmax after the first dose
AI_Ctau	Ctau accumulation index; ratio of Ctau at steady state to Ctau after the first dose
AJCC	American Joint Committee on Cancer
ALK	anaplastic lymphoma kinase
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AT	aminotransaminase
AUC	area under the concentration-time curve
AUC(TAU)	area under the concentration-time curve in 1 dosing interval
βhCG	beta-human chorionic gonadotrophin
BICR	Blinded Independent Central Review
BLRM	Bayesian Logistic Regression Model
BMI	body mass index
BMS	Bristol-Myers Squibb
BOR	best overall response
BTLA	B and T lymphocyte attenuator
BUN	blood urea nitrogen
CEA	carcinoembryonic antigen
CI	confidence interval
CLT	total body clearance
CLTp	systemic clearance

Term	Definition
Cmax	maximum observed concentration
CNS	central nervous system
COVID-19	coronavirus disease 2019
[redacted]	[redacted]
CR	complete response
CRF	case report form
Css,avg	average concentration over a dosing interval ([AUC(TAU)/tau]
CT	computed tomography
CTA	Clinical Trial Agreement
Ctau	concentration at the end of a dosing interval (eg, concentration at 24 hours, concentration at 12 hours, etc.)
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
CTLA-4	cytotoxic T lymphocyte–associated antigen 4
Ctrough	trough observed serum concentration
DCR	disease control rate
DF	degree of fluctuation or fluctuation index ([Cmax - Ctau]/Css,avg)
DICOM	Digital Imaging and Communications in Medicine
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DMC	data monitoring committee
DOR	duration of response
EBV	Epstein-Barr virus
ECG	electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
ELISA	enzyme-linked immunosorbent assay
EOI	end of infusion
EOT	end of treatment

Term	Definition
EU CTR	EU Clinical Trial Regulation
FDC	fixed-dose combination
FFPE	formalin-fixed paraffin-embedded
FSH	follicle-stimulating hormone
FU	follow-up
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBV	hepatitis B virus
HBsAg	hepatitis B surface antigen
HCC	hepatocellular carcinoma
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HED	human equivalent dose
HER-2	human epidermal growth factor receptor 2
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HNC	head and neck cancer
HPV	human papilloma virus
HRT	hormone replacement therapy
IB	Investigator Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICOS	inducible T cell costimulator
IEC	Independent Ethics Committee
IFN	interferon
IFN-γ	interferon gamma
IHC	immunohistochemistry
IION	International Immuno-Oncology Network
IL	interleukin
IMAE	immune-mediated adverse event

Term	Definition
IMP	investigational medicinal product
IO	immuno-oncology
irAE	immune-related adverse event
IRB	Institutional Review Board
irRECIST	immune-related Response Evaluation Criteria in Solid Tumors
IRT	Interactive Response Technology
ISH	in situ hybridization
IV	intravenous
IVRS	interactive voice response system
KPS	Karnofsky Performance Score
LAG-3	lymphocyte activation gene 3
LC	liquid chromatography
[redacted]	[redacted]
LDH	lactate dehydrogenase
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MAD	maximum administered dose
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
MI	myocardial infarction
MRI	magnetic resonance imaging
MS	mass spectrometry
MSI	microsatellite instability
MTD	maximum tolerated dose
MUGA	multigated acquisition scan
NCI	National Cancer Institute
NK	natural killer
NOAEL	no-observed-adverse-effect level
NSCLC	non-small cell lung cancer
ORR	objective response rate

Term	Definition
[redacted]	[redacted]
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed cell death protein ligand 1
PD-L2	programmed cell death protein ligand 2
PE	physical examination
PEE	probability of early expansion
PET	probability of early termination
PFS	progression-free survival
PID	patient identification number
PK	pharmacokinetic(s)
PR	partial response
PSA	prostate-specific antigen
PT	preferred term
Q2W	every 2 weeks
Q4W	every 4 weeks
qPCR	qualitative polymerase chain reaction
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
[redacted]	[redacted]
SAE	serious adverse event
SCCHN	squamous cell carcinoma of the head and neck
SD	stable disease
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
[redacted]	
SOC	system organ class
STD10	severely toxic dose in 10% of the animals
T3	triiodothyronine

Term	Definition
T4	thyroxine
TCIP	T cell–inflamed phenotype
[redacted]	[redacted]
TGI	tumor growth inhibition
T-HALF	terminal half-life
T-HALFeff_AUC	effective elimination half-life that explains the degree of AUC accumulation observed
T-HALFeff_Cmax	effective elimination half-life that explains the degree of Cmax accumulation observed)
TIL	tumor-infiltrating lymphocyte
TKI	tyrosine kinase inhibitor
Tmax	time of maximum observed concentration
Treg	regulatory T cell
TSH	thyroid-stimulating hormone
TTE	transthoracic echocardiogram
ULN	upper limit of normal
US IION sites	[redacted]
[redacted]	[redacted]
WOCBP	women of childbearing potential

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APPENDIX 1 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

Appendix 1 provides general information and definitions related to Women of Childbearing Potential (WOCBP) and methods of contraception that can be applied to most clinical trials. For information specific to this study regarding acceptable contraception requirements for female participants, refer to Section 3.3.1: Inclusion Criteria of the protocol. Only the contraception methods as described in Section 3.3.1: Inclusion Criteria of the protocol are acceptable for this study.

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.

Note: Females treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgement in checking serum FSH levels.

- 1 week minimum for vaginal hormonal products (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products

Other parenteral products may require washout periods as long as 6 months. If the serum FSH level is > 40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal.

End of Relevant Systemic Exposure

End of relevant systemic exposure is the time point at which the study intervention (Investigational Medicinal Product [IP/IMP] and other study interventions ie, Non-IMP/AxMP required for study) or any active major metabolites have decreased to a concentration that is no longer considered relevant for human teratogenicity or fetotoxicity. This should be evaluated in context of safety margins from the no-observed-adverse-effect level or the time required for 5 half-lives of the study intervention to pass for a total of 5 months post treatment completion.

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 post-treatment completion**.

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

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation and/or implantation (These methods of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol)[b] – oral (birth control pills) – intravaginal (rings) – transdermal • Combined (estrogen- and progestogen-containing) hormonal contraception must begin at least 30 days prior to initiation of study therapy.
• Progestogen-only hormonal contraception associated with inhibition of ovulation (This method of contraception can only be used by WOCBP participants in studies in which hormonal contraception is permitted by the study protocol.)[b] – oral – injectable • Progestogen-only hormonal contraception must begin at least 30 days prior to initiation of study therapy.
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation and/or implantation (This method of contraception can only be used by WOCBP participants in studies in which hormonal contraception is permitted by the study protocol)[b]

- Intrauterine device (IUD)[c]
- Intrauterine hormone-releasing system (IUS) (This method of contraception can only be used by WOCBP participants in studies in which hormonal contraception is permitted by the study protocol.)[b,c]
- Bilateral tubal occlusion

- Vasectomized partner

A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

- Sexual abstinence

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

- Continuous abstinence must begin at least 30 days prior to initiation of study therapy.
- 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 3.3.3.
- Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence
- Periodic abstinence (including, but not limited to, calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactation amenorrhea method (LAM) are not acceptable methods of contraception for this study.

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 treatment, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized.

[c] Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness

Less Than Highly Effective Contraceptive Methods That Are User Dependent

Failure rate of >1% per year when used consistently and correctly.

- 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 (This method of contraception cannot be used by WOCBP participants in studies where hormonal contraception is prohibited).
Unacceptable Methods of Contraception
• Periodic abstinence (calendar, symptothermal, post-ovulation methods) • Withdrawal (coitus interruptus). • Spermicide only • LAM

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 6.4 and the Appendix for Adverse Events and Serious Adverse Events Definitions and procedures for Evaluating, Follow-up and Reporting.

APPENDIX 2 RECIST 1.1

1 ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

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

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

1.1 Measurable lesions

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

- 10 mm by CT/MRI scan (CT/MRI scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest x-ray
- *Malignant lymph nodes*: To be considered pathologically enlarged *and* measurable, a lymph node must be ≥ 15 mm in ***short*** axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the ***short*** axis will be measured and followed.

1.2 Non-measurable lesions

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

1.3 Special considerations regarding lesion measurability

1.3.1 Bone lesions

- Bone scan, PET scan or plain films are ***not*** considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

- Lytic bone lesions or mixed lytic-blastic lesions, with *identifiable soft tissue components*, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the *soft tissue component* meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

1.3.2 Cystic lesions

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

1.3.3 Lesions with prior local treatment

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

1.4 Specifications by methods of measurements

1.4.1 Measurement of lesions

All measurements should be recorded in metric notation (mm). All baseline evaluations should be performed as close as possible to the treatment start and never more than 30 days before the beginning of the treatment.

1.4.2 Method of assessment

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

1.4.2.1 CT/MRI scan

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

1.4.2.2 Chest X-ray

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

1.4.2.3 Clinical lesions

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

1.4.2.4 Ultrasound

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

1.4.2.5 Endoscopy, laparoscopy

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

1.4.2.6 Tumor markers

Tumor markers ***alone*** cannot be used to assess objective tumor response.

2 BASELINE DOCUMENTATION OF 'TARGET' AND 'NON-TARGET' LESIONS

2.1 Target lesions

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

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

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

2.1.1 Lymph nodes

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

2.2 Non-target lesions

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

3 TUMOR RESPONSE EVALUATION

3.1 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.

3.1.1 Special notes on the assessment of target lesions

3.1.1.1 Lymph nodes

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

3.1.1.2 Target lesions that become 'too small to measure'

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

However, when such a lesion becomes difficult to assign an exact measure to then:

- 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 (note: in case of a lymph node believed to be present and 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).

3.1.1.3 Target lesions that split or coalesce on treatment

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

3.2 Evaluation of non-target lesions

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

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

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

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

3.2.1 Special notes on assessment of non-target lesions

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

3.2.1.1 When the subject also has measurable disease

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

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

3.2.1.2 When the subject has only non-measurable disease

- To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening such that 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.
- Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are non-measurable) a useful test that can be applied when assessing subjects 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: i.e. 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 a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'.
- If 'unequivocal progression' is seen, the subject should be considered to have had overall PD at that point.

3.2.1.3 Tumor markers

Tumor markers *alone* cannot be used to assess objective tumor responses.

3.3 New lesions

The appearance of new malignant lesions denotes disease progression. The finding of a new lesion should be unequivocal: i.e. 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 subject'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.

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

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

4 RESPONSE CRITERIA

4.1 Timepoint response

A response assessment should occur at each time point specified in the protocol.

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

Table 1: Timepoint Response - Subjects with Target (+/- Non-Target) Disease

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

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE =not evaluable.

4.1.1 Missing assessments and not evaluable designation

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

4.1.2 Confirmation Scans

- Verification of Response: Confirmation of PR and CR is required within 4 weeks to ensure responses identified are not the result of measurement error. To be assigned a status of CR or PR, changes in tumor measurements must be confirmed by consecutive repeat assessments

that should be performed no less than 28 days after the criteria for response are first met. For this study, the next scheduled tumor assessment can meet this requirement.

- 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. Additionally, see protocol section 4.3.4 "Treatment beyond Disease Progression" for information regarding verification of progression in select subjects treated beyond initial PD. Evaluation of further PD is required for subjects with treatment beyond progression.

4.2 Best overall response: All timepoints

The best overall response is determined once all the data for the subject are known. It is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. The subject's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Tumor assessments performed after subsequent antitumor therapy is initiated will not be considered in the best overall response assessment.

Best response is defined as the best response across all timepoints with subsequent confirmation. Complete or partial responses may be claimed only if the criteria for each are met at a subsequent timepoint as specified in the protocol (≥ 4 weeks later).

In this circumstance, the best overall response can be interpreted as specified in Table 2. When SD is believed to be best response, measurements must have met the SD criteria at least once no less than 6 weeks after study entry.

Table 2: Best overall response (confirmation of CR and PR required)

Overall Response First Timepoint	Overall Response Subsequent Timepoint	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
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE

Table 2: Best overall response (confirmation of CR and PR required)		
Overall Response First Timepoint	**Overall Response Subsequent Timepoint**	**BEST overall response**
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, NE = not evaluable.

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 (i.e., 6 weeks from baseline assessment). However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the subject 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.

4.3 Duration of response

4.3.1 Duration of overall response

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

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

4.3.2 Duration of stable disease

Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

APPENDIX 3 ECOG, KARNOFSKY, AND LANSKY PERFORMANCE STATUS

PERFORMANCE STATUS CRITERIA: ECOG Score	
ECOG (Zubrod)	
Score	**Description**
0	Fully active; able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of alight or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all self care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of only limited self care; confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self care; totally confined to bed or chair.

PERFORMANCE STATUS CRITERIA: Karnofsky and Lansky		
Score	**Karnofsky Description**	**Lansky Description**
100	Normal; no complaints; no evidence of disease	Fully active, normal
90	Able to carry on normal activity; minor signs or symptoms of disease.	Minor restrictions in physically strenuous activity
80	Normal activity with effort; some signs or symptoms of disease.	Active, but tires more quickly
70	Cares for self; unable to carry on normal activity or to do active work.	Substantial restriction of, and less time spent, in play activity
60	Requires occasional assistance, but is able to care for most of their personal needs.	Out of bed, but minimal active play; keeps busy with quiet activities
50	Requires considerable assistance and frequent medical care.	Gets dressed, but inactive much of day; no active play, able to participate in quiet play
40	Disabled; requires special care and assistance.	Mostly in bed; participates in some quiet activities
30	Severely disabled; hospital admission is indicated although death not imminent.	In bed; needs assistance even for quiet play
20	Very sick; hospital admission necessary; active supportive treatment necessary.	Often sleeping; play limited to passive activities
10	Moribund; fatal processes progressing rapidly.	No play; does not get out of bed
0	Dead	Unresponsive

APPENDIX 4 MANAGEMENT ALGORITHMS

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology agents and regimens.

