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A Phase 1/2 First-in-Human Study of BMS-986249 Alone and in Combination with Nivolumab in Advanced Solid Tumors

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Clinical Protocol CA030001

A Phase 1/2 First-in-Human Study of BMS-986249 Alone and in Combination with Nivolumab in Advanced Solid Tumors

Protocol Amendment 09

Incorporates Administrative Letter 07

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DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Protocol Amendment 09	14-Mar-2023	The overall rationale for this protocol amendment is to remove exploratory endpoints (modified RECIST version 1.1 for immune-based therapeutics [iRECIST] and severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]); to introduce the option of also supplying sites with 10-mL vials containing 50 mg of ipilimumab; to decrease participant and site burden by reducing pharmacokinetic (PK), anti-drug antibody (ADA), and biomarker sample collections; and to add clarifying language.
Administrative Letter 07	29-Sep-2022	Updated study personnel.
Protocol Amendment 08	22-Feb-2022	The primary reasons for Protocol Amendment 08 are to update and/or clarify the inclusion criteria to align with the current disease state and treatment landscape based on investigator feedback for Part 2.
Administrative Letter 06	09-Nov-2021	Updated study personnel.
Administrative Letter 05	17-May-2021	Addresses typographical errors for clarification purposes.
Revised Protocol 07	15-Nov-2020	This is a revised protocol to modify the treatment arms in the Part 2A Expansion Phase and define the Part 2B Expansion Phase. The Part 2A Expansion Phase will now include concurrent evaluation of 3 treatment arms in a randomized setting in melanoma (2 different dose regimens of BMS-986249 in combination with nivolumab and 1 standard-of-care reference arm) rather than the previously defined 5 treatment arms. The Part 2B Expansion Phase will evaluate a single-dose regimen of BMS-986248 in combination with nivolumab in 3 tumor-specific cohorts. This revision also includes global changes to reduce redundancies and increase readability, incorporates updated learnings for BMS-986249, nivolumab, and ipilimumab, and adds language around COVID-19.
Revised Protocol 06	05-Aug-2019	This is a revised protocol that defines the selected BMS-986249 + nivolumab doses and schedules for Part 2A Arms A - C, updates modified intermediate dose levels in Part 1B, and incorporates other minor clarifying edits.
Revised Protocol 05	01-May-2019	This is a revised protocol to explicitly mention encephalitis as an example of a possible neurological adverse event, updates management algorithms for immuno-oncology agents, updates PD-L1 stratification criteria for Part 2A, clarifies screening biopsy criteria for Part 2A, and incorporates other clarifying modifications.
Revised Protocol 04	01-Mar-2019	This is a revised protocol to define the Part 2A Expansion Phase, which includes concurrent evaluation of three different dose regimens of BMS-986249 in combination with nivolumab in relation to two standard of care reference arms in a randomized setting in melanoma. This protocol revision also updates DLT criteria, updates inclusion/exclusion criteria, changes the on-treatment biopsy timing, and provides clarifications around planned dose level modifications/intermediate dose levels, and incorporates other clarifying modifications.
Administrative Letter 04	01-Feb-2019	Part 1B combination dose escalation

Administrative Letter 03	31-Oct-2018	Dose level modification
Revised Protocol 03	25-May-2018	Change dose-limiting toxicity evaluation period, change Parts 1A and 1B treatment assignments, provide a window for clinic visits, incorporate Administrative Letter 01, and minor typographical updates were made for consistency and clarity.
Administrative Letter 02	14-May-2018	Euderact number added
Admnistrative Letter 01	14-Mar-2018	To rectify incorrect imaging requirements for new bone lesions in prostate cancer subjects captured in the Prostrate Cancer Clinical Trials Working Group 3.
Revised Protocol 02	24-Jan-2018	Expand Part 1B tumor types, clarify the change in frequency of scans up to Week 48 versus thereafter, add co-administration of BMS-986249 + nivolumab in Part 1B, update 2 year treatment duration, add PCWG3 for prostate cancer, and minor typographical updates were made for consistency and clarity of the words participants, patients, and subjects.
Revised Protocol 01	20-Nov-2017	Includes responses to FDA questions about bladder and breast cancer population inclusion criteria, DLT criteria including ocular events, discontinuation from study treatment, clarification of expression of some tumor markers, updated imaging, biopsy and infusion time language.
Original	10-Oct-2017	Not applicable

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 09:

The overall rationale for this protocol amendment is to remove exploratory endpoints (modified RECIST version 1.1 for immune-based therapeutics [iRECIST] and severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]); to introduce the option of also supplying sites with 10-mL vials containing 50 mg of ipilimumab; to decrease participant and site burden by reducing pharmacokinetic (PK), anti-drug antibody (ADA), and biomarker sample collections; and to add clarifying language.

The revisions are not considered substantial, as the primary and secondary endpoints as well as patient safety and the benefit/risk assessment remain unchanged in the trial.

The Protocol Synopsis has been updated to align with the changes in the table below.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 09

Section Number & Title	Description of Change	Brief Rationale
Title Page	Updated Medical Monitor and Clinical Scientist contact information.	Updated with the most current contact information.
Section 2: Schedule of Activities Table 2-1: Screening Schedule of Activities for All Study Parts Table 2-2: On Treatment - Schedule of Activities for Q4W Treatment Administration in Part 1A, Part 1B, Part 2A Arm E, Part 2A Arm F, and the Nivolumab Maintenance Phase of Part 2A Arms A and D Table 2-3: On Treatment - Schedule of Activities for Part 2A Arm A and Arm D Combination Therapy Phase Table 2-4: On-treatment Schedule of Activities for Part 2A Arm B and Arm C, and Part 2B	Revised adverse event (AE) and serious AE (SAE) monitoring language to indicate that for all study participants, safety reporting of AEs and SAEs should take place from the date of informed consent through 100 days post end of treatment.	AE language was made consistent throughout the protocol: For all study participants, safety reporting of AEs and SAEs should take place from the date of informed consent through 100 days post end of treatment. This was implicit in prior versions of the protocol and clarified in this version.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 09		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-5: Follow-up Procedural Outline for All Study Parts Section 5.1.5.1: Safety Follow-up Period Section 9.2.1: Time Period and Frequency for Collecting AE and SAE Information Section 9.4: Safety		
Section 2: Schedule of Activities Table 2-2: On Treatment - Schedule of Activities for Q4W Treatment Administration in Part 1A, Part 1B, Part 2A Arm E, Part 2A Arm F, and the Nivolumab Maintenance Phase of Part 2A Arms A and D Table 2-3: On Treatment - Schedule of Activities for Part 2A Arm A and Arm D Combination Therapy Phase Table 2-4: On-treatment Schedule of Activities for Part 2A Arm B and Arm C, and Part 2B Table 2-5: Follow-up Procedural Outline for All Study Parts; Section 9.4: Safety	Removed on-treatment and follow-up SARS-CoV-2 serology assessments. Added statement indicating that testing for coronavirus disease 2019 (COVID-19) to inform decisions about clinical care during the study should follow local standard practice.	Allowing sites to test for COVID-19 per local standard practice to help inform decisions about clinical care during the study will decrease participant and site burden.
Section 2: Schedule of Activities Table 2-5: Follow-up Procedural Outline for All Study Parts	Updated language about the duration of the follow-up period from “a total of 2 years” to “up to 100 days following the end of treatment.”	Revised language to reflect removal of long-term survival follow up since further formal overall survival (OS) analyses will not be conducted.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 09		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.1.5.2: Imaging Follow-up Period Section 5.1.5.3: Survival Follow-up Period	Updated survival follow up period from approximately 2 years to up to 100 days following the end of treatment. Updated imaging follow up period from approximately 2 years to up to 100 days following the end of treatment	
Section 3.2.1.6: Clinical Safety Summary	Removed statement that dose escalation is currently ongoing.	Dose escalation is complete.
Section 4: Objectives and Endpoints Table 4-2: Objectives and Endpoints: The Dose Expansion Phase in Melanoma (Part 2A) Table 4-3: Objectives and Endpoints: The Dose Expansion Phase in Additional Tumors (Part 2B)	Removed the exploratory objective to assess the impact of SARS-CoV-2 serologic status on participants receiving BMS-986249 and to support health authority requests.	Based on low incidence of COVID-19 / COVID-19-related disease reported among study participants, exploratory assessment of impact of SARS-CoV-2 on study participants is unfeasible. Removing further collection will reduce participant and site burden.
Section 9.8.1.6: Other Assessment	Removed section.	Removed section on SARS-CoV-2 serum collection.
Section 4: Objectives and Endpoints Table 4-1: Objectives and Endpoints: The Dose Escalation Phase (Part 1) Table 4-2: Objectives and Endpoints: The Dose Expansion Phase in Melanoma (Part 2A) Table 4-3: Objectives and Endpoints: The Dose Expansion Phase in Additional Tumors (Part 2B)	Removed the exploratory objectives of objective response rate (ORR), duration of response (DOR), and progression-free survival (PFS) per iRECIST by blinded independent central review (BICR) assessments for efficacy evaluation of BMS-986249 in combination with nivolumab and for ipilimumab in combination with nivolumab.	Updated to align with current Bristol-Myers Squibb Company (BMS) efficacy assessment standards.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 09		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 9.1: Efficacy Assessments		
Section 4: Objectives and Endpoints Table 4-1: Objectives and Endpoints: The Dose Escalation Phase (Part 1) Table 4-2: Objectives and Endpoints: The Dose Expansion Phase in Melanoma (Part 2A) Table 4-3: Objectives and Endpoints: The Dose Expansion Phase in Additional Tumors (Part 2B) Section 9.8: Biomarkers	Removed mention of tumor expressed and tumor-specific proteases.	Tumor-specific proteases biomarker analysis is no longer in scope for this study.
Section 4: Objectives and Endpoints	Added estimand framework language for primary objectives and endpoints for Parts 2A and 2B.	Align with BMS statistical analyses plan. Added estimand framework to clarify which event will be included in the primary endpoint of safety analysis in case of occurrence of intercurrent event like subsequent therapy.
Section 5.1.5.1: Safety Follow-up Period	Revised language regarding the timing for follow-up visits and evaluation of any new AEs after the end of treatment (EOT) visit.	Added clarifying language.
Section 5.1.5.2: Imaging Follow-up Period	Stated that the initiation of another anti-cancer treatment will indicate the end of the Imaging Follow-up Period. Imaging follow up will end at the conclusion of the safety follow up period.	Added clarifying language.
Section 5.1: Overall Design	Changed description of overall duration of study from “approximately 4 years” to “up to 2.5 years.”	Added clarifying language.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 09		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 7.3: Treatment Duration	Added Section 7.3.	
Section 7.1: Treatments Administered Table 7.1-1: Study Treatments for CA030001	Added row for 50 mg/vial (5 mg/mL) ipilimumab solution for injection.	To provide an ipilimumab vial option (50 mg/vial 5 mg/mL) that minimizes waste of drug product.
Section 7.7.3: Palliative Local Therapy	Revised language regarding evaluation of symptoms requiring palliative radiotherapy for objective evidence of disease progression.	Added clarifying language.
Section 9.5: Pharmacokinetics and Immunogenicity Assessments Table 9.5-2: PK and ADA Sampling Schedule for BMS-986249 Q4W Monotherapy in Dose Escalation (Part 1A) Table 9.5-3: PK and ADA Sampling Schedule for BMS-986249 Q4W in Combination with Nivolumab Q4W in Dose Escalation (Part 1B) Table 9.5-4: PK and ADA Sampling Schedule for Part 2A Arm A Table 9.5-5: PK and ADA Sampling Schedule for Part 2A Arm B and Arm C Table 9.5-6: PK and ADA Sampling Schedule for Part 2A Arm D Table 9.5-7: PK and ADA Sampling Schedule for Part 2A Arm E	Removed all PK and ADA samples after Cycle 3 Day 1 (C3D1), with the exception of occurrence of Grade 3+ infusion reactions. Removed footnote d in Table 9.5-4 and Table 9.5-6.	Removed sample collection after C3D1 to reduce participant and site burden as available sample collections are sufficient for proposed analysis of the secondary objective of PK characterization and the exploratory objective of ADA analysis. Footnote was removed, as it only applied to the removed samples.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 09		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 9.5-8: PK and ADA Sampling Schedule for Part 2A Arm F Table 9.5-9: PK and ADA Sampling Schedule for Part 2B		
Section 9.8.3: Biomarker Sampling Schedule Table 9.8.3-1: Biomarker Sampling Schedule for All Study Parts	Removed whole blood (germline and T cell receptor), whole blood (PAXgene), blood (immunophenotyping), plasma, serum, and anti-SARS-CoV-2 serology assessments [redacted]. Removed footnote b on anti-SARS-CoV-2 serology.	Removed sample collection after [redacted] to reduce participant and site burden as available sample collections are sufficient for proposed analysis of the exploratory endpoint.
Section 10.2: Populations for Analyses Table 10.2-1: Populations for Analyses Section 10.3.1: Analyses	Removed definition of response-evaluable population for analysis. Outlined the timing of primary analyses	Response-evaluable definition would not apply for the clinical study report. Removed for consistency and clarity. Added clarifying language
Appendix 2	Added new section: BMS Commitment to Diversity in Clinical Trials Added new section: Data Protection, Data Privacy, and Data Security	Align with BMS commitment to diversity in clinical trials. Align with BMS practice and comply with European Union Clinical Trials Regulation (EU-CTR) requirement.
All	Minor formatting and typographical corrections.	Minor, therefore, have not been summarized.