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

Updated: 27-Jun-2019

GI Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

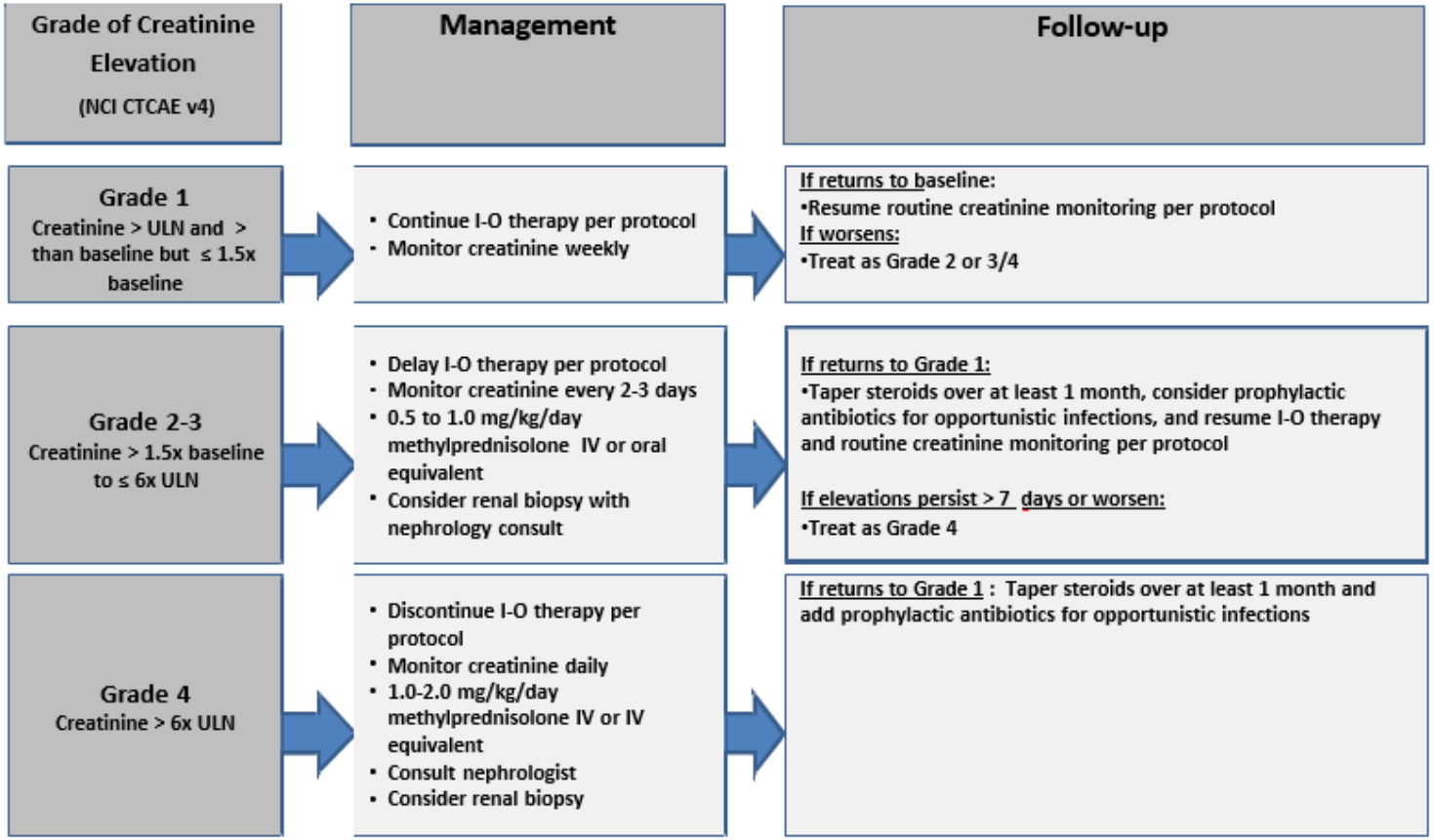
Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea:< 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hrs; not interfering with ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recur: • 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as grade 3/4
Grade 3-4 Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with ADL Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation	• Discontinue I-O therapy per protocol • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis

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

27-Jun-2019

Renal Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

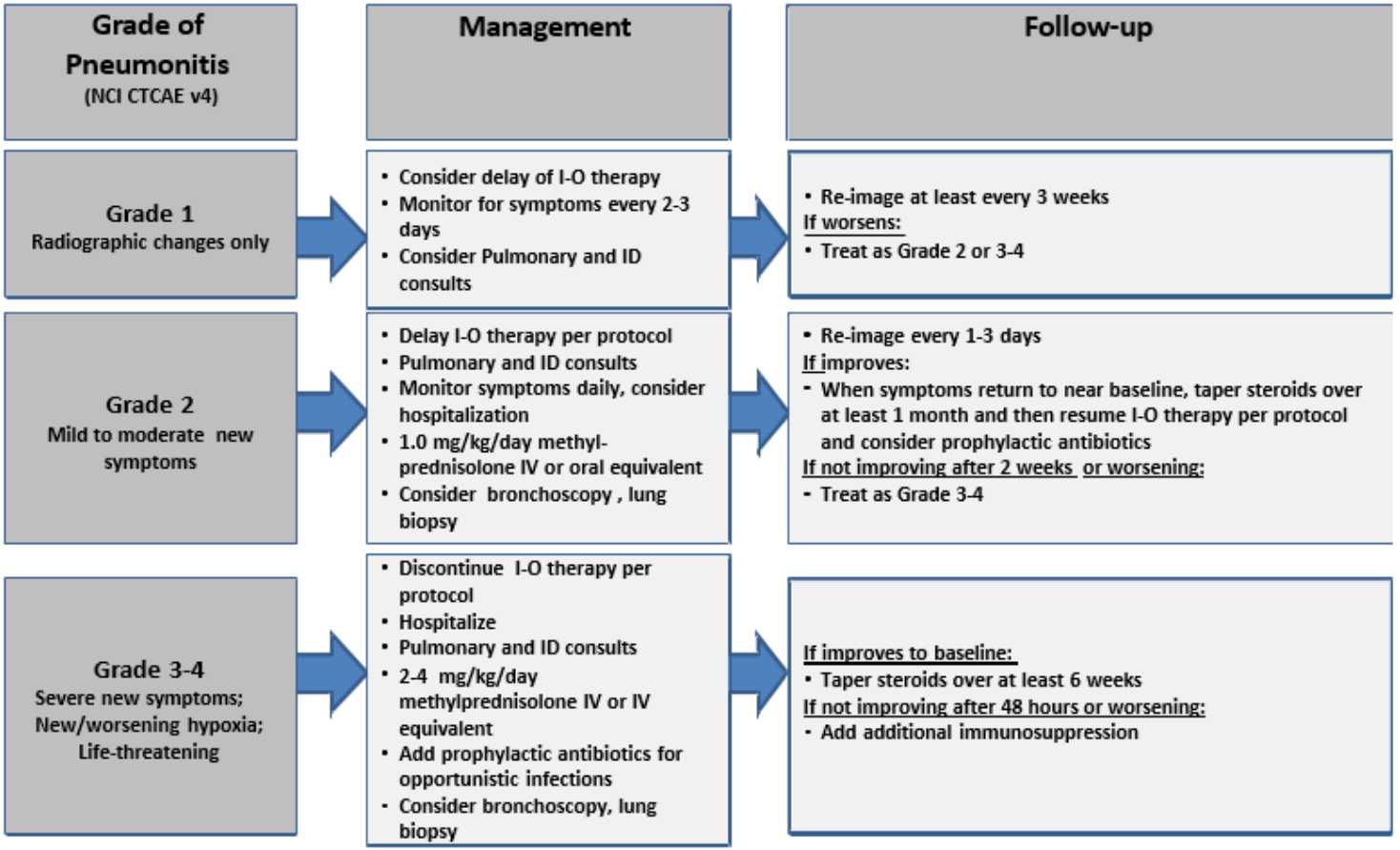


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

27-Jun-2019

Pulmonary Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.

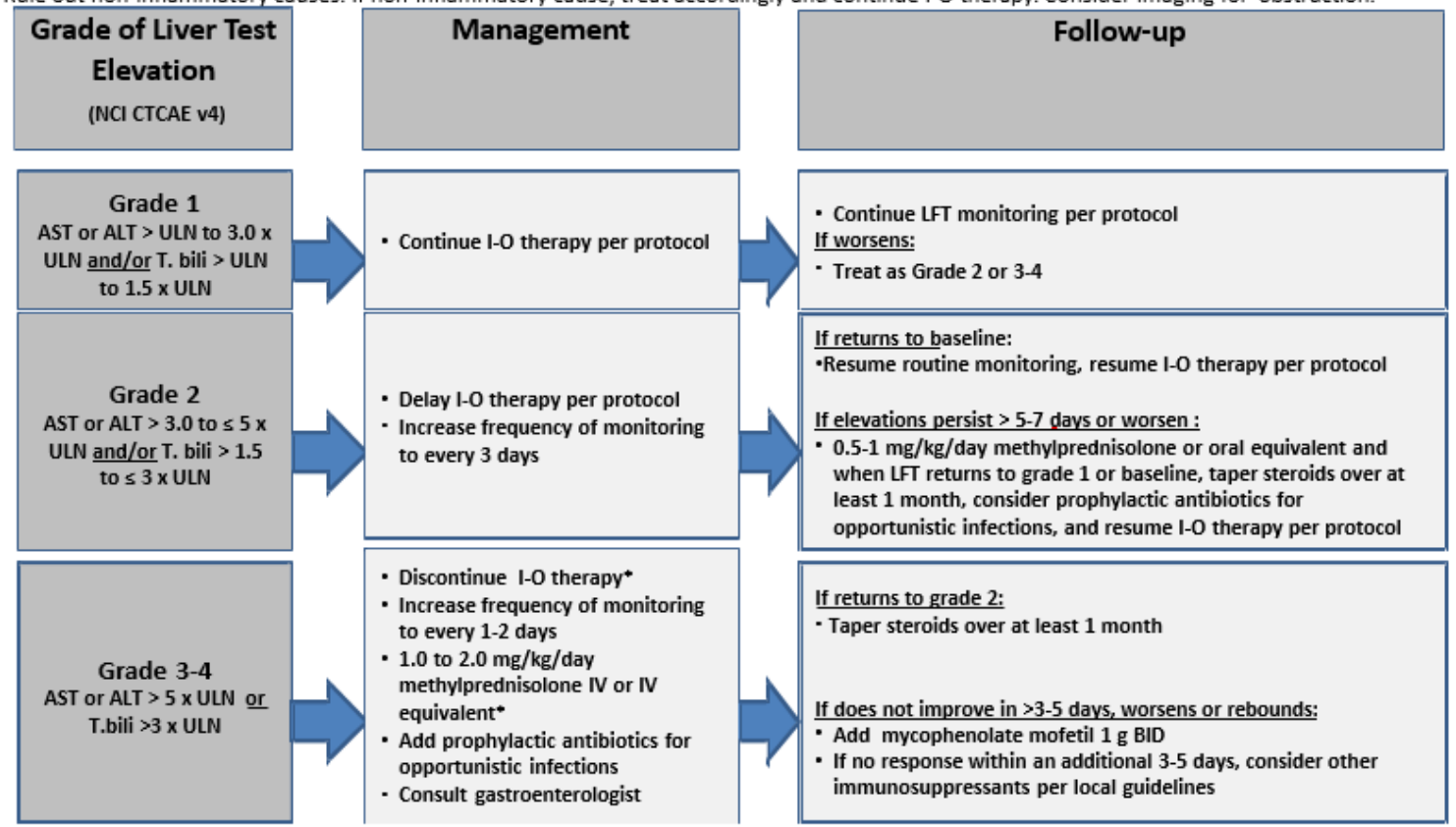


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

27-Jun-2019

Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.



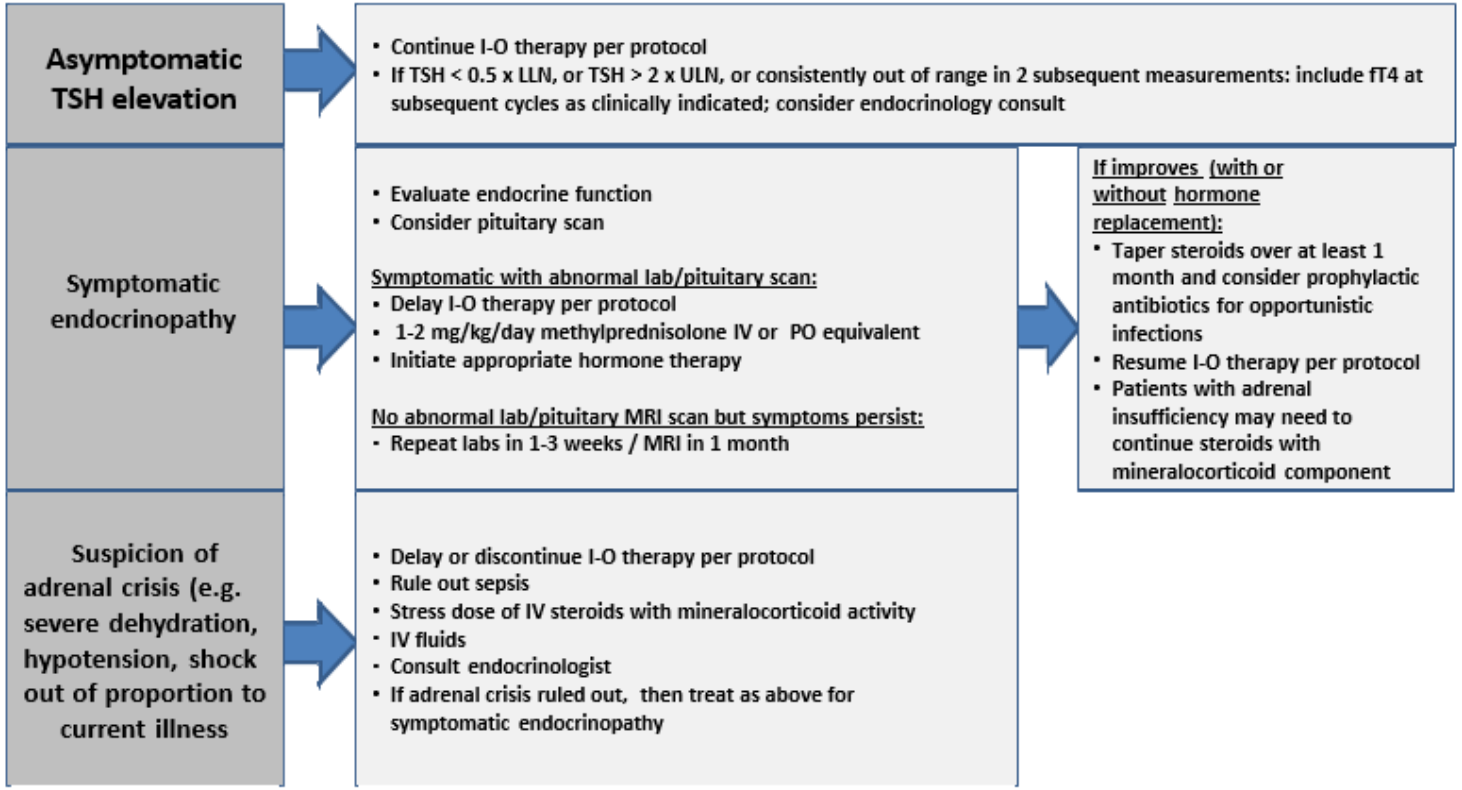
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

*The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

27-Jun-2019

Endocrinopathy Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.