TABLE OF CONTENTS

1 SYNOPSIS

Protocol Title: A Phase 1/2 First-in-Human Study of BMS-986249 Alone and in Combination with Nivolumab in Advanced Solid Tumors

Study Phase: 1/2

Rationale:

This is a Phase 1/2, first-in-human study of BMS-986249, an anti-cytotoxic T lymphocyte-associated protein 4 (CTLA-4) Probody™ (PROBODY is a trademark of CytomX Therapeutics, Inc.) monoclonal antibody (mAb) of ipilimumab, alone and in combination with nivolumab (anti-programmed cell death 1 [PD-1]), in participants with advanced solid tumors. Anti-CTLA-4 (ipilimumab) and anti-PD-1 (nivolumab) are approved immunotherapies for the treatment of select malignancies. Ipilimumab is a mAb that targets the checkpoint receptor CTLA-4 to activate anti-tumor immunity. Ipilimumab was the first checkpoint inhibitor approved for the treatment of human cancer, and it was the first therapeutic to demonstrate a survival advantage in metastatic melanoma. While ipilimumab has been shown to activate anti-tumor immune responses alone and in combination with nivolumab, this activity is often accompanied by immune-related adverse events. BMS-986249 is an anti-CTLA-4 Probody mAb made by the addition of 44 amino acids to the N-terminus of both light chains of the human anti-CTLA-4 antibody (Ab) ipilimumab. BMS-986249 contains a masking peptide with a cleavable linker containing protease cleavable sites for specific enzymes that are more prevalent and/or active in tumors than in peripheral tissues. The proform of the Ab, or "Probody," has reduced binding to the target and lower activity of the prodrug outside the tumor. When the linker is preferentially cleaved at the tumor site, the fully active form is released. Restricting activity in this manner is hypothesized to reduce the systemic autoimmune side effects normally seen after ipilimumab treatment while maintaining its full activity in the tumor microenvironment, resulting in an improved therapeutic index.

Study Population:

Participants must be at least 18 years old and have histologic or cytologic confirmation of a solid tumor that is advanced (metastatic, recurrent, and/or unresectable) with measurable disease per RECIST v1.1 (Appendix 5) or metastatic disease documented by either bone lesions on radionuclide bone scan and/or soft tissue lesions on CT/MRI per PCWG3 criteria for prostate cancer (Appendix 6) and have at least 1 soft-tissue tumor lesion accessible for biopsy. For Part 2B participants with HCC, intermediate disease is allowed.

Objectives and Endpoints:

The objectives and endpoints for the primary, secondary, and exploratory analysis of this study are shown in Table 1-1 (Part 1), Table 1-2 (Part 2A), and Table 1-3 (Part 2B).

Table 1-1: Objectives and Endpoints: The Dose Escalation Phase (Part 1)

Objectives	Endpoints
Primary	
• To characterize the safety, tolerability, and DLTs and to determine the MTD/RP2D of BMS-986249 administered as monotherapy and in combination with nivolumab in participants with advanced solid tumors (Parts 1A and 1B)	• Incidence of AEs, SAEs, AEs meeting protocol-defined DLT criteria, AEs leading to discontinuation, death, and laboratory abnormalities
Secondary	
• To characterize the PK of BMS-986249 when administered alone and in combination with nivolumab	• Summary measures of PK parameters of BMS-986249
• To assess the preliminary antitumor activity of BMS-986249 alone and in combination with nivolumab in advanced solid tumors (Parts 1A and 1B) using RECIST v1.1 or PCWG3 (for prostate cancer)	• ORR, DOR, PFS, and TTR per RECIST v1.1 or PCWG3 (for prostate cancer)
Exploratory	
[redacted]	
• To explore the associations between PK of BMS-986249 and nivolumab, safety, efficacy, and clinical biomarkers such as, but not limited to T-cell specific genes	• Association measures between BMS-986249 PK levels, select outcomes, and biomarkers of interest
[redacted]	
• To characterize the immunogenicity of BMS-986249 and nivolumab	• Incidence of ADA to nivolumab and BMS-986249
• To assess the potential effect of BMS-986249 when administered as monotherapy on the QTc interval	• Summary measures of ECG parameters and changes in QTcF (ΔQTcF) from baseline

Abbreviations: ADA = anti-drug antibody; AE = adverse event; DLT = dose-limiting toxicity; DOR = duration of response; ECG = electrocardiogram; MTD = maximum tolerated dose; ORR = Objective Response Rate; PCWG3 = Prostate Cancer Working Group 3; PFS = progression-free survival; PK = pharmacokinetics; QTc = QT interval corrected; QTcF = QT interval corrected for heart rate using Fridericia's formula; RECIST = Response Evaluation Criteria in Solid Tumors; RP2D = recommended Phase 2 dose of BMS-986249; SAE = serious adverse event; TTR = time to response.

Table 1-2: Objectives and Endpoints: The Dose Expansion Phase in Melanoma (Part 2A)

Objectives	Endpoints
Primary	
• To evaluate the preliminary safety and tolerability of BMS-986249 in combination with nivolumab (Arm C and Arm F) relative to ipilimumab in combination with nivolumab (Arm D) in participants with previously untreated, unresectable or metastatic melanoma	• Incidence of treatment-related Grade 3-5 AEs within 24 weeks
• To evaluate the preliminary efficacy of BMS-986249 in combination with nivolumab (Arm C and Arm F) relative to historic nivolumab monotherapy data in participants with previously untreated, unresectable or metastatic melanoma	• ORR as assessed by investigator using RECIST v1.1
Secondary	
• To assess the anti-tumor activity of BMS-986249 in combination with nivolumab (Arm C and Arm F) and ipilimumab in combination with nivolumab (Arm D) in participants with previously untreated, unresectable or metastatic melanoma	• ORR, DOR, PFS, and TTR as assessed by investigator using RECIST v1.1
• To assess the safety and tolerability of BMS-986249 in combination with nivolumab (Arm C and Arm F), and ipilimumab in combination with nivolumab (Arm D) in participants with previously untreated, unresectable or metastatic melanoma	• Incidence of AEs, SAEs, AEs leading to discontinuation, death, and laboratory abnormalities
• To characterize the PK of BMS-986249 when administered in combination with nivolumab	• Summary measures of PK parameters of BMS-986249 in combination with nivolumab
• To evaluate time to deterioration (TTD) in Quality of Life (QoL) and physical functioning	• TTD as defined by a minimally important decrease from baseline ≥10 points on the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 global health status/quality of life subscale (items 29 & 30) and Physical Functioning Scale (items 1 to 5)
Exploratory	
[redacted]	

Table 1-2: Objectives and Endpoints: The Dose Expansion Phase in Melanoma (Part 2A)

Objectives	Endpoints
• To explore the associations between PK of BMS-986249, ipilimumab and nivolumab, safety, efficacy, and clinical biomarkers such as, but not limited to T-cell specific genes	• Association measures between BMS-986249, ipilimumab, and nivolumab PK levels, select outcomes, and biomarkers of interest
[redacted]	[redacted]
• To characterize the immunogenicity of BMS-986249, ipilimumab and nivolumab	• Incidence of ADA to ipilimumab, nivolumab, and BMS-986249
• To explore OS of BMS-986249 in combination with nivolumab (Arm C and Arm F) and ipilimumab in combination with nivolumab (Arm D)	• OS rate at 1 and 2 years
• To evaluate changes in QoL, health status, and patient-reported tolerability	• Mean scores and post-baseline score changes for all EORTC QLQ-C30 subscales, EQ-5D-3L utility index and VAS, and n (%) of endorsing participants by arm and time point for FACIT GP5 item and PRO-CTCAE items

Abbreviations: ADA = anti-drug antibody; AE = adverse event; DOR = duration of response; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; EQ-5D-3L = European Quality of Life – 5 Dimension – 3 Level Questionnaire; FACIT GP5 = Functional Assessment of Chronic Illness Therapy General Physical item 5; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; PRO-CTCAE = Patient-reported Outcomes version of the Common Terminology Criteria for Adverse Events; QoL - Quality of Life; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; TTR = time to response; VAS = visual analogue scale.

Table 1-3: Objectives and Endpoints: The Dose Expansion Phase in Additional Tumors (Part 2B)

Objectives	Endpoints
Primary	
• To evaluate the preliminary safety and tolerability of BMS-986249 in combination with nivolumab in participants with previously treated HCC, CRPC, and TNBC.	• Incidence of treatment-related Grade 3-5 AEs within 24 weeks
Secondary	
• To assess the preliminary anti-tumor activity of BMS-986249 in combination with nivolumab in participants with previously treated HCC, CRPC, and TNBC	• ORR, DOR, PFS, and TTR as assessed by investigator per RECIST v1.1 or PCWG3 (for prostate cancer). PSA response rate for prostate cancer
• To characterize the safety and tolerability of BMS-986249 in combination with nivolumab in participants with previously treated HCC, CRPC, and TNBC	• Incidence of AEs, SAEs, AEs leading to discontinuation, death, and laboratory abnormalities
• To characterize the PK of BMS-986249 when administered in combination with nivolumab in participants with previously treated HCC, CRPC, and TNBC	• Summary measures of PK parameters of BMS-986249 in combination with nivolumab
Exploratory	
[redacted]	
• To explore the associations between PK of BMS-986249 and nivolumab, safety, efficacy, and clinical biomarkers such as, but not limited to T-cell specific genes	• Association measures between BMS-986249 and nivolumab PK levels, select outcomes, and biomarkers of interest
[redacted]	
• To characterize the immunogenicity of BMS-986249 and nivolumab	• Incidence of ADA to nivolumab and BMS-986249
• To explore OS	• OS rate at 1 and 2 years
• To evaluate changes in QoL, health status, and patient reported tolerability	• Mean scores and post-baseline score changes for all EORTC QLQ-C30 subscales, EQ-5D-3L utility index and VAS, and n (%) of endorsing participants by arm and time point for FACIT GP5 item and PRO-CTCAE items

Abbreviations: ADA = anti-drug antibody; AE = adverse event; CRPC = castration-resistant prostate cancer; DOR = duration of response; EQ-5D-3L = European Quality of Life – 5 Dimension – 3 Level Questionnaire; EORTC QLQ-C30= European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire-Core 30; FACIT

GP5 = functional assessment of chronic illness therapy general phycial item 5; HCC = hepatocellular carcinoma; ORR = Objective Response Rate; OS = overall survival; PCWG3 = Prostate Cancer Working Group 3; PFS = progression-free survival; PK = pharmacokinetics; PRO-CTCAE = patient reported outcomes common terminology criteria for adverse events; PSA = prostate-specific antigen; QoL = quality of life; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse events; TNBC = triple-negative breast cancer; TTR = time to response; VAS = visual analogue scale.

Overall Design:

This is a Phase 1/2, open-label study of BMS-986249, administered as a single agent and in combination with nivolumab in participants with advanced solid tumors. The study is composed of 2 parts: dose escalation and dose expansion.

This study will evaluate the safety, tolerability, pharmacokinetic (PK), [redacted], and preliminary efficacy profile of BMS-986249 alone and in combination with nivolumab. In the Dose Escalation Phase (Part 1) various doses of BMS-986249 will be given alone (Part 1A) or in combination with nivolumab (Part 1B). The BMS-986249 Cohort Expansion Combination Therapy Phase (Part 2) will expand a specific patient population to assess the anti-tumor activity, safety, and tolerability of BMS-986249 in combination with nivolumab.

All participants will complete up to 3 study periods: Screening (up to 30 days), Treatment (up to 2 years), and Follow-up (starting after end of treatment [EOT], and is comprised of Safety, Imaging, and Survival Follow-up). The duration of the study will approximately 2 years and 3 months (treatment up to 2 years and Follow-up Period of 100 days post EOT).

At the Sponsor's discretion, scans will be submitted to an imaging core laboratory and may be reviewed by blinded independent central review at a later date or at any time during the study.

Number of Participants:

- Part 1A Monotherapy Escalation: The total sample size is up to approximately 45 evaluable participants.
- Part 1B Combination Escalation: The total sample size is up to approximately 60 evaluable participants.
- Part 2A Expansion in Melanoma: The total sample size is up to approximately 200 evaluable participants with approximately 60 evaluable participants each treated in Arm C, Arm D, and Arm F, respectively. Prior to Revised Protocol 07, up to approximately 20 evaluable participants may have been enrolled across Arms A, B, and E, collectively.
- Part 2B Additional Tumor Cohort Expansion: The total sample size is up to approximately 120 evaluable participants with approximately 40 evaluable participants per tumor type cohort.

Treatment Arms:

- Part 1: The Dose Escalation Phase, where the dose of BMS-986249 given alone (Part 1A) or in combination with nivolumab (Part 1B) will be escalated to determine the maximum tolerated dose (MTD)/recommended Phase 2 dose.

- Part 1A, the BMS-986249 Monotherapy Dose Escalation, will escalate the dose of BMS-986249 to determine a safe and efficacious dose. The study will first evaluate the safety and tolerability of BMS-986249 monotherapy administered once every 4 weeks (Q4W) up to 2 years. Dose escalation will be based on dose-limiting toxicities using a Bayesian Logistic Regression Model employing the escalation with overdose control principle.
- Part 1B, the Safety Evaluation of Combination Doses of BMS-986249 with nivolumab, will evaluate the safety and tolerability of BMS-986249 in combination with nivolumab. Part 1B will begin only when data (safety and PK) on BMS-986429 at 240 mg (equivalent to approximately 3 mg/kg) and 800 mg (equivalent to approximately 10 mg/kg) are available from the BMS-986249 Monotherapy Dose Escalation cohort (Part 1A). The dose of BMS-986429 will be escalated, whereas the dose of nivolumab is fixed at 480 mg Q4W. However, if an MTD is identified, then additional cohorts with lower doses of nivolumab and then potential higher doses of BMS-986249 may be studied as outlined below and in the study design schematic (Figure 1-1). Alternative administration schedules of BMS-986249 (eg, every 8 weeks) may also be explored after clinical evaluation of available safety, PK, and [redacted] data. Alternative dose schedules will be initiated and documented by a note to file or administrative letter following discussions and agreement between the investigators and Medical Monitor (or designee). The goal for the combination dose escalation is to identify at least 2 dose combinations with nivolumab as follows:
  - One combination with a high dose of BMS-986249 with nivolumab that has an acceptable safety profile and with anticipation of potentially increased efficacy over what has been observed with ipilimumab and nivolumab combination
  - A second dose combination with a lower BMS-986249 dose in combination with nivolumab that has a potentially optimal safety and tolerability profile that is improved over the ipilimumab and nivolumab combination yet may yield at least comparable efficacy

- Part 2: The BMS-986249 Cohort Expansion Combination Therapy Phase will open upon an overall assessment of available preliminary safety, PK, and [redacted] data from Part 1A and Part 1B. The different dose levels selected for Part 2 will not exceed the highest dose level assessed and deemed tolerable in Part 1. Part 2 will expand a specific patient population to assess the anti-tumor activity of BMS-986249 in combination with nivolumab. Safety, tolerability, PK, [redacted], and patient-reported outcome information of BMS-986249 in combination with nivolumab will also be evaluated.
  - The BMS-986249 in Combination with Nivolumab Randomized Cohort Expansion in Melanoma (Part 2A) will include participants with previously untreated, unresectable or metastatic melanoma. Part 2A participants will be stratified by programmed death ligand-1 (PD-L1) status (≥ 1% tumor cell surface expression versus < 1% tumor cell expression/indeterminate) and American Joint Committee on Cancer M-stage Version 7 (M0/M1a/M1b versus M1c) and initially randomized 1:1:1:1:1 between 5 treatment arms:
    - Arm A: 240 mg BMS-986249 in combination with 360 mg nivolumab administered intravenously (IV) every 3 weeks (Q3W) for 4 doses (Combination Therapy Phase) as

a co-administration, followed by 480 mg nivolumab monotherapy administered IV over approximately 30 minutes Q4W (Maintenance Phase), which will begin 3 weeks after the last combination dose.

- Arm B: 800 mg BMS-986249 administered IV Q8W in combination with 480 mg nivolumab administered IV Q4W. Co-administration will continue on cycles where both study treatments are scheduled, while nivolumab will be administered IV over approximately 30 minutes when scheduled as a monotherapy.
- Arm C: 1,200 mg BMS-986249 administered IV Q8W in combination with 480 mg nivolumab administered IV Q4W. Co-administration will continue on cycles where both study treatments are scheduled, while nivolumab will be administered IV over approximately 30 minutes when scheduled as a monotherapy.
- Arm D: 3 mg/kg ipilimumab in combination with 1 mg/kg nivolumab administered IV Q3W for 4 doses (Combination Therapy Phase), followed by 480 mg nivolumab monotherapy administered IV over approximately 30 minutes Q4W (Maintenance Phase), which will begin 3 weeks after the last combination dose. Nivolumab and ipilimumab will be administered sequentially as 2 separate IV infusions. Nivolumab will be given first, over approximately 30 minutes, followed by ipilimumab over approximately 30 minutes, beginning approximately 30 minutes after completion of the infusion of nivolumab.
- Arm E: 480 mg nivolumab monotherapy administered IV over approximately 30 minutes Q4W.

- Addendum Per Revised Protocol 07: Part 2A Arm A, Arm B, and Arm E are discontinued for further enrollment/randomization. The modification of enrollment/randomization in Part 2A is not a consequence of changes in the safety or tolerability profile or benefit/risk assessment of BMS-986249. Currently active participants in these arms will continue treatment as assigned and can remain on study until protocol-defined discontinuation criteria have been met. In accordance with Revised Protocol 07, participants in Part 2A will be randomized across the study approximately 1:1:1 between 3 treatment arms:
  - Arm C: described above
  - Arm D: described above
  - Arm F: 600 mg BMS-986249 administered IV Q4W in combination with 480 mg nivolumab administered IV Q4W as a co-administration.

The BMS-986249 in Combination with Nivolumab Additional Tumor Cohort Expansion (Part 2B) will be comprised of signal seeking expansion cohorts including participants with previously treated advanced or intermediate hepatocellular carcinoma (Cohort 1), metastatic castration-resistant prostate cancer (Cohort 2), and unresectable locally advanced or metastatic triple-negative breast cancer (Cohort 3).

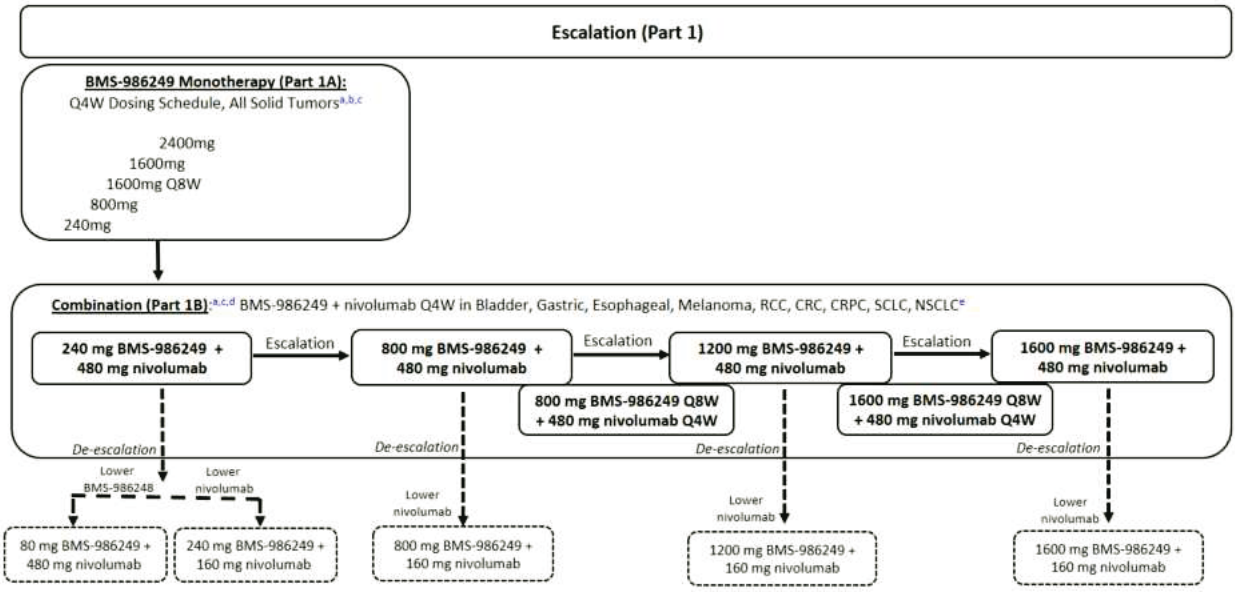
Study Treatment:

Study Treatments for CA030001		
Medication	**Potency**	**IP/Non-IP**
BMS-986249 Injection	40 mg/mL	IP
ipilimumab Injection	5 mg/mL	IP
nivolumab Injection	10 mg/mL	IP

Abbreviation: IP = investigational product.

The study design schematic is shown in Figure 1-1 (Part 1) and Figure 1-2 (Part 2).

Figure 1-1: Study Design Schematic - Part 1, the Dose Escalation Phase



Abbreviations: BMS = Bristol Myers Squibb; CRC = colorectal cancer; CRPC = castration-resistant prostate cancer; CTLA-4 = cytotoxic T lymphocyte-associated protein 4; DLT = dose-limiting toxicity; NSCLC = non-small cell lung cancer; PD-1 = programmed cell death protein 1; PD-L1 = programmed death ligand-1; Q4W = every 4 weeks; Q8W = every 8 weeks; RCC = renal cell carcinoma; SCLC = small cell lung cancer.

a Alternative dosing schedules (eg, Q8W) may occur after evaluation of available safety, PK, and [redacted] data, and upon discussion and agreement between the investigators and Medical Monitor (or designee).