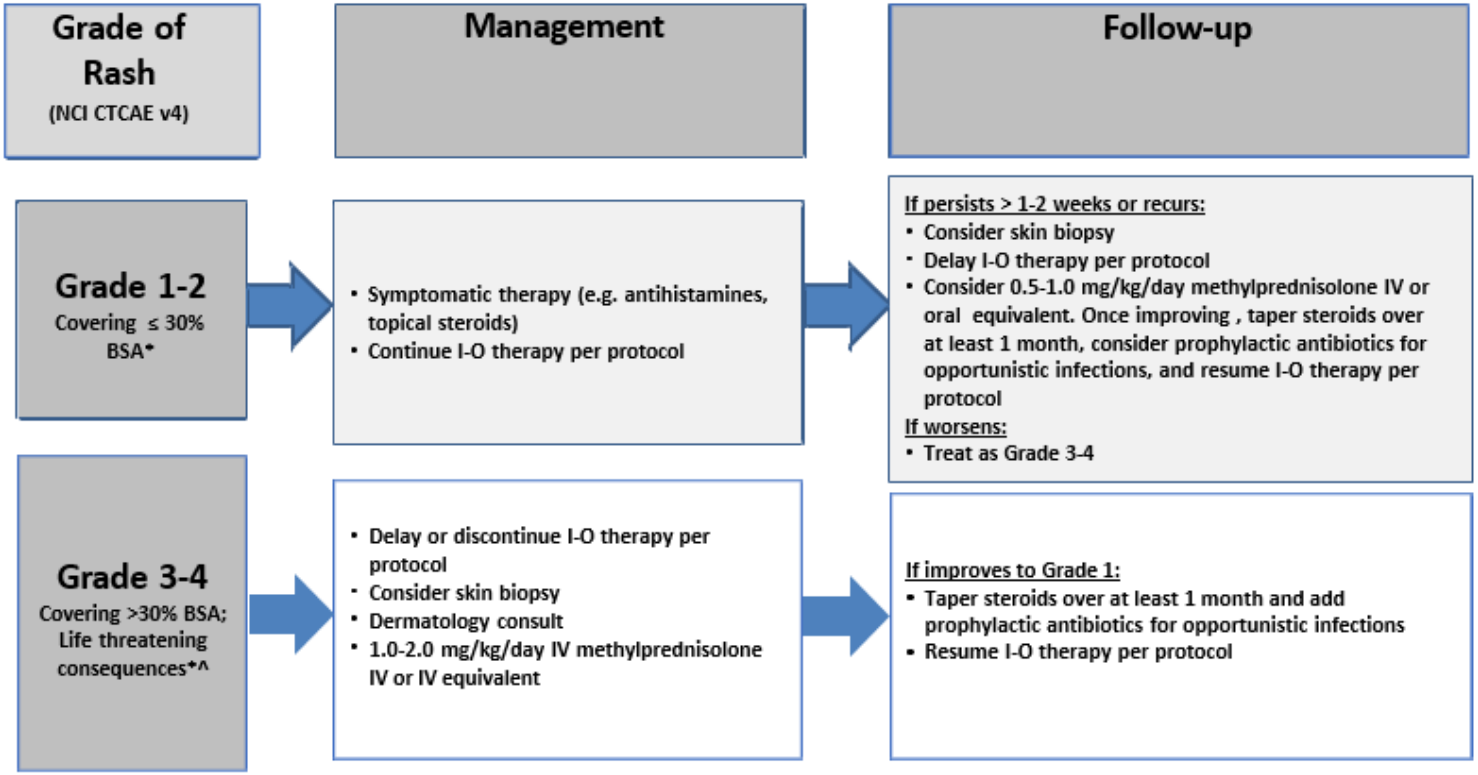


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

27-Jun-2019

Skin Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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

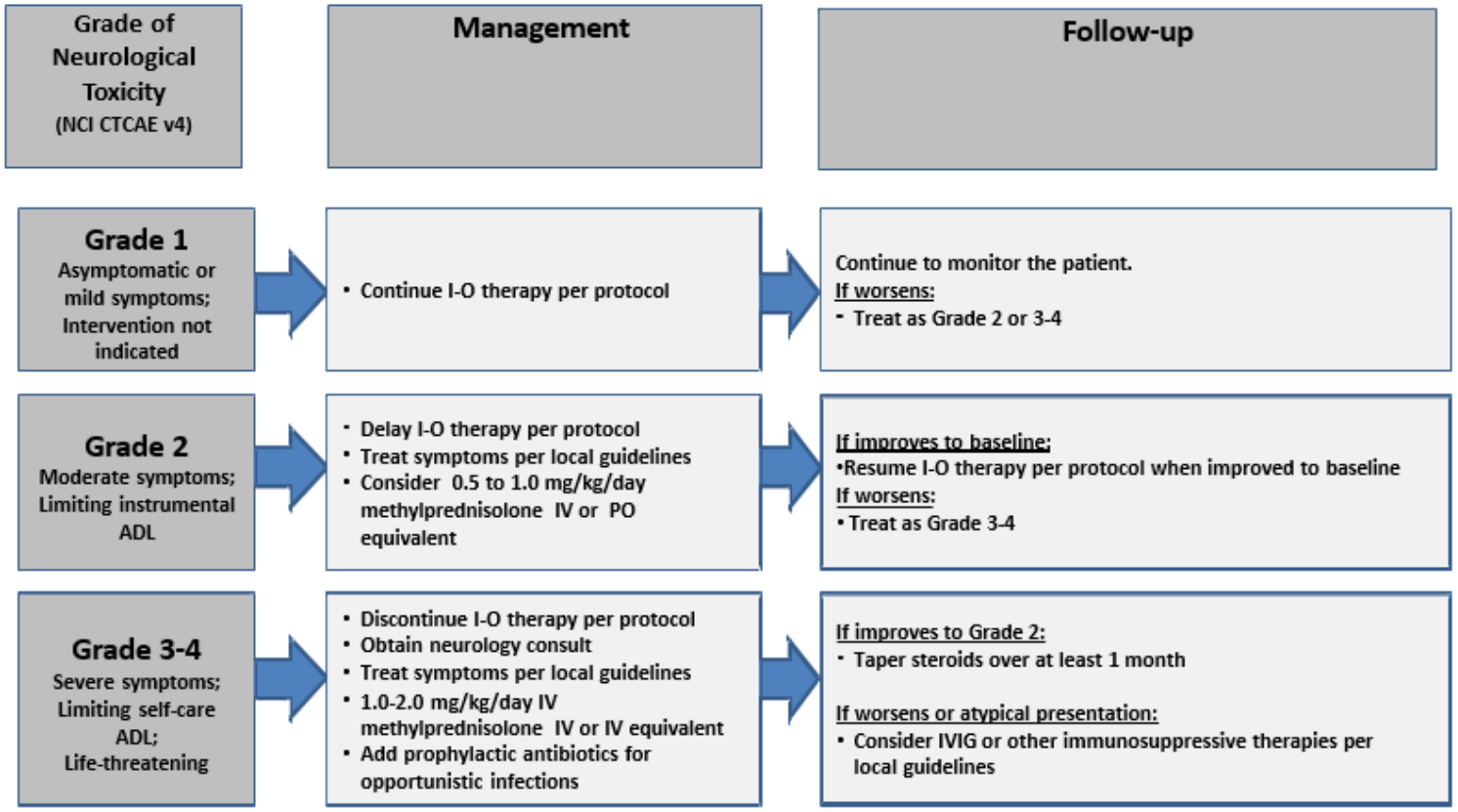
*Refer to NCI CTCAE v4 for term-specific grading criteria.

^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

27-Jun-2019

Neurological Adverse Event Management Algorithm

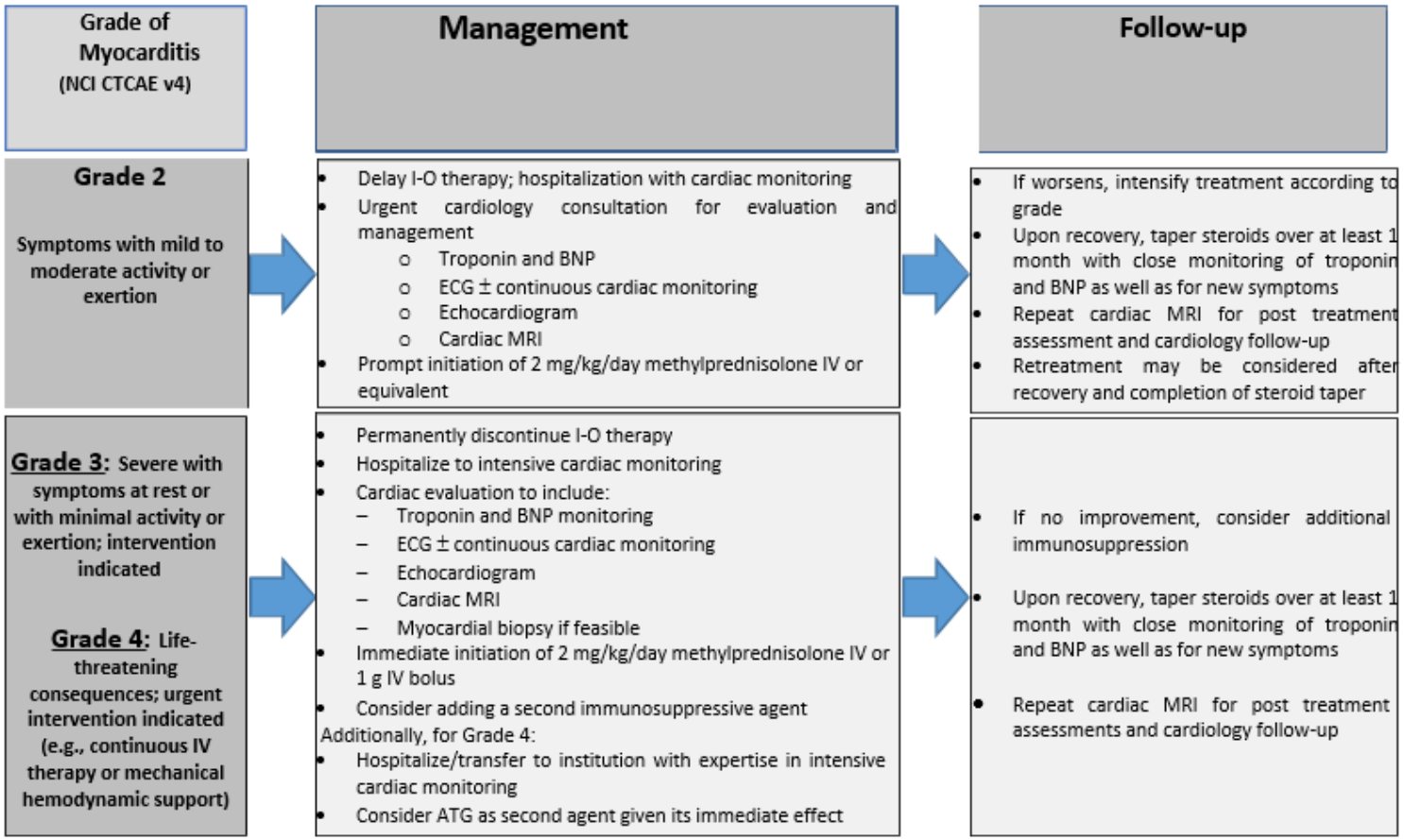
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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

27-Jun-2019

Myocarditis Adverse Event Management Algorithm



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

Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.

ATG = anti-thymocyte globulin; BNP = B-type natriuretic peptide; ECG = electrocardiogram; IV = intravenous; MRI = magnetic resonance imaging

27-Jun-2019

APPENDIX 5 MEDDRA ANAPHYLACTIC REACTIONS

Preferred Terms Included in the MedDRA Anaphylactic Reaction SMQ - Broad and Narrow Scopes

Preferred Term	Term Scope[a]
Acute respiratory failure	Broad Scope
Allergic oedema	Broad Scope
Anaphylactic reaction	Narrow Scope
Anaphylactic shock	Narrow Scope
Anaphylactic transfusion reaction	Narrow Scope
Anaphylactoid reaction	Narrow Scope
Anaphylactoid shock	Narrow Scope
Angioedema	Broad Scope
Asthma	Broad Scope
Blood pressure decreased	Broad Scope
Blood pressure diastolic decreased	Broad Scope
Blood pressure systolic decreased	Broad Scope
Bronchial oedema	Broad Scope
Bronchospasm	Broad Scope
Cardiac arrest	Broad Scope
Cardio-respiratory arrest	Broad Scope
Cardio-respiratory distress	Broad Scope
Cardiovascular insufficiency	Broad Scope
Chest discomfort	Broad Scope
Choking	Broad Scope
Choking sensation	Broad Scope
Circulatory collapse	Narrow Scope
Circumoral oedema	Broad Scope
Cough	Broad Scope
Cyanosis	Broad Scope
Diastolic hypotension	Broad Scope
Dyspnoea	Broad Scope
Erythema	Broad Scope
Eye oedema	Broad Scope
Eye pruritus	Broad Scope
Eye swelling	Broad Scope
Eyelid oedema	Broad Scope
Face oedema	Broad Scope
First use syndrome	Narrow Scope
Flushing	Broad Scope

Preferred Terms Included in the MedDRA Anaphylactic Reaction SMQ - Broad and Narrow Scopes

Preferred Term	Term Scope[a]
Generalised erythema	Broad Scope
Hyperventilation	Broad Scope
Hypotension	Broad Scope
Injection site urticaria	Broad Scope
Kounis syndrome	Narrow Scope
Laryngeal dyspnoea	Broad Scope
Laryngeal oedema	Broad Scope
Laryngospasm	Broad Scope
Laryngotracheal oedema	Broad Scope
Lip oedema	Broad Scope
Lip swelling	Broad Scope
Mouth swelling	Broad Scope
Nasal obstruction	Broad Scope
Ocular hyperaemia	Broad Scope
Oedema	Broad Scope
Oedema mouth	Broad Scope
Oropharyngeal spasm	Broad Scope
Oropharyngeal swelling	Broad Scope
Periorbital oedema	Broad Scope
Pruritus	Broad Scope
Pruritus allergic	Broad Scope
Pruritus generalised	Broad Scope
Rash	Broad Scope
Rash erythematous	Broad Scope
Rash generalised	Broad Scope
Rash pruritic	Broad Scope
Respiratory arrest	Broad Scope
Respiratory distress	Broad Scope
Respiratory failure	Broad Scope
Reversible airways obstruction	Broad Scope
Sensation of foreign body	Broad Scope
Shock	Narrow Scope
Skin swelling	Broad Scope
Sneezing	Broad Scope
Stridor	Broad Scope
Swelling	Broad Scope

Preferred Terms Included in the MedDRA Anaphylactic Reaction SMQ - Broad and Narrow Scopes

Preferred Term	Term Scope[a]
Swelling face	Broad Scope
Swollen tongue	Broad Scope
Tachypnoea	Broad Scope
Throat tightness	Broad Scope
Tongue oedema	Broad Scope
Tracheal obstruction	Broad Scope
Tracheal oedema	Broad Scope
Type I hypersensitivity	Narrow Scope
Upper airway obstruction	Broad Scope
Urticaria	Broad Scope
Urticaria papular	Broad Scope
Wheezing	Broad Scope

[a] All Narrow Scope PTs are also included in the Broad Scope.
MedDRA version 18.0

APPENDIX 6 STATISTICAL METHODOLOGY

STATISTICAL DETAILS FOR BAYESIAN LOGISTIC REGRESSION MODEL (BLRM AND BLRM-COPULA) AND PRIORS FOR DOSE ESCALATION

1 MODEL SETUP FOR BMS-986016 IN COMBINATION WITH NIVOLUMAB

1.1 Methodology Description for Combination Therapy

Toxicity profiles of BMS-986016 and nivolumab monotherapies will be incorporated to develop the BMS-986016 and nivolumab combination therapy model framework. A copula-type model will be utilized to cover all general combination cases, including subadditive, additive, and synergistic effects. The combination of the 2 treatments will be explored using a Bayesian hierarchical model by utilizing the toxicity profiles of each monotherapy as prior marginal profiles for the combination. The following copula-type model[1] will be used to describe the probability p_{ij} of toxicity when dose level i of treatment A and dose level j of treatment B are administered in combination:

$$p_{ij} = 1 - exp\left(-\left[\{-log\,(1-p_i{}^m)\}^{1/\gamma} + \{-log\,(1-q_j{}^n)\}^{1/\gamma}\right]^{\gamma}\right)$$

Where p_i is the pre-specified best guess toxicity probability for treatment A and q_j is the pre-specified best guess toxicity probability for treatment B. Here m and n characterize the individual drug effect and γ characterizes drug-drug interactive effect.