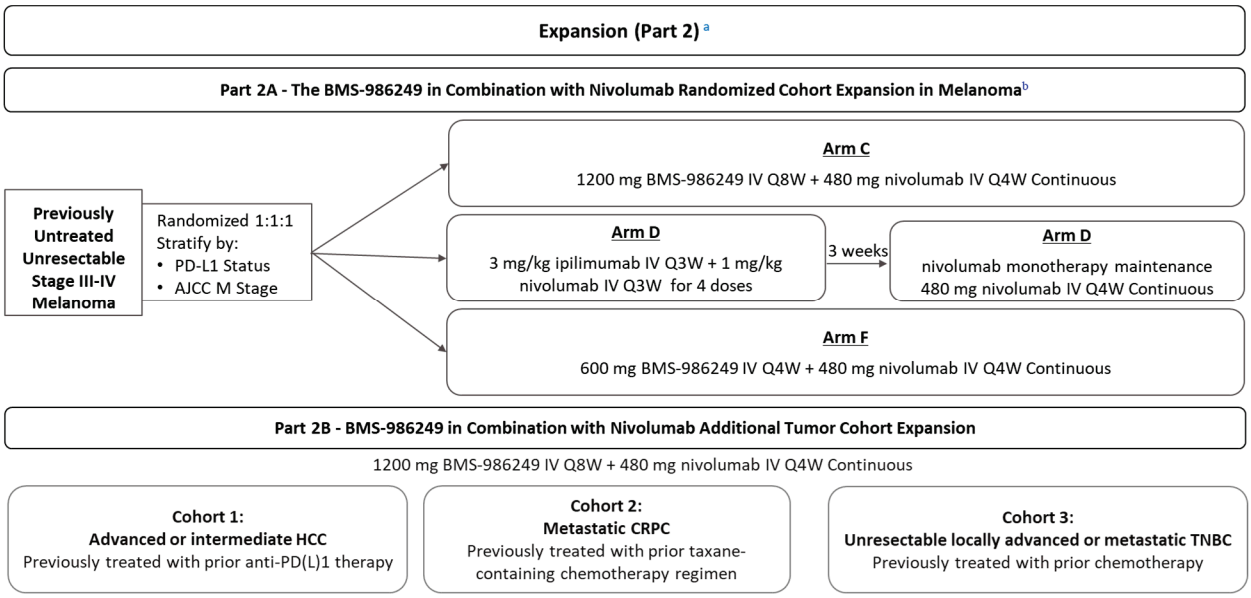
b Participants in the monotherapy arm must be anti-CTLA-4-naive. Prior anti-PD-1 or anti-PD-L1 exposure is allowed in the monotherapy arm, but at time of enrollment, participants must be at least 5 half-lives (approximately 100 days) from last dose of PD-1/PD-L1 therapy.

c Intra-participant dose escalation/reduction of BMS-986249 or nivolumab is not permitted.

d Part 1B will not start until demonstration of acceptable safety in at least 2 cohorts from Part 1A has occurred. Subsequently, treatment in both parts will occur in parallel.

e Part 1B participants with NSCLC will only be evaluated in a cohort once the DLT evaluation for that cohort has been completed.

Figure 1-2: Study Design Schematic - Part 2, the BMS-986249 Cohort Expansion Combination Therapy Phase



Abbreviations: AJCC = American Joint Committee on Cancer; CRPC = castration-resistant prostate cancer; HCC = hepatocellular carcinoma; IV = intravenous; PD-L1 = programmed death ligand-1; Q3W = every 3 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks; TNBC = triple-negative breast cancer.

a Will only open upon evaluation of available data from Parts 1A and 1B.

b Per Revised Protocol 07, Part 2A Arm A, Arm B, and Arm E were closed to enrollment and are not displayed. Part 2A Arm A 240 mg BMS-986249 IV Q3W for 4 doses followed by nivolumab monotherapy Maintenance Phase of 480 mg nivolumab IV Q4W continuous. Part 2A Arm B, 800 mg BMS-986249 IV Q8W in combination with 480 mg nivolumab IV Q4W continuous. Part 2A Arm E, 480 mg nivolumab IV Q4W continuous.

Screening: The screening period will be up to 30 days and begins by establishing the participant's initial eligibility and signing of the informed consent form. If a participant exceeds the 30-day screening period due to a study-related procedure (eg, scheduling of a tumor biopsy or waiting for a study-related laboratory value), the participant must be re-consented and will require a new participant identification number. In this situation, the fewest number of procedures from the initial screening should be repeated to qualify the participant, while maintaining participant safety and eligibility. For Part 2A participants awaiting PD-L1 results, the screening window may be extended past the 30-day period upon discussion with the Medical Monitor (or designee). However, if screening extends over a prolonged period, baseline procedures, such as tumor assessments and labs, may need to be repeated so that they fall within the acceptable protocol-specified window. Within a given disease type, participants meeting all eligibility criteria will be enrolled in the study using an Interactive Response Technology according to the part and treatment arm availability.

Treatment: The initial dosing regimen of BMS-986249 was selected as Q4W, with an additional dosing regimen of Q8W subsequently explored. All participants will be treated for up to 2 calendar years. Continuous safety evaluation and tumor assessment occurring in Part 1, Part 2A, and Part 2B

will guide the decision to treat a participant with additional cycles of study therapy if the participant has confirmed clinical benefit.

- In the BMS-986249 Monotherapy Escalation (Part 1A), BMS-986249 will initially be administered Q4W and infused initially over approximately 30 minutes for the 240 mg dose. Infusion times for subsequent dose concentrations will vary to adjust for the different drug protein concentrations.
- For the Safety Evaluation of Combination doses of BMS-986249 with nivolumab (Part 1B), both study treatments will be administered as a co-administration through the same IV bag. Initial dosing will be Q4W co-administration of 240 mg BMS-986249 in combination with 480 mg nivolumab infused over approximately 120 minutes. Infusion times will vary with subsequent co-administration doses to adjust for the different drug protein concentrations. If an alternative dosing schedule is evaluated, co-administration will continue on cycles where both study treatments are scheduled, while nivolumab will be administered IV over approximately 30 minutes when scheduled as a monotherapy.
- In the BMS-986249 in Combination with Nivolumab Randomized Cohort Expansion in Melanoma (Part 2A) cycle length and dose administration will vary with treatment arm.
- In the BMS-986249 in Combination with Nivolumab Additional Tumor Cohort Expansion (Part 2B), participants will receive 1,200 mg BMS-986249 administered IV Q8W in combination with 480 mg nivolumab administered IV Q4W. Co-administration will continue on cycles where both study treatments are scheduled, while nivolumab will be administered IV over approximately 30 minutes when scheduled as a monotherapy.
- Refer to the pharmacy manual for treatment administration, timing, and infusion details for BMS-986249, ipilimumab, and nivolumab.
- BMS-986249 infusions, as a monotherapy or co-administration, will require a 60-minute observation period after the completion of the infusion for the first 3 doses for each participant.
- Tumor progression and response endpoints will be assessed using RECIST v1.1 criteria for solid tumors or PCWG3 (for prostate).

Follow-up:

- Safety Follow-up Period:
  - Upon completion of study therapy (or up to a maximum of 2 years, if applicable) or once the decision is made to discontinue the participant from treatment, that is, at EOT, all participants will enter a Safety Follow-up Period.
  - For participants who complete all scheduled cycles of therapy, the EOT visit will be the same visit as the last scheduled and completed on-treatment visit and will be the start of the Safety Follow-up Period. For participants who do not complete all scheduled cycles of therapy, the EOT visit will be the most recent on-treatment visit (with all available safety and response data) and will not need to be repeated. Accordingly, for these participants, this visit will be considered the start of the Safety Follow-up Period.
  - After the EOT visit, follow-up study visits should occur at Days 30, 60, and 100 (±7 days) for all study participants. Safety reporting of AEs and SAEs should take place from date of informed consent through 100 days post EOT.

  - All participants should complete the 3 clinical safety follow-up visits regardless of whether new anti-cancer therapy is started, except those participants who withdraw consent for study participation.

- Imaging Follow-up Period:
  - At the time of study treatment discontinuation, participants will continue to have radiologic and clinical tumor assessments. The duration of the Imaging Follow-up Period will be 100 days post EOT or until death, or initiation of another anti-cancer treatment, whichever occurs first. Radiological assessments for participants who have ongoing clinical benefit may continue to be collected after participants complete the Survival Follow-up Period of the study. Participants who have disease progression after an initial course of study therapy will be evaluated beyond the EOT visit and will be allowed to receive other tumor-directed therapy as required. The initiation of another anti-cancer treatment will indicate the end of the Imaging Follow-up Period.
- Survival Follow-up Period:
  - In parallel with the Safety Follow-up Period, all participants will start the Survival Follow-up Period. Since further formal OS analyses will not be conducted, the maximum study duration will be through 100 days post EOT. Participants who are in the follow-up period past 100 days after EOT should be discontinued from the study. Participants will be followed by telephone (from EOT) through 100 days post EOT or until death, loss to follow-up, withdrawal of consent, or conclusion of the study, whichever comes first. For Part 2 participants, EQ-5D-3L data will be collected by telephone or email during the Survival Follow-up Period. Participants will have both the Imaging Follow-up Period and Survival Follow-up Period occur simultaneously. The duration of this follow-up will be through 100 days post EOT. Subsequent therapies will also be recorded in this Survival Follow-up Period.

2 SCHEDULE OF ACTIVITIES

Study assessments and procedures are shown in Table 2-1, Table 2-2, Table 2-3, Table 2-4, and Table 2-5.

In limited instances, scheduled events (including events other than safety assessments) can occur outside of the indicated timeframes but the Sponsor should first be notified.

If a participant has a delay in study treatment administration for any reason, then assessments and laboratory tests (with the exception of any tests needed to ensure participant safety) should be correspondingly delayed with the exception of tumor assessments. Tumor assessments continue per protocol schedule regardless of any treatment delay incurred.

The pharmacokinetic (PK), [redacted], and safety profiles of BMS-986249 are being elucidated, modifications to the procedures (ie, reduction in PK, [redacted] sampling, timing of procedures, dose schedules) currently outlined in Section 2 and Section 9 may be required. These modifications will not include the addition of new procedures and will be documented in a note to file or administrative letter.

In the event that multiple procedures are required at a single time point, the electrocardiogram (ECG) may be obtained up to 15 minutes earlier, vital signs may be obtained up to 10 minutes earlier or later, and clinical laboratory samples may be obtained up to 5 minutes earlier than the nominal time point, ensuring the PK samples can be collected on time.

Table 2-1: Screening Schedule of Activities for All Study Parts

Procedure	Screening Visit (Days -30 to -1)	Notes
Eligibility Assessments		
Informed Consent	X	Must be obtained prior to performing any screening procedures. A participant is considered enrolled only when a protocol-specific ICF is signed.
Contact IRT	X	After the participants meet all eligibility criteria, sites will use IRT for participant number assignment. Register in IRT to obtain participant number. Subsequent visits will be registered into the IRT system for drug supply. See Section 5.1.1. If the IRT system is not available, participants will be enrolled manually. The participant number will be created in the IRT system upon availability.
Inclusion/Exclusion Criteria	X	Must be confirmed prior to randomization/treatment assignment. See Section 6.1 and Section 6.2.
Medical History	X	All medical history relevant to the disease under study. Include any toxicities or allergies related to previous treatments.
Prior Cancer Therapies	X	
Child-Pugh Score	X	For Part 2B participants with HCC only. Child-Pugh A score is required. See Appendix 13.
Safety Assessments		
PE, Measurements, Vital Signs, and Performance Status	X	Height, weight, ECOG performance status of 0 or 1 (see Appendix 7), seated/supine blood pressure, heart rate, body temperature, respiratory rate, and oxygen saturation by pulse oximetry at rest. Blood pressure and heart rate should be measured after the participant has been resting quietly for at least 5 minutes. Must be collected within 15 days prior to randomization/treatment assignment. If the screening PE is performed within 72 hours prior to dosing on Day 1, then a single examination may count as both the screening and predose evaluation.
Concomitant Medication Collection	X	Within 15 days prior to randomization/treatment assignment. Vaccine use within 30 days prior to first study treatment.
ECG	X	ECGs should be recorded after the participant has been supine for at least 5 minutes and prior to blood draws. See Section 9.4.3.