The joint toxicity framework models the toxicity rates of all 2 treatments as well as their interaction effects in a multi-parameter hierarchical model, where each of the monotherapy dose-toxicity relationships will be characterized by a 2-parameter BLRM model.[2,3]

For example, the dose-toxicity relationship for BMS-986016 alone is assumed to follow a logistic model:

$$logit(p_i) = log(\alpha_1) + \beta_1 log\left({}^{d_{1i}}/_{d_1^*}\right)$$

where p_i is the probability of toxicity at dose level d_{1i}. Note that the α_1 and β_1 parameters are assumed positive, and d_1^* is the reference dose for BMS-986016 (α_1 and β_1 are defined in Section 1.2.1).

There are 3 additional parameters for the copula-type model, 1 for each treatment (m and n) as well as 1 for the interaction term (γ). A dose-toxicity surface will be characterized for different dose combinations of these 2 treatments.

As there are currently no historical data or prior knowledge to indicate how much information to be borrowed for each of the single treatments, parameters m and n are all set to be 1, meaning borrowing 100% of the information from all 3 treatments. The above formula is then simplified into a 5-parameter model as follows:

$$p_{ij} = 1 - exp\left(-\left[\{-log\ (1-p_i)\}^{1/\gamma} + \{-log\ (1-q_j)\}^{1/\gamma}\right]^{\gamma}\right.$$

Posteriors for the corresponding 5 parameters (2 logistic regression parameters [α_1,β_1] for BMS-986016, 2 logistic regression parameters for nivolumab [α_2,β_2], and 1 interaction parameter for the copula-type model [γ, see details in Section 1.2]) will be fit into the in-house developed model, which implements the above described theoretical setup.

1.2 Priors Specification for BMS-986016 and Nivolumab Combination Therapy

1.2.1 Marginal Prior for BMS-986016

The Bayesian approach requires the specification of prior distributions for model parameters, which include parameters (α_1,β_1) for BMS-986016. At the beginning, a weakly informative prior will be used for parameters (α_1,β_1) for BMS-986016 to allow for considerable prior uncertainty.

Further details are provided below.

Weakly Informative Prior

- The median DLT rate at the reference dose (BMS-986016 at 1600 mg Q4W) was assumed to be 30%, that is, mean (log(α_1)) = -0.847.
- A doubling in dose was assumed to double the odds of DLT, that is, mean(log(β_1)) = 0.

The standard deviation of log(α_1) was set to 1.53 using the following steps:

- If the toxicity probability range was set to be [1%, 99%], then the toxicity interval would be logit (0.99)-logit (0.01) = 9.19.
- To cover 99.7% of the variance, the toxicity interval will cover 6*sd (log(α_1)).

Correspondingly, the standard deviation of log(β_1) was set to 2, which allows for considerable larger prior uncertainty for the dose toxicity.

1) The correlation between log(α_1) and log(β_1) was set to 0.
2) Log(α_1) and log(β_1) follow a bivariate normal distribution.

Table 1: Prior Distribution for Model Parameters for BMS-986016

Parameter	Means	Standard Deviations	Correlation
log(α_1), log(β_1)	(-0.847, 0)	(1.53, 2)	0

1.2.2 Marginal Prior for Nivolumab Parameters (log(α2), log(β2))

Similar to BMS-986016 monotherapy, the logistic model for nivolumab is as follows:

$$logit(q_j) = log(\alpha_2) + \beta_2 log\left(d_{2j}/d_2^*\right),$$

where q_j is the probability of toxicity at dose level d_{2j}. Note that the α_2 and β_2 parameters are assumed positive, and d_2^* is the reference dose for nivolumab.

The toxicity profile of nivolumab has been studied in several studies. A bivariate normal prior for the nivolumab model parameters (log(α_2), log(β_2)) was obtained by extracting a posterior of nivolumab using incidence of treatment-related Grade 3 to 4 AEs from a Phase 1 dose-escalation study and several Phase 3 nivolumab studies, which are used later as the MAP prior for nivolumab. These include a Phase 1 dose-escalation study of nivolumab (Study CA209003, N=306 in doses of 0.1, 0.3, 1, 3, and 10 mg/kg across multiple tumor types), a randomized Phase 3 study in advanced melanoma subjects progressing post anti-CTLA-4 therapy (Study CA209037, N=268 in a dose of 3 mg/kg), a Phase 3 study in previously treated subjects with squamous cell NSCLC (Study CA209017, N=131 in a dose of 3 mg/kg), a Phase 3 study in previously treated subjects with non-squamous cell NSCLC (Study CA209057, N=287 in a dose of 3 mg/kg), and a Phase 3 study in previously treated subjects with clear-cell RCC (Study CA209025, N=406 in a dose of 3 mg/kg). The results from the simulation of nivolumab flat dose exposures, the corresponding exposure-response analyses, and review of nivolumab safety support nivolumab flat dose and the overall distributions of nivolumab exposures are comparable after treatment with either 3 mg/kg Q2W or 240 mg Q2W nivolumab. In addition, dose proportionality of nivolumab exposures supports nivolumab 240 mg Q2W being comparable to 480 mg Q4W.

The MAP prior for the model parameters (log(α_2), log(β_2)) was obtained in the following steps.

- First, a prior distribution for nivolumab was developed:
  - The median toxicity rate at the nivolumab reference dose (3 mg/kg every 2 weeks) was assumed to be 10%, that is, mean (log(α_2)) = logit(0.10) = log(0.1/0.9) = -2.197.
  - A doubling in dose was assumed to double odds of toxicity, ie, mean(log(β_2)) = 0.
  - The standard deviation of log(α_2) was set to 2, and the standard deviation of log(β_2) was set to 1, which allows for considerable prior uncertainty for the dose-toxicity profile.
  - The correlation between log(α_2) and log(β_2) was assumed to be 0 (assuming independence of log(α_2) and log(β_2)).
  - In addition, heterogeneity between the historical studies and the current study was incorporated using a MAP by defining between-trial standard deviations τ_1 and τ_2 for log(α_2) and log(β_2), respectively. The between-trial variability is assumed to be moderate, therefore, τ_1 and τ_2 were set to follow a log-normal distribution, with mean log(0.25) and log(0.125), respectively, with a common standard deviation log(2)/1.96.

- With this prior, the clinical trial data below (Table 2) were used to generate the posterior for nivolumab, which is then used as the MAP prior for this study (Table 3).

Table 2: Data from Nivolumab Studies

Nivolumab Flat Dose (mg), Q4W	Dose of Nivolumab (mg/kg), Q2W	Toxicity[a]
	0.1	29% (5/17)
	0.3	17% (3/18)
160	1	14% (12/86)
480	3	13% (150/1146)
	10	16% (21/131)

[a] % of subjects with treatment-related Grade 3 or higher AEs

Abbreviation: Q2W = every 2 weeks.

Table 3: Marginal Prior Distribution for Model Parameters for Nivolumab (ie, Posterior from MAP Method)

Parameter	Means	Standard Deviations	Correlation
$\log(\alpha_2)$, $\log(\beta_2)$	(-1.856, -2.131)	(0.404, 0.546)	-0.009

1.2.3 Prior for Interaction Parameters for Joint Toxicity of BMS-986016 and Nivolumab Combination Therapy

A gamma prior distribution for the interaction parameter γ is derived to reflect the current uncertainty about the toxicity profile of the combination of BMS-986016 and nivolumab. Although no pharmacokinetic (PK) drug-drug interaction is expected, the possibility of a significant positive interaction between BMS-986016 and nivolumab cannot be totally excluded. The interaction parameter γ was chosen accordingly but with a degree of uncertainty to allow for the possibility that the interaction may be positive or negative. Therefore, the following assumptions are made for the interaction parameter:

- γ follows a gamma distribution with a mean centered at 1.2, which means the combination of 2 agents is likely to have only a small synergistic effect.
- The standard deviation of γ is 0.5 such that there is a 61% prior probability that γ is larger than 1.

This model assigns the highest probability to there being small synergistic interaction and also allows for the potential of larger synergism of the toxic profiles. It also does not completely ignore the possibility of antagonism because there is a 39% prior probability that γ is less than 1.

The final prior information to be used in the model will be continuously updated when additional toxicity information from different monotherapy or doublet combinations are available. Safety information for BMS-986016 from CA224020 study will be used to update the prior distribution before being used for dose escalation.

2 DECISION RULE FOR DOSE ESCALATION

2.1 Parameters for Dose escalation

BLRM-copula model will be utilized for dose recommendations after DLT information becomes available for each safety cohort. Final dose selection for expansion will be based on BLRM-copula dose recommendations with the totality of data available on all dosed subjects, after discussion and agreement between investigators and the BMS Medical Monitor.

The Bayesian Logistic Regression Method (BLRM)-copula with an overdose control principle (escalation with overdose control [EWOC])[4] was selected as an appropriate design for the dose escalation part B of this study. BLRM -Copula is similar to the rule-based method (ie, 3 + 3 design) in that the cohort size is approximately 3 subjects for each subject cohort and the toxicity boundaries are set at a minimum 16% (~ 1 in 6) dose-limiting toxicity (DLT) rate and a maximum 33% (~ 1 in 3) DLT rate. These boundaries were chosen in order to target a dose that has meaningful activity but not unacceptably high toxicity. A minimum 16% DLT rate ensures that the model does not guide to use of too low a dose and sacrifice opportunity for benefit without meaningful improvement in safety. The 33% maximum is chosen as this would be the maximum DLT rate where a positive benefit/risk ratio is likely to be demonstrated.

Compared with the rule-based method, BLRM-copula offers more accuracy and efficiency in determining the safety by incorporating historical data and all previous on-study safety/DLT data. The model also quantifies the benefit and risk during the dose level decision making process. When DLT data are incorporated into the model, the distribution of predicted DLT rates (based on posterior estimation) for a specific dose level will be updated accordingly. The predicted DLT rates will be categorized according to the following 3 categories:

- “Under-dosing” defined as a predicted DLT rate between 0% and up to 16%.
- “Target dosing” defined as a predicted DLT rate between over 16% and up to 33%.
- “Overdosing” defined as a predicted DLT rate between over 33% and 100%.

Following the principle of EWOC, after DLT information is obtained from each cohort, a dose cohort will be declared safe if the the dose level has less than 35% chance of excessive toxicity for combination therapies. For dose expansion, the final recommended maximum tolerated dose (MTD)/recommended Phase 2 dose (RP2D) of BMS-986016 in combination with nivolumab will be based on the recommendation from the BLRM (-copula) model and a synthesis of all the data available on all dosed subjects, including clinical and laboratory safety assessments, PK and pharmacodynamic data, and efficacy data from all treated subjects. BLRM-copula model with

prior information will also be used to help with dose de-escalation on finding intermediate doses if needed.

During dose escalation for BMS-986016 in combination with nivolumab, initially a cohort of approximately 3 subjects will be treated at the selected dose level. The DLT data collected will be used in the BLRM-copula method to obtain the posterior joint toxicity probability profile for that combination dose. BLRM-copula dose recommendation will be used to evaluate the safety of the selected dose. If the current dose is deemed safe, approximately 3 subjects will be treated at the next higher dose level based on the model recommendation. If the current dose is not deemed safe, a lower dose cohort may be explored. A minimum of 6 DLT-evaluable subjects will be treated at a specific dose before using that dose for expansion. Up to 15 subjects may be treated per dose level for the dose escalation.

3 REFERENCES

[1] Yin G, Yuan Y. Bayesian dose escalation in oncology for drug combinations by copula regression. J R Stat Soc Ser C Appl Stat 2009;58(2):211-24.

[2] Neuenschwander B, Branson M, Gsponer T. Critical aspects of the Bayesian approach to Phase I cancer trials. Stat Meed 2008;27:2420-39.

[3] Neuenschwander B, Capkun-Niggli G, Branson M, et al. Summarizing historical information on controls in clinical trials. Clin Trials 2010;7:5-18.

[4] Babb J, Rogatko A, Zacks S. Cancer Phase I clinical trials: efficient dose escalation with overdose control. Stat Med 1998;17:1103-20.

APPENDIX 7 REVISED PROTOCOL SUMMARY OF CHANGE HISTORY

Overall Rationale for Protocol Amendment 14, 28-Oct-2022

The CA224020 study started with the first patient enrolled on 01-Nov-2013 and is closed to enrollment as of 30-Jul-2021 with the last patient enrolled on 30-Jul-2021.

The purpose of this protocol amendment is to clarify the study duration for patients remaining on treatment beyond 5 years, remove the rechallenge period among patients currently on the study, align the protocol with the current coronavirus disease 2019 (COVID-19) guidance, and update the contraceptive guidance.

Currently, study duration is defined as approximately 5 years from the first dose of study drug including 5 years of follow-up for survival and will remain as such except for those patients who remain on treatment beyond 5 years and are still deriving clinical benefit. Patients who discontinue treatment before 5 years will complete a 135-day clinical follow-up period and a survival follow-up period for up to 5 years after the first dose. Patients who continue study treatment for longer than 5 years will complete a 135-day clinical follow-up period once the criteria for treatment discontinuation are met, but will not participate in a survival follow-up period. The study will end when all patients have completed their respective follow-up periods.

[redacted] Current literature is not sufficient to give clear recommendations on the clinical utility of immunotherapy rechallenge. Furthermore, data concerning rechallenge utilizing combination treatments from randomized cohorts with similar clinical characteristics is limited or missing. Given the lack of rechallenge data from randomized clinical trials, no standardized approach exists; however, the current practice is to switch therapies upon progression. Given this limited data and [redacted], the decision was made to suspend future participation in the rechallenge period. All subjects who discontinue primary study treatment following implementation of this amendment will not be eligible for rechallenge. Subjects currently receiving rechallenge treatment will be allowed to continue, and subjects currently in the rechallenge-eligible Survival Follow-up as of this Protocol Amendment remain eligible for rechallenge.

Summary of Key Changes for Protocol Amendment 14		
Section Number & Title	**Description of Change**	**Brief Rationale**
Synopsis	Incorporates changes below as applicable.	Updated to reflect study changes.
Section 1.5: Overall Benefit-risk Assessment	Added language on benefit-risk of COVID-19 vaccine use in this trial.	Added to align with language from COVID-19 guidance

Summary of Key Changes for Protocol Amendment 14		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 3.1: Study Design and Duration	• As of Protocol Amendment 14, rechallenge is not permitted. Clarified that rechallenge-eligible Survival Follow-up may continue for up to 5 years from the first dose. • Added clarification that study duration may be extended for those subjects who are remaining on treatment beyond 5 years and still deriving clinical benefit.	• Given the limited data on rechallenge [redacted], no new treatment rechallenges among patients currently on study will be allowed. For patients currently in rechallenge-eligible Survival Follow-up, clarified the duration of the follow-up period to be consistent with the survival follow-up period for all other parts of the study. • Provided clarification that study treatment may be continued beyond 5 years as several patients have approached the 5-year treatment mark and are still deriving clinical benefit on this study.
Figure 3.1-4: Detailed Study Schematic	As of Protocol Amendment 14, rechallenge is not permitted.	• Given the limited data on rechallenge [redacted] no new treatment rechallenges among patients currently on study will be allowed. • For patients currently in rechallenge-eligible Survival Follow-up, clarified the duration of the follow-up period to be consistent with the survival follow-up period for all other parts of the study.
Section 3.1.2.4: Rechallenge in Dose Escalation (Parts A and B) and Cohort Expansion Parts (A1, C, D and E)	As of Protocol Amendment 14, rechallenge is not permitted. Clarified that Survival Follow-up may continue for up to 5 years from the first dose for rechallenge-eligible patients.	
Section 3.3.1: Inclusion Criteria	Updated women of childbearing potential contraceptive duration and modified contraceptive requirements for male participants.	Changes were made to reflect the latest nivolumab and relatlimab contraceptive guidance.
Section 3.4.3: Permitted Therapy	Added language on COVID-19 vaccination.	Added to align with language from COVID-19 guidance.

Summary of Key Changes for Protocol Amendment 14		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 5.1-1: Screening Procedural Outline	As of Protocol Amendment 14, rechallenge is not permitted.	Given the limited data on rechallenge [redacted] no new treatment rechallenges among patients currently on study will be allowed.
Table 5.1-2: On-treatment Procedural Outline for Q2W and Q4W BMS-986016/Nivolumab Treatment Regimens Parts A through E	• As of Protocol Amendment 14, rechallenge is not permitted. • Removed male contraceptive language. • Added a footnote on treatment beyond 5 years.	• Given the limited data on rechallenge [redacted] no new treatment rechallenges among patients currently on study will be allowed. • Aligned with latest relatlimab/nivolumab contraceptive guidance. • Clarified that patients may continue to be treated past the 5-year mark if they are still deriving clinical benefit.
Table 5.1-3: Follow-up Procedural Outline Parts A Through E	• Removed male contraceptive language. • Removed diagnostic imaging duplicate row and added survival follow-up imaging to existing row. • Added a footnote on treatment beyond 5 years.	• Aligned with latest relatlimab/nivolumab contraceptive guidance. • Removed repetitive language. • Clarified that patients may continue to be treated past the 5-year mark if they are still deriving clinical benefit.

Summary of Key Changes for Protocol Amendment 14		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 5.3.1-1: Biomarkers by Tumor Type: All Cohorts Except for Subjects Crossing Over or Rechallenged Table 5.5.1-2: PK and ADA Sampling Schedule for BMS-986016 and Nivolumab for Dose Expansion Part C Q2W Dosing (After First 6 Subjects) and for Cohort with Crossover or Rechallenge Table 5.5.1-4: PK and ADA Sampling Schedule for BMS-986016 and Nivolumab for Dose Expansion Part C Bladder Cohort (After Approximately First 6 Subjects), Part D1 Arm 1, Part D1 (Arm 2 and Arm 3, After First 12 Subjects), Part D2, Part E and Rechallenge Table 5.7-2: Parts A1 and C (Cohort Expansion) and Cohorts for Crossover or Rechallenge: Biomarker Sampling Table 5.7-3: Biomarker Sampling for Part D Melanoma Prior IO Extended Expansion and Rechallenge Table 5.7-4: Biomarker Sampling for Part E Exposure/Response Expansion Q4W Dosing and Rechallenge Section 5.4.2: Efficacy Assessment for the Study	• As of Protocol Amendment 14, rechallenge is not permitted.	• Given the limited data on rechallenge [redacted] no new treatment rechallenges among patients currently on study will be allowed.

Summary of Key Changes for Protocol Amendment 14		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 5.5.1-1: PK and ADA Sampling Schedule for BMS-986016 and Nivolumab for Dose Escalation Parts A and B Q2W Dosing and Expansion Parts A1 and C (Approximately the First 6 Subjects in Each Cohort Only) Table 5.5.1-2: PK and ADA Sampling Schedule for BMS-986016 and Nivolumab for Dose Expansion Part C Q2W Dosing (After First 6 Subjects) and for Cohort with Crossover or Rechallenge Table 5.5.1-3: PK and ADA Sampling Schedule for BMS-986016 and Nivolumab for Dose Escalation Parts B and C (Bladder Cohort Approximately First 6 Subjects) with Q4W Regimen Table 5.5.1-4: PK and ADA Sampling Schedule for BMS-986016 and Nivolumab for Dose Expansion Part C Bladder Cohort (After Approximately First 6 Subjects), Part D1 Arm 1, Part D1 (Arm 2 and Arm 3, After First 12 Subjects), Part D2, Part E and Rechallenge Table 5.5.1-5: PK and ADA Sampling Schedule for BMS-986016 and Nivolumab for Part D1 (Arm 2 and 3, First 12 Subjects) Table 5.7-3: Biomarker Sampling for Part D Melanoma Prior IO Extended Expansion and Rechallenge Table 5.7-4: Biomarker Sampling for Part E Exposure/Response Expansion Q4W Dosing and Rechallenge Section 8.3.2.3: Immunogenicity	• Updated PK and ADA sampling schedule. • Updated biomarker sampling schedule.	• Nivolumab+relatlimab has shown low immunogenic potential over 24 months of treatment period and is considered to be not clinically relevant. Hence, additional PK and immunogenicity beyond 24 months or after the treatment discontinuation is not required. • Nivolumab and relatlimab exposure after the first dose is established as a meaningful exposure metric in characterizing the exposure-response for the safety events of ≥ Grade 3 TRAEs and ≥ Grade 2 IMAEs. Nivolumab+relatlimab has shown a low immunogenicity rate, and presence of ADA was not associated with safety. Hence, PK and immunogenicity collection upon the occurrence of ≥ Grade 3 AEs is not required.
Section 8.3.2.3: Immunogenicity	Updated text on timing of ADA assessment.	Changes were made to maintain consistency with other immunogenicity text in the protocol.

Summary of Key Changes for Protocol Amendment 14		
Section Number & Title	**Description of Change**	**Brief Rationale**
Appendix 1: Women of Childbearing Potential Definitions and Methods of Contraception	Updated women of childbearing potential contraceptive duration and removed contraceptive requirements for male participants. Added text on "End of Relevant Systemic Exposure."	Changes were made to reflect the latest nivolumab and relatlimab contraceptive guidance.
Appendix 8: Country Specific requirements/difference	Added France and Italy to list of countries.	Clarified country/site specific requirements/differences.

Overall Rationale for the Revised Protocol 13, 29-Jul-2021

[redacted].

Revisions are applicable to future participants in the study, and where applicable, to all participants currently enrolled.

Summary of key changes for Protocol Amendment 13		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	Updated clinical scientist and medical monitor contact information.	Changes have been made to reflect the correct study team information.
Synopsis	Incorporates changes below as applicable.	Updated to reflect study changes.
[redacted]		
Section 1.4.1.2: Toxicity	Updated text to refer to current Investigator's Brochure (IB) of relatlimab.	Provided flexibility for any updates to the relatlimab IB in the future.
[redacted]		

Summary of key changes for Protocol Amendment 13		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		

Summary of key changes for Protocol Amendment 13		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 7.1 Data Monitoring Committee	Updated the frequency which the data monitoring committee (DMC) meets to reflect frequency as outlined in the DMC charter.	To align with DMC charter.

Overall Rationale for the Revised Protocol 12, 05-Feb-2020

This revision reflects changes made at the request of the [redacted]. As a result, duration of response was added as a secondary objective for Part E and PK and Biomarker tables were updated to add sample collection upon occurrence of ≥ Grade 3 adverse events.

Summary of key changes for Revised Protocol 12		
Section Number & Title	**Description of Change**	**Brief Rationale**

Summary of key changes for Revised Protocol 12		
Section Number & Title	**Description of Change**	**Brief Rationale**
Global	Typographical and grammatical errors were corrected, and edits were made for consistency and clarity.	Editorial
1.3.2, Secondary Objectives	Added the following secondary objective: To evaluate the clinical benefit of the 480 mg BMS-986016 + 480 mg nivolumab Q4W dosing regimen using DOR in melanoma participants who have not received prior systemic anticancer therapy for unresectable or metastatic melanoma and for melanoma participants who experienced disease progression on prior anti-PD-1 therapy.	[redacted]
3.1, Study Design and Duration	Added the following sentence: Survival follow-up visits will be scheduled based on the last clinical follow up visit.	Clarify when visits will be scheduled
3.1, Study Design and Duration Figure 3.1-4: Detailed Study Schematic	For subjects who discontinue at the investigator's discretion with CR, PR, or SD, imaging must be performed every 12 weeks until disease progression	Clarified that imaging is until disease progression.
3.3.2, Exclusion Criteria	Added the following to criterion h) under 2) Medical History and Concurrent Diseases: NOTE: Testing for HIV must be performed at sites where mandated locally. Added criterion b) under 3) Allergies and Adverse Drug Reactions: History of allergy or hypersensitivity to study drug components	To bring in line with current program standards.
5.1, Flow Chart/Time and Events Schedule	Added the following paragraphs: Additional measures, including nonstudy required laboratory tests, should be performed as clinically indicated or to comply with local regulations. Laboratory toxicities (eg, suspected drug induced liver enzyme evaluations) will be monitored during the follow-up phase via on-site/local labs until all study drug-related toxicities resolve, return to baseline, or are deemed irreversible. If a participant shows pulmonary-related signs (hypoxia, fever) or symptoms (eg. dyspnea, cough, fever) consistent with possible pulmonary adverse events, the participant should be immediately evaluated to rule out pulmonary toxicity, according to the suspected pulmonary toxicity management algorithm in the BMS-936558 (nivolumab) Investigator Brochure. Some of the assessments referred to in this section may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.	To bring in line with current program standards.

Summary of key changes for Revised Protocol 12		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 5.1-2: On-Treatment Procedural Outline for Q2W and Q4W BMS-986016/Nivolumab Treatment Regimens Parts A through E	In the notes for Efficacy Assessments, Diagnostic imaging, the timing of imaging was defined as every 8 weeks until disease progression or discontinuation of study treatment.	Clarified timing of imaging.
Table 5.1-3: Follow-Up Procedural Outline Parts A through E	In the notes for Efficacy Assessments, Diagnostic imaging and Survival Status, Diagnostic imaging, the timing of imaging was defined as every 12 weeks until disease progression.	Clarified that imaging is until disease progression.
5.3.1, Laboratory Test Assessments	Added the following sentence to first paragraph: Investigators must document their review of each laboratory safety report.	To bring in line with current template language.
5.4.1, Imaging Assessment for the Study	Added the following sentence to the second paragraph: Sites should be trained prior to scanning the first study participant. Added paragraph to end of section: Any additional imaging that may demonstrate tumor response or progression (including scans performed at unscheduled time points and/or at an outside institution) should be collected for RECIST v1.1 tumor assessment and submitted to the BICR.	To bring in line with current template language and program standards.
5.5.1, Pharmacokinetics: Collection and Processing	Added the following sentence: Effective with Revised Protocol 12, PK samples should be taken coincident with the occurrence of a study drug-related ≥ Grade 3 AE.	[redacted]
Table 5.5.1-1, Table 5.5.1-2, Table 5.5.1-3, Table 5.7-1, Table 5.7-2, Table 5.7-3, and Table 5.7-4	In the PK and Biomarker Sampling Schedule tables under the heading Upon drug-related AE the category was changed from: Upon occurrence of ≥ 2 drug-related pneumonitis or neurological AE to: Upon occurrence of ≥ Grade 3 drug-related AE	[redacted]
Table 5.5.1-1 to Table 5.5.1-5	In the PK Sampling Schedule Tables, redefined stopping point of alternate treatment cycles from Cycle 11 to End of Treatment	Clarify timing of sample collection.
Table 5.5.1-4 and Table 5.5.1-5	In the PK Sampling Schedule tables the following header and category was added to table: Header: Upon drug-related AE Category: Upon occurrence of ≥ Grade 3 drug-related AE	[redacted]

Summary of key changes for Revised Protocol 12		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 5.7-3 and Table 5.7-4	In the Biomarker Sampling Schedule tables for Part D and Part E, timing of samples for Cycle 2 to end of treatment was clarified and header was changed to: Cycle 2 and Alternate Treatment Cycles (Starting from Cycle 3 to End of Treatment)	Clarify timing of sample collection.
[redacted]		

Overall Rationale for the Revised Protocol 11, 11-Oct-2019

Changes reflect the update from the February 2019 evaluation of the BMS-986016 480 mg + nivolumab 480 mg Q4W dosing regimen. Inclusion criteria for adjuvant/neoadjuvant subjects were updated to exclude anti-PD-1 or anti-PD-L1 therapy with the exception of the Expanded Eligibility Cohort under certain conditions.