Table 2-1: Screening Schedule of Activities for All Study Parts

Procedure	Screening Visit (Days -30 to -1)	Notes
Clinical Laboratory Assessments[a]	X	On-site/local laboratory tests must be performed within 15 days prior to randomization/treatment assignment. See Section 9.4.4 and Table 9.4.4-1.
Urinalysis	X	Microscopic urine reflex only for urinalysis positive for blood/protein/leukocytes. See Section 9.4.4 and Table 9.4.4-1.
Serology	X	Viral testing is to be completed within 30 days prior to randomization/treatment assignment. All participants must have hepatitis C Ab, hepatitis B surface antigen, and HIV-1 and HIV-2 Ab testing completed. To be performed onsite/locally per local standards. Additional testing for viral hepatitis is required and must be completed at the central laboratory for HCC participants only and includes Epstein-Barr virus antibody, hepatitis B surface antibody, hepatitis B core antibody, hepatitis B DNA viral load (PCR), HCV RNA viral load (PCR), hepatitis D antibody (if chronic HBV infection). Local laboratory serology results can be used to assess eligibility if the central laboratory result is not available in time. See Section 9.4.4 and Table 9.4.4-1.
Pregnancy Test (WOCBP Only)	X	Serum or urine pregnancy test (minimum sensitivity equivalent units 25 IU/L or equivalent units of hCG) to be done at screening visit and repeated within 24 hours prior to first dose of study treatment.Serum pregnancy test may be taken on the first day of treatment, provided results are available prior to starting study therapy. If pregnancy test is taken within 24 hours of dosing (C1D1), a further pregnancy test is not required. See Section 9.4.4 and Table 9.4.4-1.
FSH	X	Women only, as needed to document postmenopausal status. Females under the age of 55 years must have a serum FSH level > 40 mIU/mL to confirm menopause. See Section 9.4.4 and Table 9.4.4-1.
Serum Alpha-fetoprotein	X	Required for Part 2B participants with HCC only. To be performed onsite/locally with clinical laboratory assessments. See Section 9.4.4 and Table 9.4.4-1.
PSA	X	Required for Part 2B participants with prostate cancer only. To be performed by local lab prior to participant receiving their first dose of study treatment. See Section 9.4.4 and Table 9.4.4-1.

Table 2-1: Screening Schedule of Activities for All Study Parts

Procedure	Screening Visit (Days -30 to -1)	Notes
Testosterone	X	Required for Part 2B participants with prostate cancer only. To be performed by local lab prior to participant receiving their first dose of study treatment. See Section 9.4.4 and Table 9.4.4-1.
Adverse Event Reporting		
Assessment of Signs/Symptoms/ Clinical Complaints	X	
SAE Assessment	X	For all study participants, safety reporting of AEs and SAEs should take place from date of informed consent through 100 days post EOT, including all AEs (SAEs or non-serious AEs) associated with SARS-CoV-2 infection.
Tumor Assessments		
Body Imaging	X	Must be performed within 30 days prior to randomization/treatment assignment. See Section 9.1.1. For participants with HCC, a triphasic CT/MRI of the liver is required. For participants with TNBC without measurable lesions outside of the breast, contrast-enhanced MRI of the breasts should be performed.
Brain Imaging	X	MRI of the brain without and with contrast is required for participants with known or suspected brain metastases who have not had brain imaging within 30 days of anticipated first study treatment administration. See Section 9.1.1.
Other: Bone Scan	X	Required for participants with prostate cancer only (PCWG3 Assessment, see Appendix 6). Others only as clinically indicated per local standards. See Section 9.1.1.

Table 2-1: Screening Schedule of Activities for All Study Parts

Procedure	Screening Visit (Days -30 to -1)	Notes
Biomarker Assessment		
Collection of Tumor Tissue	X	**All study parts: Consent for tumor biopsy samples is mandatory for enrollment**. Instructions for the collection and processing of all samples will be provided in the Laboratory Manual. Biopsy tissue should be obtained from core biopsy, punch biopsy, excisional biopsy, or surgical specimen. Bone lesion biopsies are unacceptable for analyses. See Section 9.8.2. **Part 1:** A fresh biopsy should be performed during screening with sufficient tumor tissue. Archived tumor specimens are optional in addition to fresh specimens. **Part 2A/Part 2B:** A fresh biopsy should be performed during screening with sufficient tumor tissue. A fresh screening biopsy will not be required if archived tumor specimens fulfill all the following conditions: 1) obtained in the metastatic setting or from an unresectable site that has not been previously irradiated, 2) are not older than 3 months with no intervening systemic anti-cancer treatment between time of acquisition and enrollment, 3) are of sufficient quality and quantity (as instructed in the Laboratory Manual), and 4) are submitted prior to randomization/treatment assignment. If despite best efforts, the above-mentioned criteria cannot be met, a fresh biopsy should occur; however, submission of the archival tumor sample beyond the above criteria may be acceptable in some circumstances following discussion with Medical Monitor or designee. In order to be randomized in Part 2A, a participant must have quantifiable PD-L1 expression (≥ 1% or < 1% tumor cell membrane staining) or be classified as PD-L1 indeterminate.
SARS-CoV-2 Serology	X	Serum collected to be used for potential future measurements of anti-SARS-CoV-2 serology (anti-SARS-CoV-2 total or IgG).

Abbreviations: Ab = antibody; AE = adverse event; C1D1 = Cycle 1 Day 1; CT = computed tomography; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FSH = follicle stimulating hormone; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; HIV = human immunodeficiency virus; ICF = informed consent form; IRT = Interactive Response Technology; MRI = magnetic resonance imaging; PCR = polymerase chain reaction; PCWG3 = Prostate Cancer Working Group 3; PD-L1 = programmed death ligand-1; PE = physical examination; PSA = prostate-specific antigen; RNA = ribonucleic acid; SAE = serious adverse events; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TNBC = triple-negative breast cancer; WOCBP = women of childbearing potential.

Table 2-2: On Treatment - Schedule of Activities for Q4W Treatment Administration in Part 1A, Part 1B, Part 2A Arm E, Part 2A Arm F, and the Nivolumab Maintenance Phase of Part 2A Arms A and D

Procedure	Cycle 1 (28 Days in Length)				Cycle 2 (28 Days in Length)				Cycles 3[a] and Beyond (Each Cycle 28 Days in Length)	EOT[b,c]	Notes
	D1	D8 (± 2 days)	D15 (± 2 days)	D22 (± 2 days)	D1 (± 2 days)	D8 (± 2 days)	D15 (± 2 days)	D22 (± 2 days)	D1 (± 2 days)		
Safety Assessments											
Targeted PE, Measurements, and ECOG Performance Status[d]	X				X				X	X	Weight and ECOG Performance Status (see Appendix 7).
Oxygen Saturation	X				X				X		
Symptom Directed PE		X	X	X		X	X	X			
Vital Signs[d]	X	X	X	X	X	X	X	X	X	X	Includes body temperature, respiratory rate, blood pressure and heart rate.
ECG[e]	X				X				X	X	ECG collections apply to Parts 1A, 1B, and 2A.

Table 2-2: On Treatment - Schedule of Activities for Q4W Treatment Administration in Part 1A, Part 1B, Part 2A Arm E, Part 2A Arm F, and the Nivolumab Maintenance Phase of Part 2A Arms A and D

Procedure	Cycle 1 (28 Days in Length)				Cycle 2 (28 Days in Length)				Cycles 3[a] and Beyond (Each Cycle 28 Days in Length)	EOT[b,c]	Notes
	D1	D8 (± 2 days)	D15 (± 2 days)	D22 (± 2 days)	D1 (± 2 days)	D8 (± 2 days)	D15 (± 2 days)	D22 (± 2 days)	D1 (± 2 days)		
Clinical Laboratory Assessments	X	X	X	X	X	X	X	X	X	X	Perform onsite/local laboratory testing within 72 hours prior to each dose. For the first treatment visit, labs need not be repeated if they were performed within 72 hours and the results are available and have been reviewed for eligibility. See Section 9.4.4 for the list of laboratory tests to be conducted. Coagulation assessment at screening only.
Urinalysis	X				X				As clinically indicated; microscopic urine reflex only for urinalysis positive for blood/ protein/ leukocyte esterase	X	
Pregnancy Test (WOCBP only)[f]	X				X				X	X	

Table 2-2: On Treatment - Schedule of Activities for Q4W Treatment Administration in Part 1A, Part 1B, Part 2A Arm E, Part 2A Arm F, and the Nivolumab Maintenance Phase of Part 2A Arms A and D

Procedure	Cycle 1 (28 Days in Length)				Cycle 2 (28 Days in Length)				Cycles 3[a] and Beyond (Each Cycle 28 Days in Length)	EOT[b,c]	Notes
	D1	D8 (± 2 days)	D15 (± 2 days)	D22 (± 2 days)	D1 (± 2 days)	D8 (± 2 days)	D15 (± 2 days)	D22 (± 2 days)	D1 (± 2 days)		
Adverse Event Reporting and Concomitant Medication Assessments											
Monitor for Non-SAEs	For all study participants, safety reporting of all AEs including non SAEs and SAEs should take place from date of informed consent through 100 days post EOT.										For all study participants, all AEs (SAEs or non-serious AEs), including those associated with SARS-CoV-2 infection, must be collected from date of informed consent through 100 days post EOT. See Appendix 3 and Section 9.2.
Monitor for SAEs	For all study participants, safety reporting of all AEs including SAEs and non SAEs should take place from date of informed consent through 100 days post EOT.										
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	
PK Assessments											
Serial Blood Sampling	See Section 9.5 and corresponding tables for the PK sampling schedule.										Refer to outlined protocol sections for all required collections.
Immunogenicity (ADA) Assessments	See Section 9.5 and corresponding tables for the immunogenicity sampling schedule.										Refer to outlined protocol sections for all required collections.

[redacted]

Table 2-2: On Treatment - Schedule of Activities for Q4W Treatment Administration in Part 1A, Part 1B, Part 2A Arm E, Part 2A Arm F, and the Nivolumab Maintenance Phase of Part 2A Arms A and D

Procedure	Cycle 1 (28 Days in Length)				Cycle 2 (28 Days in Length)				Cycles 3[a] and Beyond (Each Cycle 28 Days in Length)	EOT[b,c]	Notes
	D1	D8 (± 2 days)	D15 (± 2 days)	D22 (± 2 days)	D1 (± 2 days)	D8 (± 2 days)	D15 (± 2 days)	D22 (± 2 days)	D1 (± 2 days)		
Imaging Assessments											
Body Imaging	Part 1: Tumor imaging assessments should occur Q8W starting from the first dose (±7 days) up until Week 48, and then continue Q12W (±7 days). Part 2A: The first tumor imaging assessment should occur 12 weeks (±7 days) from first dose. Subsequent tumor imaging assessments should occur Q8W (±7 days) from the date of the first tumor imaging assessment until Week 52 then continue Q12W (±7 days) thereafter.										The same imaging modality is to be used for all assessments, per RECIST v1.1. See Appendix 5. Tumor assessment to be performed prior to initiating next cycle of treatment. See Section 9.1.1.
Brain Imaging	See Section 9.1.1. Participants with history of brain metastasis should have surveillance MRI performed approximately Q12W or sooner if clinically indicated. CT of the brain without and with contrast can be performed if MRI is contraindicated.										
Other: Bone Scan	See Section 9.1.1. Required for participants with prostate cancer only (PCWG3 Assessment, see Appendix 6). For participants with prostate cancer, bone scans should occur Q8W starting from the first dose (±7 days) up until Week 48, and then continue Q12W (±7 days). Others only as clinically indicated per local standards.										

Table 2-2: On Treatment - Schedule of Activities for Q4W Treatment Administration in Part 1A, Part 1B, Part 2A Arm E, Part 2A Arm F, and the Nivolumab Maintenance Phase of Part 2A Arms A and D

Procedure	Cycle 1 (28 Days in Length)				Cycle 2 (28 Days in Length)				Cycles 3[a] and Beyond (Each Cycle 28 Days in Length)	EOT[b,c]	Notes
	D1	D8 (± 2 days)	D15 (± 2 days)	D22 (± 2 days)	D1 (± 2 days)	D8 (± 2 days)	D15 (± 2 days)	D22 (± 2 days)	D1 (± 2 days)		
Biomarker Assessments											See Sections 9.5, 9.8, and Table 9.8.3-1.
On-treatment Tumor Biopsy	Part 1: Mandatory tumor biopsies must be performed at [redacted]; specimens may be collected within 3 days of the time point and must be obtained prior to administration of study treatments. Bone lesion biopsies are unacceptable for submission. See Table 9.8.3-1 Part 2A: The on-treatment biopsy will be collected on [redacted] for approximately the first 75 participants treated (about 25 participants per active Arm), and then collected per Investigator preference on [redacted] for approximately the next 105 participants treated (about 35 participants per active Arm). Specimens may be collected within 3 days of the time point. Bone lesion biopsies are unacceptable for submission. See Section 9.8.2 and Table 9.8.3-1.										.
Required Post-Progression Tumor Biopsy											See Section 9.8.2.
[redacted]											
Exploratory Biomarker Assessments											See Sections 9.5, 9.8, and Table 9.8.3-1.
Clinical Treatment Supplies											
Randomization	For Part 2A, randomization should occur no more than 7 business days prior to the first day of treatment on C1D1, unless otherwise agreed upon with the Medical Monitor (or designee).										Part 2A only. PD-L1 result is required for randomization.
BMS-986249 Planned Administration Q4W	X				X				X		Study treatments to be supplied by BMS.