Summary of key changes for Revised Protocol 11		
Section Number & Title	**Description of Change**	**Brief Rationale**
Global	Typographical and grammatical errors were corrected, and edits were made for consistency and clarity.	Minor; therefore have not be summarized
1.1.7, Rationale for Part E (Melanoma Expansion) 1.1.9.7, Part E: Co-administration of BMS-986016 and Nivolumab 1.4.1.4.2, Clinical Safety 3.1, Study Design and Duration 3.1.2.6, Part E Exposure Response Evaluation (Co-administration)	Updated information about the safety of BMS-986016 480/960/1440 mg + nivolumab 480 mg Q4W dosing regimen	Regimen was being evaluated in Part B (Dose Escalation with DLT criteria) of this study in Feb 2019. That evaluation is complete and text was updated accordingly.
1.1.9.8, Dose Rationale for Adolescents 3.1, Study Design and Duration	Removed reference to 3 mg/kg BMS-986016 and 6 mg/kg of nivolumab Q4W	The weight based dose of 6 mg/kg BMS-986016 and 6 mg/kg of nivolumab Q4W will correspond to fixed dose of 480/480 Q4W.
1.4.1.4.3, Clinical Efficacy-Monotherapy (Part A) versus Combination Therapy (Part B): CA224020 Study	Updated number of subjects treated with BMS-986016 and nivolumab in Part B and Part C	Reflects subjects treated as of most recent cutoff.

Summary of key changes for Revised Protocol 11		
Section Number & Title	**Description of Change**	**Brief Rationale**
3.1, Study Design and Duration Figure 3.1-1 CA224020 Study Schematic, Footnotes Figure 3.1-4, Detailed Study Schematic, Footnotes 4.1.3, Handling and Dispensing	Added timing of infusion for 960 mg (and higher) doses of relatlimab following 480 mg nivolumab	Updated to reflect the changes based on the completion of the dose regimen evaluation in part B.
Figure 3.1-3 Part E	Removed statement from figure indicating that LAG3 status is determined prior to randomization.	To add clarification
3.1, Study Design and Duration Figure 3.1-4, Detailed Study Schematic 3.1.2.4, Re-challenge in Dose Escalation (Parts A and B) and Cohort Expansion Parts (A1, C, D, and E) Table 5.1-2 On-Treatment Procedural Outline for Q2W and Q4W BMS-986016/Nivolumab Treatment Regimens Parts A through E 5.4.2, Efficacy Assessment for the Study	Removed from Treatment period references to up to twelve 8-week treatment cycles.	Removed the treatment limit.
3.1, Study Design and Duration Figure 3.1-4, Detailed Study Schematic Table 5.1-3 Follow-Up Procedural Outline Parts A through E	Changed Survival Follow-up period to say length is up to 5 years following the first dose of study drug.	To add clarification
3.1, Study Design and Duration Figure 3.1-4, Detailed Study Schematic 3.5 Discontinuation of Subjects from Treatment	Removed confirmed complete response and completion of the maximum number of twelve 8 week cycles from discontinuation criteria	Patients will not be treated until disease progression, clinical deterioration, or meeting other discontinuation criteria. Removed the treatment limit.
3.1, Study Design and Duration Figure 3.1-4, Detailed Study Schematic, footnote Table 5.1-3 Follow-Up Procedural Outline Parts A through E 5.4.2, Efficacy Assessment for the Study	Changed timing of diagnostic imaging to every 8 weeks until disease progression and every 12 weeks for subjects who discontinue due CR, PR, or SD at investigators discretion.	To add clarification

Summary of key changes for Revised Protocol 11		
Section Number & Title	**Description of Change**	**Brief Rationale**
3.1, Study Design and Duration Figure 3.1-4, Detailed Study Schematic 3.1.2.4, Re-challenge in Dose Escalation (Parts A and B) and Cohort Expansion Parts (A1, C, D, and E)	Removed from re-challenge period that subjects could receive therapy for up to 6 additional eight-week cycles	Removed the treatment limit.
3.3.1, Inclusion Criteria; 1) Signed Written Informed Consent, b) Consent for tumor biopsy samples, i) and ii) Table 5.1-1 Screening Procedural Outline (CA224020) Table 5.7-1 to Table 5.7-4, footnote Table 5.7-5 Tumor Tissue Requirements	Updated sample language, so that participants must have tumor tissue submitted, [redacted] On-treatment biopsies for all sites, with the exception of US IION sites are optional. Updated Screening Procedural Outline (CA224020) table, Biomarker Sampling tables, and Tumor Tissue Requirements table to reflect these changes.	To add clarification
3.3.1, Inclusion Criteria; 2) Target Population, v) Part D1 Melanoma Prior IO Extended Expansion: Focused Eligibility Cohort	Changed criteria for Adjuvant/Neoadjuvant therapy: Adjuvant (or neo-adjuvant) anti-PD-1 or anti-PD-L1 therapy is not allowed. Other adjuvant (or neoadjuvant) melanoma therapies, including anti-CTLA-4, are allowed.	Change made to make consistent with current program standards
3.3.1, Inclusion Criteria; 2) Target Population, vi) Part D2 Melanoma Prior IO Extended Expansion: Expanded Eligibility Cohort	Changed criteria for Adjuvant/Neoadjuvant therapy: Patients with prior adjuvant or neo-adjuvant anti-PD-1 therapy are allowed as long as one of the two conditions are met, 1) progression occurred during or within 6 months of the last dose of adjuvant anti-PD-1 therapy, or 2) there has been subsequent progression on additional anti-PD-1 therapy in the metastatic setting	Change made to make consistent with current program standards
3.3.1, Inclusion Criteria; 2) Target Population, vii) Part E: Exposure Response Evaluation in Melanoma Participants, (1) Melanoma participants who experienced disease progression on prior anti PD 1 therapy	Changed criteria for Adjuvant/Neoadjuvant therapy: Adjuvant (or neo-adjuvant) anti-PD-1 or anti-PD-L1 therapy is not allowed. Other adjuvant (or neoadjuvant) melanoma therapies, including anti-CTLA 4, are allowed.	Change made to make consistent with current program standards

Summary of key changes for Revised Protocol 11		
Section Number & Title	**Description of Change**	**Brief Rationale**
3.3.1, Inclusion Criteria; 2) Target Population, vii) Part E: Exposure Response Evaluation in Melanoma Participants, (2) Melanoma participants who have not received prior systemic anticancer therapy for unresectable or metastatic melanoma	Added the following criterion: Uveal melanoma subjects are NOT eligible	To bring in line with other melanoma treatment groups in the study.
3.4.1, Prohibited and/or Restricted Treatments	Updated second bulled about concurrent administration of anticancer therapies so that the bullet now reads: Concurrent administration of any anticancer therapies (investigational or approved) in the Treatment Period, with the exception of subjects in Clinical Follow-up period as well as the Survival period of the study	To add clarification
Table 5.1-1 Screening Procedural Outline (CA224020)	Removed Archived tumor tissue sample row	Made redundant based on changes to reflect new guidance on submission of pre-treatment tumor tissue.
5.4.1, Imaging Assessment for the Study	The following paragraph was added: Tumor assessments at other time points may be performed, if clinically indicated, and should be submitted to the central imaging vendor as soon as possible. Unscheduled CT/MRI should be submitted to central imaging vendor. X-rays and bone scans that clearly demonstrate interval progression of disease, for example most commonly as unequivocal lesions that are unmistakably new since the prior CT/MRI, should be submitted to central imaging vendor. Otherwise, they do not need to be submitted centrally.	Outlines procedures for tumor assessments done outside of scheduled assessments, if clinically indicated.

Overall Rationale for the Revised Protocol 10, 15-Feb-2019

The purpose of revised protocol 10 is to 1) add four additional Part B combination dosing cohorts: 480 mg, 960 mg , 1440 mg, and 1600 mg BMS-986016 (relatlimab) + 480 mg nivolumab, every four weeks (Q4W), 2) change the dose escalation statistical methodology from 3+3+3 to an adaptive Bayesian Logistic Regression Model (BLRM) Copula design for Part B, which will more precisely predict the safety profile, 3) change the dose-limiting toxicity period from 8 weeks to 6 weeks 4) add Part E exposure-response evaluation cohorts (melanoma participants who experienced disease progression on prior anti-PD-1 therapy and melanoma participants who have not received prior systemic anticancer therapy for unresectable or

metastatic melanoma), and. Additionally, details of clinical safety and pharmacokinetic sections were reduced as the information is available in the Investigator Brochure(s) and Opdivo ® (nivolumab) package insert.

Sections in the synopsis have been updated to align with the protocol section changes listed below.

Summary of key changes for Revised Protocol 10		
Section Number & Title	**Description of Change**	**Brief Rationale**
1) PART B CHANGES:		
Section 3.1, Figure 3.1-1, 3.1-4, Table 3.1.1.2-1	Added 480 mg, 960 mg, 1440 mg and 1600 mg doses of BMS-986016 plus 480 mg nivolumab, Q4W to the Part B dosing cohorts.	To complete the stated primary objective of the dose escalation portion of the protocol.
Section 1.1.9.3 Part B BMS-986016 Dose Escalation (Applies to only a sub-set of sites 1-6) To provide clarity on participation in Part B of the study.	Clarified that Part B (Dose Escalation) is limited to a sub-set of sites. Updated the section title and provided updated safety information for BMS-986016 from Phase 1/2 studies.	To provide clarity on participation in Part B of the study. To provide the most up-to-date safety information for BMS-986016 and include the risk/benefit assessment for Part E.
2) STATISTICAL METHODOLOGY CHANGES:		
Section 3.1 Investigational Plan, Figure 3.1-1; Table 3.1.1.2-1 “Dose Escalation Schedule for Part B BMS-986016 in Combination with Nivolumab every 4 week dosing”; Section 8.1.1 Dose Escalation (Parts A and B)	Include the BLRM (Bayesian Logistic Regression Model)-Copula design (for part B only), Figure 3.1-1 study schematic was updated to include additional doses for Part B, Table 3.1.1.2-1 was updated to include additional doses for Part B Described the BLRM design for Part B.	Statistical methodology was changed from 3+3+3 to an adaptive BLRM to more precisely predict the safety profile.
3) PART E CHANGES		
Section 1.1.7 Rationale for Part E (Melanoma Exposure-Response Evaluation), Section 1.1.9.7 Part E: Co-administration of BMS-986016 and Nivolumab; Section 1.2 Research Hypothesis; Section 1.3 Primary Objectives; Section 3.1.2.6 Part E Exposure-Response Evaluation (Co-	Added the rationale for adding new Part E (Melanoma Exposure Response Evaluation) into the protocol. Added Part E to the research hypothesis and primary objectives. Added Part E to the cohort expansion section	Part E was added to the study to more fully elucidate the exposure-response curve in melanoma participants.

Summary of key changes for Revised Protocol 10		
Section Number & Title	**Description of Change**	**Brief Rationale**
administration) Figure 3.1-3, Figure 3.1-4 Section 3.3.1 Inclusion Criteria 2) Target Population (6); vii) Part E: Exposure Response Evaluation in Melanoma Participants Table 5.1-1 Screening Procedural Outline; Table 5.1-2 On-Treatment procedural Outline Section 4.2 Method of Assigning Subject Identification Table 5.5.1-4 Pharmacokinetic Sampling Schedule Table 5.7-4 Part E Biomarker Sampling Schedule; 8.1.5 Sample size Exposure/Response Expansion Q4W Dosing (Part E)	Figure 3.1-3 Part E was added and Figure 3.1-4 was updated to include Part E Added inclusion criteria for Part E participants Added tumor tissue requirements for Part E participants, and Part E participants need to be screened for BRAF mutation, added part E dosing Added assignment criteria for Part E participants Added time points for Part E New Table 5.7-4 was added for Part E biomarker testing schedule Added the rationale for Part E sample size Added rationale for sample size for new Part E	
4) DLT CHANGES:		
Section 3.1.3 Dose-Limiting Toxicities; 3.1.3.1 Rationale for 6-week DLT period in Part B	Dose-Limiting Toxicities (DLT) period was changed from 56 days (8 weeks) to 42 days (6 weeks); new rationale section added for the reduced DLT period in Part B.	Dose Limiting Toxicity (DLT) observation period reduced from 8 weeks to 6 weeks as (1) we now have acquired safety data, with relatlimab in combination with nivolumab, from over 800 patients since the initiation of the program and (2) need to reduce the incidence of patients developing progressive disease, and becoming unevaluable, during the DLT period.
ADDITIONAL MISC CHANGES:		
Section 1.4.1.2 Toxicity	Added results of BMS-986016 3-month IV toxicity study in cynomolgus monkeys Updated IB version number	To align this section of the protocol with the most recent version of the IB

Summary of key changes for Revised Protocol 10		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 1.4.1.4.1 Clinical Pharmacology	Updated to include the results of the relatlimab Population PK model, [redacted], and relatlimab immunogenicity results.	To reflect the most up-to-date clinical pharmacology data for BMS-986016
Section 1.4.1.4.2 Clinical Safety	Updated using clinical cut-off date of 18-Jun-2018	To reflect the most up-to-date safety information for BMS-986016
Section 1.5 Overall Risk/Benefit Assessment	Updated using clinical cut-off date of 18-Jun-2018	To reflect the most up-to-date safety information for BMS-986016
Section 2.1 Good Clinical Practice	Section was updated to align with current BMS language describing Good Clinical Practice	To align with the latest BMS standards.
Section 3.3 Study Population	Language added allowing retesting of laboratory parameters and/or other assessments within any single Screening or Lead-in period	To clarify that retest is allowed during screening
Section 3.3.1 Inclusion Criteria 2) Target Population (6); 3) Age and Reproductive Status; Appendix 4	Added :"Weight ≥ 40 kg" as an inclusion criterion for all participants; Added inclusion criteria for Part E; allow certain adjuvant and neo-adjuvant therapies Updated criteria 3) e) related to male contraceptive requirements for all males (even azoospermic males).	Weight requirement was added to ensure that all dosing was in accord with ICH guidance on impurities for pharmaceutical products. Guidance added for azoospermic males regarding exposure of partners to seminal fluid from study participant and contraception methods were updated to align with latest BMS policy.
Section 3.3.1 Exclusion Criteria 2) Medical History and Concurrent Diseases; Exclusion 2) o)	Troponin criteria was clarified and simplified as follows: Troponin T (TnT) or I (TnI) > 2 × institutional ULN. Between > 1 to 2 x ULN will be permitted if a repeat assessment remains ≤ 2 x ULN and subject undergoes a cardiac evaluation	To clarify the criteria for exclusion regarding Troponin T (TnT) or I (TnI) test result.
Section 3.4.2	Language added prohibiting live or attenuated vaccines during treatment and until 100 days post last dose	To align with the latest BMS standards for subjects who may be treated with nivolumab
Section 3.4.3 Permitted Therapy	Language added as guidance for subjects who need to undergo elective surgery (not tumor-related) during the study	Provide guidance for subjects who need to undergo elective surgery.
Section 4.4 Blinding/Unblinding	Updated the text to clarify that designated staff of the Sponsor can access IRT treatment codes prior to the formal locking of the study database.	To facilitate the access to treatment codes for interim data analyses.

Summary of key changes for Revised Protocol 10		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 4.1 Study treatments, Table 4.1-1	Added relatimab Injection 80 mg/vial to product description and dosage form	To reflect current packaging of relatimab
Table 5.1-2	Changed visit window for Q4W to ± 3 days	Visit window of ± 3 days is appropriate for a 4-week interval
[redacted]		
Section 6 Adverse Events	Entire section was updated to align with the updated BMS standards for defining adverse events, assessment of causality, pregnancy and overdose language.	To align with the latest BMS standards.
Inclusion/Exclusion Criteria	Clarification that prior disease progression on anti-PD-1 antibodies is limited to only nivolumab and pembrolizumab anti-PD-1 antibodies	Only nivolumab and pembrolizumab have a documented, verifiable clinical safety and efficacy safety profile.
Appendix 1 Women of Childbearing Potential Definitions and Methods of Contraception	Highly Effective Methods of Contraception, Less Than Highly Effective Contraceptive Methods That Are User Dependent were updated to align with BMS policy. CONTRACEPTION GUIDANCE FOR MALE PARTICIPANTS WITH PARTNER(S) OF CHILD BEARING POTENTIAL- added requirement for use of a condom by male participants during any sexual activity while on study plus 5 half-lives of study treatments plus 90 days	To align with the latest BMS standards
Appendix 4 Management Algorithms	Updated Appendix 4 Management Algorithms to the most recent version	To align with the latest BMS standards
Appendix 6 Myocarditis Adverse Event Management Algorithm	Added Appendix 6 Adverse Event Management Algorithm	Adding myocarditis algorithm to reflect evolving safety information for relatlimab
All	Minor formatting and typographical corrections	Made corrections for clarity and consistency within the document.

Overall Rationale for the Revised Protocol 09, 31-Jan-2018

The purpose of this amendment is to incorporate testing of the relatlimab/nivolumab fix dose combination (FDC) drug product BMS-986213 into Part D1. The primary objective will be to compare the safety of the FDC drug product with co-administration of relatlimab and nivolumab. Additional analyses are added and clarified to assess PK of the FDC drug product as well as confirm the efficacy and safety of the every four-week dosing schedule.

Additionally this revised protocol reflects the changes that were mentioned in approved administrative letters 05 and 06 and are not included in the summary of key changes listed below.

Revisions apply to future participants enrolled in the study and where applicable to all participants currently enrolled.

Summary of key changes for Revised Protocol 09		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 1.1.6 Rationale for Part D Expansion;	Clarification added as per new data	Clarification and definition of FDC drug product use.
Section 1.1.8 Rationale for Dose Selection	Clarification text has been added for BMS-986016 and Nivolumab administered for subjects in Parts A, A1, B, C and D.	Dosage clarification based on revised study design for Part D.
Section 1.1.8.4 Parts B, C -Nivolumab and Combination Dosing - Sequential infusion	Clarification about infusion time has been added for Part B.	To clarify that only for Part B nivolumab infusion are approximately 60 minutes, vs. Part C where the infusion is 30 minutes.
Section 1.1.8.5 Rationale for 30 minute Nivolumab Infusion	New section added	Section has been added as nivolumab is infused over 30 minutes in Part C.
Section 1.1.8.6 Part D: Co-administration) or Fixed Dose Combination (FDC); Section 3.1.2.5 Part D Melanoma Prior IO Extended Expansion (Co-administration or treatment with FDC(BMS-986213))	Clarification text added about fixed dose combination	Treatment clarifications based on revised study design for Part D.
Synopsis, Study Design, Section 1.1.8.7 Dose Rationale for Adolescents	The text has been modified as the fixed dose combination is added to Part D1 in this amendment.	Changing dosing for adolescents to flat dosing for those at least 40 kg and weight based dosing for those below 40 kg.
Synopsis; Section 1.2 Research Hypothesis	Additional text about Part D1 treatment with fixed dose combination has been added.	Hypothesis statement regarding FDC drug product.
Synopsis; Section 1.3.1	Clarification text for Part D1-Q4W and	Objectives for testing of the FDC

Summary of key changes for Revised Protocol 09		
Section Number & Title	**Description of Change**	**Brief Rationale**
Primary Objectives; Section 1.3.2 Secondary Objectives	Part D1-Q2Whas been added	product have been added
Synopsis; Section 1.3.3 Exploratory Objectives	Additional objective has been added to characterize PK and Immunogenicity when administered in combination with BMS-986016	Objectives for testing of the FDC product have been added
Section 1.4.1.4.2 Clinical Safety- Monotherapy (Part A) versus Combination Therapy (Part B) in CA224020; Section 1.4.1.4.3 Clinical Efficacy- Monotherapy (Part A) versus Combination Therapy (Part B): CA224020 Study	Sections has been updated and modified as new clinical data is available	Update of efficacy data from the Part C melanoma prior anti-PD-1 cohort.
Section 1.4.3 BMS-986213 (Fixed Dose Combination Product)	New section added	New information of the FDC product have been added
Section 1.5 Overall Risk/Benefit Assessment	Minor safety updates	To provide the latest safety information, however overall Risk/benefit assessment did not change.
Synopsis; Section 3.1 Study Design and Duration	Schema design has been updated to show three treatment arms for Part D1	Study design for Part D1 was revised to include a FDC treatment arm
	Clarification about fixed dose combination product has been added for Part D. Also modified the text for adolescents weight based dosing.	Information of the FDC product has been added. Clarification text added for the adolescents weighing less than 40 kg.
Section 3.1 Study Design; Table 5.1-3 Follow-Up Procedural Outline; Section 5.4.1 Imaging Assessment for the Study	Statement about imaging to be acquired until withdrawal of consent death, or initiation of another anti-cancer treatment was added.	Clarification text about acquiring imaging has been added.
Synopsis; Section 3.1.2.5 Part D Melanoma Prior IO Extended Expansion (Co-administration or treatment with FDC(BMS-986213))	Part D1 Safety lead-in language has been added	Given the theoretical risk of infusion reactions with the FDC drug product an acute safety lead-in is being employed.

Summary of key changes for Revised Protocol 09		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 3.1.3 Dose-Limiting Toxicities	Clarification about dose escalation in Part B has been added	Given the change in schedule to once every four week dosing needed to state how many doses are needed within the DLT period to define DLT evaluable.
Section 4.3.2. Dose Delay Criteria; Section 4.3.3. Criteria to Resume Treatment After Dose Delay; Section 4.3.5 Guidelines for Permanent Discontinuation	Clarification text for troponin elevations and myocarditis was added	Clarifications of rules for treatment delay and discontinuation based upon troponin elevations and myocarditis adverse events to align with the current relatlimab program language.
Section 3.3.1 Inclusion Criteria	Explicit statement that for Part D2 eligibility subjects must not qualify for Part D1	Clarified that subjects need to be evaluated for Part D1 first, before being evaluated for Part D2
Section 3.3.2 Exclusion Criteria	Criteria 1b) has been removed after implementation of this revised protocol	No longer needed
	Criteria 2h) has been modified to not include HCC subjects	Fixing omission from prior amendment.
	Criteria 2e) iii) has been updated to add “poorly controlled atrial fibrillation”	Clarification on eligibility for potential subjects with atrial fibrillation.
	Criteria 2e) v) has been modified to be read as “poorly controlled venous thrombosis” instead of “deep venous thrombosis”	Clarification in defining an example of a clinically significant DVT.
	Criteria 2q) has been removed after implementation of this revised protocol	There is no more weight exclusion and no longer needed.
	Criteria 2m) ii) has been modified to remove “investigational” for cytotoxic drug.	Clarification as “investigational” is not required in the definition.
Section 4.1 Study Treatments; Section 4.1.1 Investigational Product	Information about investigational product BMS-986213 (relatlimab/nivolumab) has been added	Description of FDC drug product.
	Under Table 4.1-1 - removed information about BMS-986016 injection vial of 11 mg/mL	No longer applicable
Section 4.1.3 Handling and Dispensing	The text has been modified to include the infusion time for nivolumab and BMS-986016.	Clarification of infusion time
Section 4.2 Method of Assigning Subject Identification	Clarification text has been added for the subjects enrolled in Part D1 randomization treatment arms.	Definition of treatment arms for the D1 randomization and rules governing assignment of treatment.
Synopsis; Section 3.1.3 Dose-Limiting Toxicities;	Clarification text has been added that - subjects may be dosed no less than 12	Clarification of dose delay for the Q4W regimen.

Summary of key changes for Revised Protocol 09		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 4.3.2 Dose Delay Criteria	days in Q2W regimen and 25 days in Q4W from the previous dose. Also clarified that dosing visits will follow either every 2 weeks or every 4 weeks after the delayed dose.	
Section 4.3.4 Treatment beyond Disease Progression	Section updated to align with the Nivolumab program guidelines for Treatment beyond progression.	Improves efficiency of study conduct. The protocol contains detailed criteria for Investigators to determine clinical judgement of the risk/benefit of continuing treatment beyond progression. This change also results in alignment with the Nivolumab program standards.
Section 4.3.5 Guidelines for Permanent Discontinuation	Added additional discontinuation criteria "Grade 3 infusion reaction that does not return to Grade 1 in 6 hours or less requires discontinuation.	Given the emerging and evolving understanding on optimal duration of immunotherapies this allows the investigator to apply up to date clinical judgement in deciding if an individual patient should continue or stop study treatment in the setting of confirmed complete response.
Table 5.1-1: Screening Procedural Outline (CA224020)	Added more information in Notes section about minimum time points to be submitted for prior to diagnostic imaging procedure	To provide guidance to clinical sites of the suggested pre-study diagnostic imaging timepoints to be submitted to BICR.
Table 5.1-2: On-Treatment Procedural Outline for Q2W and Q4W Treatment Regimens	Added "FDC" in vital signs procedure Also separated Part D study drug administration into Part D1 and Part D2	Incorporation of FDC in procedures tables.
	Removed notes from Weight procedure	There is no more weight exclusion and so no longer needed.
	For "Laboratory tests" procedure statement in notes about Serology tumor markers to be performed on Day 1 of each cycle was removed.	Clerical change of duplication.
	For "OPTIONAL Post-progression (PD) tumor biopsy" comments in Notes section was modified to remove the tumor tissue to be sent to central lab.	Deletion of incorrect information
	Additional information for subjects enrolled in Part C at Q4W was added.	To clarify there is a cohort in Part C which will treat subjects with a Q4W regimen
Section 5.3.1 Laboratory Test Assessments	Added "Leukocyte count" under Endocrine Panel.	Added Leukocyte count to provide flexibility in reporting for certain

Summary of key changes for Revised Protocol 09		
Section Number & Title	**Description of Change**	**Brief Rationale**
	Added "Australia antigen" for Hepatitis B surface antigen and removed Hepatitis A antibody from Serology (screening only).	countries. Added description for Hepatitis B surface antigen. Hepatitis A is not a specific eligibility criteria lab, it's not a standard requirement in nivolumab protocols.
Section 5.4.2 Efficacy Assessment for the Study	Added more information in about minimum time points to be submitted. Clarification text - "regardless of dose delays" has been added for tumor status assessment statement	To provide guidance to clinical sites of the suggested pre-study diagnostic imaging timepoints to be submitted to BICR.
Section 5.5.1 Pharmacokinetics: Collection and Processing	References to Table 5.5.1-4 and Table 5.5.1-5 has been added	To align PK collections with new study design for Part D.
Table 5.5.1-5: PK and ADA Sampling Schedule for BMS-986016 and Nivolumab for - Part D1 (Arm 2 and 3, first 12 subjects)	New table has been added to show the sampling schedule for the subjects enrolled in Part D1 Arm 2 and Arm 3	PK collections for Part D1 FDC drug product.
Table 5.7-4 Tumor Tissue Requirement	Added a note in Type of Speciment Baseline: "Note: In lieu of a biopsy during screening, acceptable MANDATORY pre-treatment biopsies include samples obtained [redacted].	This text was added to clarify language regarding the mandatory tissue collection requirements for clinical trial participation. It will clarify what is an acceptable MANDATORY pre-treatment biopsy.
[redacted]		
Synopsis; Section 8.1.4.1	Clarification text has been added	To align with new study design for Part

Summary of key changes for Revised Protocol 09		
Section Number & Title	**Description of Change**	**Brief Rationale**
Melanoma Prior IO Extended Expansion (Part D1-Q2W)		D
Synopsis; Section 8.1.4.2 Melanoma Prior IO Focused Eligibility Expansion (Part D1-Q4W)	Clarification text has been added	To align with new study design for Part D
Synopsis; Section 8.1.4.3 Melanoma Prior IO Expanded Eligibility Expansion (Part D2)	Clarification text has been added	To align with new study design for Part D
Synopsis; Section 8.3.1 Primary Endpoints; Section 8.4.3 Safety Analyses	Clarification text about AE in the MedDRA Anaphylactic Reaction broad scope SMQ for Part D1-Q4W has been added	Improved description of how to assign and enter IMAEs and description of Anaphylactic Reaction SMQ which will be used for acute toxicity assessments.
Section 8.3.2.5 Safety (Part D1 Q4W)	New section for Part D1 Q4W has been added	Description of statistical analyses surrounding FDC drug product endpoints.
Synopsis; Section 8.3.2.1 Pharmacokinetics; Section 8.4.4 Pharmacokinetic Analyses	Clarification text for PK comparison in Part D1-Q4W and Part D1-Q2W has been added	To align with new study design for Part D.
Appendix 5 MedDRA Anaphylactic Reactions	New appendix has been added	Anaphylactic Reactions PT listings

Overall Rationale for the Revised Protocol 08, 13-Jul-2017

There are 4 main changes to the protocol: Revised Protocol 08 adds 1) a bladder cancer cohort to Part C of the study. 2) Data from Part C of the study, specifically subjects with advanced melanoma and whose tumor associated immune cells express more LAG-3, showed an improved response rate. Therefore, Part D (melanoma expansion) is being added to the study to further evaluate efficacy. 3) Due to the increasing incidence of melanoma in childhood and adolescent populations, (Part C melanoma only) and Part D will allow adolescents. 4) BMS-986016 and nivolumab will be co-administered in Part D. See below for further details.