Table 2-2: On Treatment - Schedule of Activities for Q4W Treatment Administration in Part 1A, Part 1B, Part 2A Arm E, Part 2A Arm F, and the Nivolumab Maintenance Phase of Part 2A Arms A and D

Procedure	Cycle 1 (28 Days in Length)				Cycle 2 (28 Days in Length)				Cycles 3[a] and Beyond (Each Cycle 28 Days in Length)	EOT[b,c]	Notes
	D1	D8 (± 2 days)	D15 (± 2 days)	D22 (± 2 days)	D1 (± 2 days)	D8 (± 2 days)	D15 (± 2 days)	D22 (± 2 days)	D1 (± 2 days)		
(Part 1A, Part 1B, and Part 2A Arm F)											Q8W treatments and requirements for Part 1A and Part 1B are outlined in Appendix 12.[g]
Nivolumab Administration Q4W (Part 1B, Part 2A Arm E, Arm F and the Maintenance Phase of Part 2A Arm A and Arm D)	X				X				X		Study treatments to be supplied by BMS.
Patient-reported Outcomes											Patient-reported outcomes for Part 2A participants only. See Section 9.9.
EORTC QLQ-C30	X				X				X	X	For C1D1, performed after randomization but prior to first dose. All other cycles collected prior to dosing.
EQ-5D-3L	X				X				X	X	For C1D1, performed after randomization but prior to first dose. All other cycles collected prior to dosing.
FACIT GP5	X	X	X	X	X	X	X	X	X	X	For C1D1, performed after randomization but prior to first

Table 2-2: On Treatment - Schedule of Activities for Q4W Treatment Administration in Part 1A, Part 1B, Part 2A Arm E, Part 2A Arm F, and the Nivolumab Maintenance Phase of Part 2A Arms A and D

Procedure	Cycle 1 (28 Days in Length)				Cycle 2 (28 Days in Length)				Cycles 3[a] and Beyond (Each Cycle 28 Days in Length)	EOT[b,c]	Notes
	D1	D8 (± 2 days)	D15 (± 2 days)	D22 (± 2 days)	D1 (± 2 days)	D8 (± 2 days)	D15 (± 2 days)	D22 (± 2 days)	D1 (± 2 days)		
											dose. All other cycles collected prior to dosing.
PRO-CTCAE	X	X	X	X	X	X	X	X	X	X	For C1D1, performed after randomization but prior to first dose. All other cycles collected prior to dosing.

Abbreviations: ADA = anti-drug antibody; AE = adverse event; BMS = Bristol Myers Squibb; CT = computed tomography; CXDY = Cycle X Day Y, as an example; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; EOT = end of treatment; EQ-5D-3L = European Quality of Life – 5 Dimension – 3 Level Questionnaire; FACIT GP5 = Functional Assessment of Chronic Illness Therapy General Physical item 5; hCG = human chorionic gonadotropin; MRI = magnetic resonance imaging; PCWG3 = Prostate Cancer Working Group 3; PD-L1 = programmed death ligand-1; PE = physical examination; PK = pharmacokinetic; PRO-CTCAE = Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; Q4W = every 4 weeks; Q8W = every 8 weeks; Q12W = every 12 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WOCBP = women of childbearing potential.

[a] For Part 2A Arm A and Arm D, the first dose of nivolumab monotherapy maintenance will be C5 of treatment, hence Table 2-2 activities should start under column “Cycles 3 and beyond.” For Part 2A Arm A and Arm D, C5 nivolumab monotherapy maintenance begins 3 weeks after C4 of the combination dose, refer to Table 2-3. Part 2A Arm A and Arm D participants who do not complete all scheduled combination therapy cycles will not be eligible for the nivolumab monotherapy Maintenance Phase and should enter follow-up (Table 2-5).

[b] EOT is defined as the visit where the decision is made to discontinue the participant from treatment. Evaluations will be performed prior to study discharge, or for participants who are prematurely discontinued.

[c] For participants who complete all scheduled cycles of therapy, the EOT visit will be the same as the last scheduled and completed on-treatment visit (eg, C26D1) and the start of the Safety Follow-up Period. For participants who do not complete all scheduled cycles of therapy, the EOT visit will be the most recent on-treatment visit (with all available safety and response data); it does not need to be repeated and will be considered as the start of the Safety Follow-up Period.

[d] For the first 3 infusions including BMS-986249 (C1D1, C2D1, and C3D1), vital signs will be obtained before the infusion and then every 15 minutes (± 5 minutes) until 60 minutes after completion of the infusion; oxygen saturation to also be performed in conjunction with vital signs monitoring on these days. For all infusions that do not include BMS-986249 and for all cycles after C3, vital signs and oxygen saturation are to be taken before the infusion and at the end of infusion. If any vital sign is abnormal (based upon clinician assessment) at the final check, the participant must be observed further for a period of time, as clinically indicated.

[e] ECGs should be recorded after the participant has been supine for at least 5 minutes and prior to blood draws. For Part 1A, triplicate ECGs are performed at predose and EOI on C1D1 and C4D1. Single predose safety ECGs to be performed for all other time points For Part 1B, single predose ECGs are performed for all time points and also at EOI for C1D1 and C4D1. For Part 2A, single predose ECGs at all time points. See Section 9.4.3.

[f] Serum/urine to be collected within 24 hours prior to dosing. Pregnancy test may be completed on the first day of treatment, provided the results are available before the start of study therapy. Serum or urine pregnancy test must be performed within 24 hours prior to administration of study treatment (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG).

[g] Refer to Appendix 12 (if applicable) for potential alternative schedules that may be explored in Part 1 following evaluation of preliminary safety, PK, and [redacted] data. Decisions to initiate exploration of these alternative dose schedules will be made after discussion and agreement between the Investigators and the Medical Monitor (or designee). Implementation of these alternative dose schedules will not include the addition of new procedures and will be documented in a note to file or administrative letter.

Table 2-3: On Treatment - Schedule of Activities for Part 2A Arm A and Arm D Combination Therapy Phase

Procedure	Study Treatment Every 3 Weeks for 4 Cycles			EOT[b,c]	Notes
	Cycle 1, 2, 3, 4 (each cycle 21 days in length)[a,c]				
	D1	D8 (± 2 days)	D15 (± 2 days)		
Safety Assessments					
PE, Weight, and ECOG Performance Status	X			X	
Symptom Directed PE		X	X		
Vital Signs[d]	X	X	X	X	Includes body temperature, respiratory rate, blood pressure and heart rate.
Oxygen Saturation[d]	X				
ECG	X			X	ECGs should be recorded after the participant has been supine for at least 5 minutes and prior to blood draws. Single safety ECGs to be done prior to each infusion for all treatment cycles.
Laboratory Tests	X	X	X	X	To be performed onsite/locally. There will be a 72-hour window for collection of laboratory tests on D1. If laboratory tests performed at screening are within 72 hours of C1D1, then they can also be used for C1D1. Coagulation assessment at screening only. See Section 9.4.4 and Table 9.4.4-1.
Urinalysis	X			X	For C3 and C4, as clinically indicated; microscopic urine reflex only for urinalysis positive for blood/protein/ leukocyte esterase. See Section 9.4.4 and Table 9.4.4-1.
Pregnancy Test (WOCBP only)[e]	X			X	See Section 9.4.4 and Table 9.4.4-1.

Table 2-3: On Treatment - Schedule of Activities for Part 2A Arm A and Arm D Combination Therapy Phase

Procedure	Study Treatment Every 3 Weeks for 4 Cycles			EOT[b,c]	Notes
	Cycle 1, 2, 3, 4 (each cycle 21 days in length)[a,c]				
	D1	D8 (± 2 days)	D15 (± 2 days)		
Adverse Event Reporting and Concomitant Medication Assessments					
Monitor for Non-SAEs	For all study participants, safety reporting of all AEs (non SAEs and SAEs) should take place from date of informed consent through 100 days post EOT.				All AEs (SAEs or non-serious AEs), including those associated with SARS-CoV-2 infection must be collected from date of informed consent through 100 days post EOT. See Appendix 3 and Section 9.2.
AE Assessment	For all study participants, safety reporting of all AEs (non SAEs and SAEs) should take place from date of informed consent through 100 days post EOT.				
Concomitant Medications	X	X	X	X	
PK Assessments					
Serial Blood Sampling	See Section 9.5,Table 9.5-4 and Table 9.5-9 for the PK sampling schedule.				Refer to outlined protocol sections for all required collections.
Immunogenicity (ADA) Assessments	See Section 9.5, Table 9.5-4and Table 9.5-6 for the immunogenicity sampling schedule.				Refer to outlined protocol sections for all required collections.
[redacted]					
Imaging Assessments					
Body Imaging	The first tumor imaging assessment should occur 12 weeks (±7 days) from first dose. Subsequent tumor imaging assessments should occur Q8W (± 7 days) from the date of the first tumor imaging assessment until Week 52 then continue Q12W (±7 days) thereafter. See Section 9.1.1.				The same imaging modality is to be used for all assessments, per RECIST v1.1. See Appendix 5. Tumor assessment to be performed prior to initiating next cycle of treatment.
Brain Imaging	Participants with history of brain metastasis should have surveillance MRI performed approximatelyQ12W or sooner if clinically indicated. CT of the brain without and with contrast can be performed if MRI is contraindicated. See Section 9.1.1.				

Table 2-3: On Treatment - Schedule of Activities for Part 2A Arm A and Arm D Combination Therapy Phase

Procedure	Study Treatment Every 3 Weeks for 4 Cycles Cycle 1, 2, 3, 4 (each cycle 21 days in length)[a,c]			EOT[b,c]	Notes
	D1	D8 (± 2 days)	D15 (± 2 days)		
Other: Bone Scan	See Section 9.1.1.Only as clinically indicated per local standards.				
Biomarker Assessments					See Sections 9.5 and 9.8, and Table 9.8.3-1.
On-Treatment Tumor Biopsy	For Part 2A, the on-treatment biopsy will be collected on [redacted] for approximately the first 75 participants treated (about 25 participants per active Arm), and then collected per Investigator preference on [redacted] or [redacted] for approximately the next 105 participants treated (about 35 participants per active Arm).Specimens may be collected within 3 days of the time point. Bone lesion biopsies are unacceptable for submission. See Table 9.8.3-1.				
Required Post-progression Tumor Biopsy					See Section 9.8.2.
[redacted]					
Exploratory Biomarker Assessments					See Sections 9.5 and 9.8 and Table 9.8.3-1 for all required collections.
Clinical Treatment Supplies					
Randomization	Randomization should occur no more than 7 business days prior to the first day of treatment on C1D1, unless otherwise agreed upon with the Medical Monitor (or designee).				PD-L1 result is required for randomization.
BMS-986249 Administration Q3W (Part 2A Arm A Combination Therapy Phase)	X				BMS-986249 to be supplied by BMS. BMS-986249 to be administered for up to a maximum of 4 doses.