3) Adding bladder (urothelial) cancer cohort to Part C

   Bladder cancers have been shown to be responsive to immunotherapy (anti-PD-(L)1 therapy) but the large majority of subjects do not obtain significant benefit. The study combination will thus be tested in immunotherapy naive subject to assess potential for increased rates and duration of response.

4) Addition of Part D: Melanoma prior IO Extended Expansion

   As of cut-off date of April 7, 2017, preliminary proof of concept efficacy has been revealed in the Part C combination treatment expansion cohort of advanced melanoma with prior treatment with anti-PD1/PDL1. All subjects were treated with BMS-986016 80 mg + nivolumab 240 mg every two weeks. The overall objective response rate (ORR) was 12.5% (n=48 response evaluable) with a disease control rate of 54%. Biomarker analyses showed that patients whose tumor expressed more LAG-3 had a higher response rate, with a nearly a three-fold increase in ORR observed in patients with evidence of LAG-3 expression in at least one percent (n=25) of nucleated cells within and including the tumor margin, compared to less than 1 percent LAG-3 expression (n=14) (20 percent and 7.1 percent, respectively). Overall Anti-LAG-3 (BMS 986016) in combination with nivolumab demonstrated encouraging initial efficacy with a safety profile similar to nivolumab monotherapy

   Therefore, based on initial efficacy signal in advanced melanoma subjects who progressed on anti-PD1/PDL1 therapy, additional subjects in this subset population for further clinical testing is justified. Assessment in this population will be extended in two sub-parts, Part D1 and D2. D1 will test the combination in a focused eligibility population while D2 will allow assessment in a broader population under expanded eligibility criteria. Given the improved response rate in subjects whose tumor associated immune cells express more LAG-3, efficacy analysis in Part D1 will be the primary focus. Subjects whose tumors are LAG 3 negative will also be evaluated to determine the role of LAG-3 expression on the anti-tumor activity of BMS 986016. Part D2 will explore safety and efficacy in a broader patient population including those with ECOG up to 2 and among those with a more diverse set of prior therapies.

5) Allowing adolescents to participate

   Adding eligibility to adolescents (ages 12-17) in Part C (melanoma only) and in Part D. Melanoma can afflict adolescents and adolescents are vastly underrepresented in clinical trials. This addition will allow access and testing in this underserved population of patients

with high unmet need. Dosing in adolescents will be weight based (and capped at the adult flat doses) and individual countries and sites have the option of opting out of adolescent eligibility.

6) Co-administration of study drug

Co-administration of both study medications in Part D. For Part D only, both BMS 986016.and nivolumab will be co-administered through the same IV bag. This will decrease the treatment burden on study subjects and medical staff. The rest of the study will remain consistent with current sequential administration

Additionally, the revised protocol incorporates Administrative Letter 04 which clarified the collection of biopsies and clarified inclusion criteria for Part C, Non-small cell lung cancer (NSCLC).

Revisions apply to future participants enrolled in the study, and where applicable to all participants currently enrolled.

Summary of key changes of Revised Protocol 08		
Section Number & Title	**Description of Change**	**Brief Rationale**
Synopsis	Updated the number of subjects and Parts C & D of the study will enroll adolescent subjects.	Parts C and D will enroll additional subjects to the study due the increasing incidence of melanoma in childhood and adolescent populations.
Section 1.1 Study Rationale	Sections updated or added as appropriate for the addition of bladder cancer cohort to Part C, adolescents in Parts C (melanoma only) and Part D, (Melanoma Prior IO Extended Expansion), co-administration of nivolumab and BMS-986016	Updated based on recent data received
Section 1.2 Research Hypothesis, Synopsis	Added Part D1	To align the hypothesis with the addition of Part D of the study.
Section 1.3 Objectives, Synopsis	Added Part D1 to the objectives.	To align the study objectives with the additional parts of the study.
Section 1.4.1.4.2 Clinical Safety Monotherapy (Part A) versus Combination Therapy (Part B) in CA224020	Safety data updated	To provide updated safety data as of 07-Apr-2017.

Summary of key changes of Revised Protocol 08		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 1.4.1.4.3 Clinical Efficacy-Monotherapy (Part A) versus Combination Therapy (Part B): CA224020 Study	Data updated	To provide updated efficacy data based on results from this study as of 07-Apr-2017.
Section 1.4.2.4 Clinical Safety	Added an overview of safety results from subjects treated with nivolumab 480 mg Q4W.	To summarize safety data for nivolumab 480 mg Q4W dosing regimen.
Section 1.4.2.6 Clinical Activity	Updated various indications such as urothelial carcinoma, esophageal cancer SCLC, Merkel Cell carcinoma, and combined malignant tumors.	To align with the current Nivolumab IB
Section 1.5 Overall Risk Benefit Assessment	Safety and efficacy results updated	To provide updated risk:benefit profile as of 07-Apr-2017.
Section 2.3 Informed Consent	Added informed consent requirements for minors	Updated to incorporate language to allow minors to participate according to ICH Guidelines.
Section 3.1 Study Design and Duration, Synopsis,	Schematics and descriptions updated for Part C (bladder cohort), Part D (Melanoma Prior IO Extended Expansion).	To describe Part C addition of bladder cohort and Part D of the study (including co-administration).
Section 3.3.1 Inclusion Criteria	Target Population was revised for NSCLC and Head and Neck Cancer [redacted] (j) Added bladder carcinoma to Part C of the study iv) Part A1 Cohort Expansion-Monotherapy Where applicable, the requirement of scans to be collected and submitted to BICR. v) Part D1 Focused Eligibility Cohort (vi) Part D2 Expanded Eligibility Cohort Added Lansky for pediatrics to the Karnofsky and ECOG Performance status xi) [redacted] moved to exclusion criteria	Target population revised as [redacted] Updated for addition of Part C (bladder cohort) and Part D of the study. Revised inclusion criteria to allow prior exposure to other IOs. [redacted] Lansky Performance Status added for the addition of adolescents to the study Revised for the addition of adolescents to the study. For clarification of requirements Revised for the addition of adolescents to the study

Summary of key changes of Revised Protocol 08		
Section Number & Title	**Description of Change**	**Brief Rationale**
	Age and Reproductive Status was revised to allow adolescents ≥ 12 years of age into the study for Parts C (melanoma only) and Part D where allowed.	
Section 3.3.2 Exclusion Criteria, Section 5.3.1 Laboratory Test Assessments	Exclusion criteria h i), ii), iii), was revised to clarify hepatitis exclusion criteria. [redacted] was moved from inclusion criteria to exclusion criteria. Added prior treatment with LAG-3 targeted agents added adolescent body weight requirement of at least 30 kg.	Hepatitis exclusion criteria was updated to be less restrictive. [redacted] was moved for clarification of requirements. Weight requirement added for combination dose drug concentration stability reasons.
Section 4.1.3 Handling and Dispensing	In Part D BMS-986016 and nivolumab will be co-administered in a single IV bag Adolescents will be dosed based on weight	For Part D to allow co-administration using a single IV bag and update the timing and weight based dosing regimen.
Table 5.1-2 On-Treatment Procedural Outline for Q2W and Q4W Treatment Regimens, Section 5.4.1 Imaging Assessment for the Study	On-Treatment Procedural Outline has been updated Brain imaging- subjects with known CNS disease updated requirements for imaging assessments Updated throughout to add Part D and co-administration. Brain imaging: Subjects with known CNS disease must have imaging assessments at least every 12 weeks.	Part D dosing schedules and procedures added to the tables to specify procedures to be conducted in Part D For consideration of subject safety
Table 5.1-3 Follow-Up Procedural Outline	Updated throughout to add Part D	To align with the addition of Part D to the study.
Section 5.4 Efficacy Assessments, Synopsis	Updated to include Part D	To align with the addition of Part D to the study
Section 5.5.1 Pharmacokinetics Collection and Processing, Table 5.5.1-2, Table 5.5.1-3, 5.5.1-4	Table 5.5.1-2, 5.5.1-3, and 5.5.1-4 have been updated:	Pharmacokinetic collection schedules revised for the addition of Part D of the study.
Section 5.7 Exploratory	Table 5.7-1: Revised the title to specify Q2W or Q4W regimen and	Biomarker table revised for the addition of Part

Summary of key changes of Revised Protocol 08		
Section Number & Title	**Description of Change**	**Brief Rationale**
Biomarker Assessments Table 5.7-1	table has been updated.	D of the study.
[redacted]		
Section 5.7.11 Additional Research Collection	Added details regarding banking of residual samples.	To define which samples will be banked for further testing in the future if needed.
Section 7.1 Data Monitoring Committee	Updated text	To further expand the DMC to expansion cohorts of the study (Parts C & D).
Section 8 Statistical Considerations, Synopsis	All applicable sections updated to include all new and revised parts of the study.	To align with the addition of Part D to the study and co-administration.
All	Minor formatting and typographical corrections	Minor, therefore have not been summarized

APPENDIX 8 COUNTRY SPECIFIC REQUIREMENTS/DIFFERENCES

Country/Location Requirement	Section Number	Country-specific Language or Differences
France (per country-specific amendment; 29-Jul-2019)	Synopsis, Dose Escalation-Sequential Infusion (Part B):	Add the following statement to the end of this section: "Note: subjects are excluded from Part B."
	Synopsis, Part E Exposure Response Evaluation in Melanoma Participants	Add the following statement to the end of this section: "Melanoma patients with high tumor burden should have been offered targeted therapy."
	Section 3.3.1, Inclusion Criteria, 2) Target Population, a) Subjects must have histologic or cytologic confirmation of an incurable solid malignancy that is advanced (metastatic and/or unresectable): ii) Part B: Dose Escalation: BMS-986016 + nivolumab	The following criteria are not applicable. Criterion (3), NSCLC subjects progressing while on or after therapy with anti-PD-1 or anti-PD-L1 antibody (for Part B this does not need to be the most recent therapy). Criterion (3), (b) Cannot have had therapy discontinued due to serious and/or life-threatening anti-PD-1 or anti-PD-L1 antibody-related toxicity (e.g., dose-limiting toxicity in prior study) per Investigator's assessment in consultation with the BMS Medical Monitor. Criterion (3), (e) Subjects with targetable EGFR or ALK genetic aberrations must have previously received prior targeted therapy. Criterion 5 (a), For first line NSCLC subjects: The drug regimen with the highest likelihood of benefit with toxicity deemed acceptable to both the physician and the patient should be given as initial therapy for advanced lung cancer. Subjects should be offered chemotherapy if appropriate and available. Patients may refuse these standard treatments. The reason for why a subject does not receive standard first line metastatic therapy must be documented. Subjects with targetable EGFR or ALK genetic aberrations must have previously received prior targeted therapy. Criterion 5 (c), For first line NSCLC subjects: Prior adjuvant or neoadjuvant chemotherapy, or definitive chemo/radiation, is permitted as long as the last administration of the prior regimen occurred at least 6 months prior to enrollment; while prior IO therapies are not allowed.
	Section 3.3.1, Inclusion Criteria, 2) Target Population, a) Subjects must have histologic or cytologic confirmation of an incurable solid malignancy that is advanced (metastatic and/or unresectable): ii) Part B: Dose Escalation:	**Replace**: "(5) Subjects must have received, and then progressed or been intolerant to, at least one standard treatment regimen or refused standard therapy in the advanced or metastatic setting, if such a therapy exists; except for NSCLC and melanoma, where treatment as 1st line therapy is allowed." **With**: "(5) Subjects must have exhausted all approved treatment options for their respective tumor type." Removed NSCLC Cohort **Replace**: (7) Selected tumor types (and all subtypes) include melanoma, RCC, NSCLC, head and neck (any histology), gastric

<table>
<tr><td></td><td>BMS-986016 + nivolumab</td><td>(includes gastro-esophageal junction) cancer, hepatocellular, cervical, ovarian, colorectal and bladder cancers.

With: (7) Selected tumor types (and all subtypes) include melanoma, RCC, head and neck (any histology), gastric (includes gastro-esophageal junction) cancer, hepatocellular, cervical, ovarian, colorectal and bladder cancers.</td></tr>
<tr><td></td><td>Section 3.3.1, Inclusion Criteria, 2) Target Population, a) Subjects must have histologic or cytologic confirmation of an incurable solid malignancy that is advanced (metastatic and/or unresectable): vii) Part E: Exposure Response Evaluation in Melanoma Participants, (2) Melanoma participants who have not received prior systemic anticancer therapy for unresectable or metastatic melanoma:</td><td>Add a note to criterion (c):

Replace: (c) Participants must not have had prior systemic anticancer therapy for unresectable or metastatic melanoma.

With:

(c) Participants must not have had prior systemic anticancer therapy for unresectable or metastatic melanoma*

(i) *except for BRAF mutated patient with high-tumor burden and life-threatening progression (who should have been offered a targeted therapy).</td></tr>
<tr><td>Italy (per site 13-specific amendment; 03-Oct-2016)</td><td>5.7 Exploratory Biomarker Assessments</td><td>Add the following text:

Table 5.7.2a details the biomarker sub-study collection for site 013.

<table>
<tr><th>Collection Timing</th><th>Serum</th><td rowspan="6"></td><th>Tumor</th></tr>
<tr><th>Study Day</th><th>Soluble Biomarkers (Serum Biomarkers)</th><th>“Fresh” Tumor Biopsy</th></tr>
<tr><td>Screening</td><td></td><td>X</td></tr>
<tr><td colspan="3">Cycle 1</td></tr>
<tr><td>Day 1</td><td>X</td><td rowspan="3"></td><td></td></tr>
<tr><td>Day 15</td><td>X</td><td></td></tr>
<tr><td>Day 29</td><td>X</td><td>X [c]</td></tr>
<tr><td colspan="3">Upon Progression</td></tr>
<tr><td>Upon Progression</td><td>X</td><td></td><td>X</td></tr>
</table>
</td></tr>
</table>

		[redacted] NOTE: All samples are to be drawn pre-dose
	5.7.1 Soluble Biomarkers (Serum Biomarkers)	Add the following statement: Samples collected will be analyzed for circulating PDL1 and LAG-3 levels with ELISA, and Cytokinome (27+21 multiplex) in whole blood samples.
	[redacted]	
Italy (per site 14-specific amendment; 17-Oct-2016)	5.7 Exploratory Biomarker Assessments	Add the following text: Table 5.7.2a details the biomarker sub-study collection for site 014.

Collection Timing	[redacted]	**Tumor**
Study Day		**"Fresh" Tumor Biopsy**
Screening		X

		Cycle 1 Day 1 [redacted] Day 5 Day 8 Day 15 Day 29 X [c] **Cycle 2, 3, 5, 7, 9 and 11** Day 1 [redacted] **Upon Progression** Upon Progression [redacted] X [c] [redacted] NOTE: All samples are to be drawn pre-dose