Table 2-3: On Treatment - Schedule of Activities for Part 2A Arm A and Arm D Combination Therapy Phase

Procedure	Study Treatment Every 3 Weeks for 4 Cycles			EOT[b,c]	Notes
	Cycle 1, 2, 3, 4 (each cycle 21 days in length)[a,c]				
	D1	D8 (± 2 days)	D15 (± 2 days)		
Ipilimumab Administration Q3W (Part 2A Arm D Combination Therapy Phase)	X				Ipilimumab to be supplied by BMS. Ipilimumab to be administered for up to a maximum of 4 doses.
Nivolumab Administration Q3W (Part 2A Arm A and Arm D Combination Therapy Phase)[c]	X				Nivolumab to be supplied by BMS.
Patient-Reported Outcomes					See Section 9.9
EORTC QLQ-C30	X			X	For C1D1, performed after randomization but prior to first dose. All other cycles collected prior to dosing.
EQ-5D-3L	X			X	For C1D1, performed after randomization but prior to first dose. All other cycles collected prior to dosing.
FACIT GP5	X	X	X	X	For C1D1, performed after randomization but prior to first dose. All other cycles collected prior to dosing.
PRO-CTCAE	X	X	X	X	For C1D1, performed after randomization but prior to first dose. All other cycles collected prior to dosing.

Abbreviations: ADA = anti-drug antibody; AE = adverse event; BMS = Bristol Myers Squibb; C= cycle; CT = computed tomography; CXDY = Cycle X Day Y, as an example; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; EOT = end of treatment; EQ-5D-3L = European Quality of Life – 5 Dimension – 3 Level Questionnaire; FACIT GP5 = Functional Assessment of Chronic Illness Therapy General Physical item 5; hCG = human chorionic gonadotropin; MRI = magnetic resonance imaging; PD-L1 = programmed death ligand-1; PE = physical examination; PK = pharmacokinetic; PRO-CTCAE = Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; Q3W = every 3 weeks; Q8W = every 8 weeks; Q12W = every 12 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WOCBP = women of childbearing potential.

[a] Participants may be treated no less than 19 days between doses.

[b] EOT is defined as the visit where the decision is made to discontinue the participant from treatment. Evaluations will be performed only for participants who are prematurely discontinued (eg, do not complete all 4 planned combination treatment cycles). The EOT visit will be the most recent on-treatment visit (with all available safety and response data); it does not need to be repeated and will be considered as the start of the Safety Follow-up Period.

[c] Participants who complete all 4 scheduled cycles of BMS-986249 or ipilimumab in combination with nivolumab therapy will move to the nivolumab monotherapy Maintenance Phase (Table 2-2), beginning 3 weeks after the Cycle 4 BMS-986249 or ipilimumab in combination with nivolumab dose. The first dose of nivolumab monotherapy maintenance will be C5 of treatment (Table 2-2).

[d] For the first 3 infusions including BMS-986249 (C1D1, C2D1, and C3D1), vital signs will be obtained before the infusion and then every 15 minutes (± 5 minutes) until 60 minutes after completion of the infusion; oxygen saturation to also be performed in conjunction with vital signs monitoring on these days. For C4D1 and beyond, vital signs and oxygen saturation are to be taken before the infusion and at the end of infusion. If any vital sign is abnormal (based upon clinician assessment) at the final check, the participant must be observed further for a period of time, as clinically indicated.

[e] Serum/urine to be collected within 24 hours prior to dosing. Pregnancy test may be completed on the first day of treatment, provided the results are available before the start of study therapy. Serum or urine pregnancy test must be performed within 24 hours prior to administration of study treatment (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG).

Table 2-4: On-treatment Schedule of Activities for Part 2A Arm B and Arm C, and Part 2B

Procedure	Cycle 1 (28 days in length)				Cycle 2 (28 days in length)				Cycles 3 and Beyond (each cycle 28 days in length)	EOT[a,b]	Notes
	D1	D8	D15	D22	D1	D8	D15	D22	D1		
		(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)		
Safety Assessments											
PE, Weight, and ECOG Performance Status	X				X				X	X	
Symptom-directed PE		X	X	X		X	X	X			
Child-Pugh Score	X				X				X	X	For HCC participants only. See Appendix 13.
Vital Signs[c]	X	X	X	X	X	X	X	X	X	X	Includes body temperature, respiratory rate, blood pressure and heart rate.
Oxygen Saturation[c]	X				X				X		
ECG	X				X				X	X	ECGs should be recorded after the participant has been supine for at least 5 minutes and prior to blood draws. Single safety ECGs to be done prior to each infusion for all treatment cycles.

Table 2-4: On-treatment Schedule of Activities for Part 2A Arm B and Arm C, and Part 2B

Procedure	Cycle 1 (28 days in length)				Cycle 2 (28 days in length)				Cycles 3 and Beyond (each cycle 28 days in length)	EOT[a,b]	Notes
	D1	D8 (± 2 days)	D15 (± 2 days)	D22 (± 2 days)	D1 (± 2 days)	D8 (± 2 days)	D15 (± 2 days)	D22 (± 2 days)	D1 (± 2 days)		
Laboratory Tests	X	X	X	X	X	X	X	X	X	X	To be performed onsite/locally. There will be a 72-hour window for collection of laboratory tests on D1. If screening laboratory tests are within 72 hours of C1D1, laboratory tests performed at screening can be used for C1D1. PT/INR and aPTT required on D1 for HCC and CRPC participants; for all others, coagulation assessment at screening only. See Section 9.4.4 and Table 9.4.4-1.
Urinalysis	X				X				As clinically indicated; microscopic urine reflex only for urinalysis positive for blood/ protein/ leukocyte esterase.	X	See Section 9.4.4 and Table 9.4.4-1. There will be a 72-hour window for collection of laboratory tests on D1

Table 2-4: On-treatment Schedule of Activities for Part 2A Arm B and Arm C, and Part 2B

Procedure	Cycle 1 (28 days in length)				Cycle 2 (28 days in length)				Cycles 3 and Beyond (each cycle 28 days in length)	EOT[a,b]	Notes
	D1	D8 (± 2 days)	D15 (± 2 days)	D22 (± 2 days)	D1 (± 2 days)	D8 (± 2 days)	D15 (± 2 days)	D22 (± 2 days)	D1 (± 2 days)		
Alpha-fetoprotein	X				X				X	X	For HCC participants only. To be performed onsite/locally with laboratory tests. There will be a 72-hour window for collection of laboratory tests on D1. See Section 9.4.1 and Table 9.4.4-1.
Viral Markers	X				X				X	X	For HCC participants only. To be completed at central laboratory. For HCV infected; HCV RNA. For HBV infected; HBV DNA. There will be a 72-hour window for collection of laboratory tests on D1. See Section 9.4.4 and Table 9.4.4-1.
PSA	X				X				X	X	For CRPC participants only. If screening PSA is within 72 hours of C1D1, laboratory tests performed at screening can be used for C1D1. There will be a 72-hour window for collection of laboratory tests on D1. Performed onsite/locally D1 of C1 to

Table 2-4: On-treatment Schedule of Activities for Part 2A Arm B and Arm C, and Part 2B

Procedure	Cycle 1 (28 days in length)				Cycle 2 (28 days in length)				Cycles 3 and Beyond (each cycle 28 days in length)	EOT[a,b]	Notes
	D1	D8 (± 2 days)	D15 (± 2 days)	D22 (± 2 days)	D1 (± 2 days)	D8 (± 2 days)	D15 (± 2 days)	D22 (± 2 days)	D1 (± 2 days)		
											C5 (prior to treatment), then D1 of every odd-numbered cycle (C7, C9, C11, etc). See Section 9.4.4 and Table 9.4.4-1.
Testosterone									X	X	For CRPC participants only. Performed onsite/locally at start of C7, then every fourth cycle starting with C11D1 until EOT (C11D1, C15D1, C19D1, etc.). See Section 9.4.4 and Table 9.4.4-1.

Table 2-4: On-treatment Schedule of Activities for Part 2A Arm B and Arm C, and Part 2B

Procedure	Cycle 1 (28 days in length)				Cycle 2 (28 days in length)				Cycles 3 and Beyond (each cycle 28 days in length)	EOT[a,b]	Notes
	D1	D8 (± 2 days)	D15 (± 2 days)	D22 (± 2 days)	D1 (± 2 days)	D8 (± 2 days)	D15 (± 2 days)	D22 (± 2 days)	D1 (± 2 days)		
Pregnancy Test (WOCBP only)[d]	X				X				X	X	See Section 9.4.4 and Table 9.4.4-1.
Adverse Event Reporting and Concomitant Medication Assessments											
Monitor for Non-SAEs	For all study participants, safety reporting for non SAEs should take place from date of informed consent through 100 days post EOT.										For all participants, all AEs (SAEs or non-serious AEs), including those associated with SARS-CoV-2 infection, must be collected from the date of the participant's written consent through 100 days following EOT (Safety Follow up). See Appendix 3 and Section 9.2.
Monitor for SAEs	For all study participants, safety reporting of SAEs should take place from date of informed consent through 100 days post EOT.										
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	Including antiviral therapy for HCC participants.
PK Assessments											
Serial Blood Sampling	See Section 9.5, Table 9.5-5 and Table 9.5-9 for the PK sampling schedule.										Refer to outlined protocol sections for all required collections.
Immunogenicity (ADA) Assessments	See Section 9.5, Table 9.5-5 and Table 9.5-9 for the immunogenicity sampling schedule.										Refer to outlined protocol sections for all required collections.

Table 2-4: On-treatment Schedule of Activities for Part 2A Arm B and Arm C, and Part 2B

Procedure	Cycle 1 (28 days in length)				Cycle 2 (28 days in length)				Cycles 3 and Beyond (each cycle 28 days in length)	EOT[a,b]	Notes
	D1	D8	D15	D22	D1	D8	D15	D22	D1		
		(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)		
[redacted]											
Imaging Assessments											
Body Imaging	See Section 9.1.1. Additional imaging may be performed as clinically indicated. For Part 2A: The first tumor imaging assessment should occur 12 weeks (± 7 days) from first dose. Subsequent tumor imaging assessments should occur Q8W (±7 days) from the date of the first tumor imaging assessment until Week 52 then continue Q12W (±7 days) thereafter. For Part 2B: Tumor imaging assessments should occur Q8W starting from the first dose (±7 days) up until Week 48, and then continue Q12W (±7 days) thereafter. For participants with HCC, a triphasic CT/MRI of the liver is required. For participants with TNBC without measurable lesions outside of the breast, contrast-enhanced MRI of the breasts should be performed along with body imaging.										The same imaging modality is to be used for all assessments, per RECIST v1.1. See Appendix 5. Tumor assessment to be performed prior to initiating next cycle of treatment.
Brain Imaging	See Section 9.1.1. Participants with history of brain metastasis should have surveillance MRI performed approximately Q12W or sooner if clinically indicated. CT of the brain without and with contrast can be performed if MRI is contraindicated.										
Other: Bone Scan	See Section 9.1.1. For CRPC participants, should occur Q8W starting from the first dose (± 7 days) up until Week 48, and then continue Q12W (±7 days) or until disease progression is assessed by the investigator or treatment is discontinued (whichever occurs later). Evidence of progressive disease as per PCWG3 (Appendix 6). All other participants only as clinically indicated per local standards.										
Biomarker Assessments											See Sections 9.5, 9.8, and Table 9.8.3-1 for all required collections

Table 2-4: On-treatment Schedule of Activities for Part 2A Arm B and Arm C, and Part 2B

Procedure	Cycle 1 (28 days in length)				Cycle 2 (28 days in length)				Cycles 3 and Beyond (each cycle 28 days in length)	EOT[a,b]	Notes
	D1	D8	D15	D22	D1	D8	D15	D22	D1		
		(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)		
On-treatment Tumor Biopsy	For Part 2A: The on-treatment biopsy will be collected on [redacted] for approximately the first 75 participants treated (about 25 participants per active Arm), and then collected per Investigator preference on [redacted] or [redacted] for approximately the next 105 participants treated (about 35 participants per active Arm). For Part 2B: The on-treatment biopsy will be collected on [redacted]. Specimens may be collected within 3 days of the time point. Bone lesion biopsies are unacceptable for submission. See Table 9.8.3-1.										
Required Post-progression Tumor Biopsy											See Section 9.8.2
[redacted]											
Exploratory Biomarker Assessments											See Sections 9.5, 9.8, and Table 9.8.3-1 for all required collections.
Clinical Treatment Supplies											
Randomization	For Part 2A, randomization should occur no more than 7 business days prior to the first day of treatment on Cycle 1 Day 1, unless otherwise agreed upon with the Medical Monitor (or designee).										For Part 2A, PD-L1 result required for randomization.

Table 2-4: On-treatment Schedule of Activities for Part 2A Arm B and Arm C, and Part 2B

Procedure	Cycle 1 (28 days in length)				Cycle 2 (28 days in length)				Cycles 3 and Beyond (each cycle 28 days in length)	EOT[a,b]	Notes
	D1	D8 (± 2 days)	D15 (± 2 days)	D22 (± 2 days)	D1 (± 2 days)	D8 (± 2 days)	D15 (± 2 days)	D22 (± 2 days)	D1 (± 2 days)		
BMS-986249 Administration Q8W (Part 2A Arm B and Arm C, and Part 2B)	X								X Every other cycle starting at C3 [eg, C3, C5, C7, etc]		BMS-986249 to be supplied by BMS.
Nivolumab Administration Q4W (Part 2A Arm B and Arm C, and Part 2B)	X				X				X		Nivolumab to be supplied by BMS.
Patient-Reported Outcomes											See Section 9.9
EORTC QLQ-C30	X				X				X	X	For C1D1, performed after randomization but prior to first dose. All other cycles collected prior to dosing.
EQ-5D-3L	X				X				X	X	For C1D1, performed after randomization but prior to first dose. All other cycles collected prior to dosing.
FACIT GP5	X	X	X	X	X	X	X	X	X	X	For C1D1, performed after randomization but prior to first dose. All other cycles collected prior to dosing.

Table 2-4: On-treatment Schedule of Activities for Part 2A Arm B and Arm C, and Part 2B

Procedure	Cycle 1 (28 days in length)				Cycle 2 (28 days in length)				Cycles 3 and Beyond (each cycle 28 days in length)	EOT[a,b]	Notes
	D1	D8 (± 2 days)	D15 (± 2 days)	D22 (± 2 days)	D1 (± 2 days)	D8 (± 2 days)	D15 (± 2 days)	D22 (± 2 days)	D1 (± 2 days)		
PRO-CTCAE	X	X	X	X	X	X	X	X	X	X	For C1D1, performed after randomization but prior to first dose. All other cycles collected prior to dosing.

Abbreviations: ADA = anti-drug antibody; AE = adverse event; aPTT = activated partial thromboplastin time; BMS = Bristol Myers Squibb; C = cycle; CRPC = castration-resistant prostate cancer; CT = computed tomography; CXDY = Cycle X Day Y, as an example; D = day; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; EOT = end of treatment; EQ-5D-3L = European Quality of Life – 5 Dimension – 3 Level Questionnaire; FACIT GP5 = Functional Assessment of Chronic Illness Therapy General Physical item 5; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; INR = international normalized ratio; MRI = magnetic resonance imaging; PCWG3 = Prostate Cancer Working Group 3; PD-L1 = programmed death ligand-1; PE = physical examination; PK = pharmacokinetic; PRO-CTCAE = Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; PSA = prostate-specific antigen; PT = prothrombin time; Q4W = every 4 weeks; Q8W = every 8 weeks; Q12W = every 12 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; RNA = ribonucleic acid; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TNBC = triple-negative breast cancer; WOCBP = women of childbearing potential.

[a] EOT is defined as the visit where the decision is made to discontinue the participant from treatment. Evaluations will be performed prior to study discharge, or for participants who are prematurely discontinued.

[b] For participants who complete all scheduled cycles of therapy, the EOT visit will be the same as the last scheduled and completed on-treatment visit (eg, C26D1) and the start of the Safety Follow-up Period. For participants who do not complete all scheduled cycles of therapy, the EOT visit will be the most recent on-treatment visit (with all available safety and response data); it does not need to be repeated and will be considered as the start of the Safety Follow-up Period.

[c] Vital signs will be obtained before the first 3 infusions including BMS-986249 (C1D1, C3D1, and C5D1) and then every 15 minutes (± 5 minutes) until 60 minutes after completion of the infusion; oxygen saturation to also be performed in conjunction with vital signs monitoring on these days. For all cycles after C5 and for the nivolumab monotherapy infusions, vital signs and oxygen saturation are to be taken before the infusion and at the end of infusion. If any vital sign is abnormal (based upon clinician assessment) at the final check, the participant must be observed further for a period of time, as clinically indicated.

[d] Serum/urine to be collected within 24 hours prior to dosing. Pregnancy test may be completed on the first day of treatment, provided the results are available before the start of study therapy. Serum or urine pregnancy test must be performed within 24 hours prior to administration of study treatment (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG).

Table 2-5: Follow-up Procedural Outline for All Study Parts

Procedure	Safety Follow-up			Imaging Follow-up	Survival Follow-up	Notes
	Follow-up 1 30 Days[a] (± 7 Days)	Follow-up 2 60 Days[a] (± 7 Days)	Follow-up 3 100 Days[a] (± 7 Days)			
Safety Assessments						
PE and Vital Signs	X	X	X			Includes body temperature, seated/supine blood pressure, and heart rate.
Laboratory Tests	X	X	X			To be performed onsite/locally. Laboratory tests also as clinically indicated; PT/INR and aPTT required for HCC and CRPC participants; for all others, coagulation assessment at screening only. For details of laboratory assessments, see Section 9.4.4 and Table 9.4.4-1.
Urinalysis	As clinically indicated. See Section 9.4.4.					
Alpha-fetoprotein	X	X	X			For participants with HCC only. To be performed onsite/locally with laboratory tests. See Section 9.4.4 and Table 9.4.4-1.
Pregnancy Test	X	X	X			For WOCBP, serum/urine pregnancy test is to be performed (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG). See Section 9.2.5, Section 9.4.4 and Table 9.4.4-1.

Table 2-5: Follow-up Procedural Outline for All Study Parts

Procedure	Safety Follow-up			Imaging Follow-up	Survival Follow-up	Notes
	Follow-up 1 30 Days[a] (± 7 Days)	Follow-up 2 60 Days[a] (± 7 Days)	Follow-up 3 100 Days[a] (± 7 Days)			
Viral Markers	X	X	X			For participants with HCC only. To be completed at central laboratory. For HCV-infected; HCV RNA. For HBV-infected; HBV DNA. See Section 9.4.4 and Table 9.4.4-1.
PSA	For participants with CRPC only. To be performed onsite/locally. PSA performed Q8W (± 7 days) in follow-up until radiographic progression or the start of subsequent systemic cancer therapy, whichever occurs later. PSA evaluation beyond radiographic progression or the start of subsequent systemic cancer therapy to confirm PSA response or PSA progression should be performed as needed.					
Adverse Event Reporting and Concomitant Medication Assessments						
Monitor for Non-SAEs[b]	X	X	X			For all study participants, safety reporting of AEs and SAEs should take place from date of informed consent through 100 days post EOT.
Monitor for SAEs[b]	X	X	X			For all study participants, safety reporting of AEs and SAEs should take place from date of informed consent through 100 days post EOT.
Concomitant Medication Assessments	X	X	X			Including antiviral therapy for HCC participants.

Table 2-5: Follow-up Procedural Outline for All Study Parts

Procedure	Safety Follow-up			Imaging Follow-up	Survival Follow-up	Notes
	Follow-up 1 30 Days[a] (± 7 Days)	Follow-up 2 60 Days[a] (± 7 Days)	Follow-up 3 100 Days[a] (± 7 Days)			
Sample Collection						See Section 9.5, and Table 9.5-2 through Table 9.5-9 for the sample collection schedule.
Efficacy Assessments						
Tumor/Response Assessments	Part 1: Tumor assessments should occur Q12W (± 7 days), starting from the date of the last on-treatment tumor assessment. Part 2A: The first tumor imaging assessment should occur 12 weeks (± 7 days) from first dose. Subsequent tumor imaging assessments should occur Q8W (±7 days) from the date of the first tumor imaging assessment until Week 52 then continue Q12W (±7 days) thereafter. For Part 2B: Tumor imaging assessments should occur Q8W starting from the first dose (±7 days) up until Week 48, and then continue Q12W (± 7 days). For participants with HCC, a triphasic CT/MRI of the liver is required. For participants with TNBC without measurable lesions outside of the breast, contrast-enhanced MRI of the breasts should be performed along with body imaging. For all study parts: The duration of the Imaging Follow-up Period will be 100 days post EOT, or until initiation of another anti-cancer treatment, or death, whichever occurs first. See Section 9.1.1.					
Brain Imaging	Participants with history of brain metastasis should have surveillance MRI performed approximately Q12W or sooner if clinically indicated. CT of the brain without and with contrast can be performed if MRI is contraindicated. See Section 9.1.1.					
Other: Bone Scan	Required for participants with prostate cancer only (PCWG3 Assessment). Should occur Q8W starting from the first dose (±7 days) up until Week 48, and then continue Q12W (±7 days) until disease progression is assessed by the investigator. Others only as clinically indicated per local standards. See Section 9.1.1.					
Subsequent Treatments (Anti-cancer)	X	X	X		X	

Table 2-5: Follow-up Procedural Outline for All Study Parts

Procedure	Safety Follow-up			Imaging Follow-up	Survival Follow-up	Notes
	Follow-up 1 30 Days[a] (± 7 Days)	Follow-up 2 60 Days[a] (± 7 Days)	Follow-up 3 100 Days[a] (± 7 Days)			
Assessment of Participant Survival Status	X	X	X		X	Participant status will be assessed by any documented clinic visit, email, or telephone contact through 100 days post EOT.
Patient-Reported Outcomes						Patient-reported outcomes for Part 2A and 2B participants only. See Section 9.9.
EORTC QLC-C30	X	X	X			
EQ-5D-3L	X	X	X		X	Can be collected via telephone or email during assessment of participant survival status.
FACIT GP5	X	X	X			
PRO-CTCAE	X	X	X			

Abbreviations: ADA = anti-drug antibody; AE = adverse event; aPTT = activated partial thromboplastin time; CRPC = castration-resistant prostate cancer; CT = computed tomography; DNA = deoxyribonucleic acid; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; EOT = end of treatment; EQ-5D-3L = European Quality of Life – 5 Dimension – 3 Level Questionnaire; FACIT GP5 = Functional Assessment of Chronic Illness Therapy General Physical item 5; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; INR = international normalized ratio; MRI = magnetic resonance imaging; PCWG3 = Prostate Cancer Working Group 3; PE = physical examination; PRO-CTCAE = Patient-reported Outcomes version of the Common Terminology Criteria for Adverse Events; PSA = prostate-specific antigen; PT = prothrombin time; Q8W = every 8 weeks; Q12W = every 12 weeks; RNA = ribonucleic acid; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TNBC = triple-negative breast cancer; WOCBP = women of childbearing potential.

[a] Follow-up visits at Days 30 (±7 days), 60 (±7 days), and 100 (±7 days) should occur relative to the last dose of study treatment or date of discontinuation, whichever is later.

[b] Participants will be followed for all SAEs, non-serious AEs of special interest (as defined in Section 9.2), and all AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection until resolution, the condition stabilizes, the event is otherwise explained, the event is deemed irreversible, the participant is lost to follow-up (as defined in Section 8.3), or for suspected cases, until SARS-CoV-2 infection is ruled out.

3 INTRODUCTION

Ipilimumab is a fully human monoclonal antibody (mAb) that binds the negative immunoregulatory protein, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). Treatment with ipilimumab as a monotherapy or in combination with nivolumab (an anti-programmed cell death protein 1) [PD-1] mAb) results in clinically meaningful anti-tumor activity in several malignancies; however, it is also associated with a high frequency of immune-related adverse events (irAEs). Strategies to reduce the frequency and severity of ipilimumab-associated irAEs while preserving anti-tumor activity could improve the benefit/risk of ipilimumab-containing treatment regimens.

3.1 Study Rationale

Anti-CTLA-4 (ipilimumab) and anti-PD-1 (nivolumab) are approved immunotherapies for the treatment of select malignancies. Ipilimumab was the first immunotherapy to show a survival advantage in late-stage metastatic melanoma and has also demonstrated a significant 25% reduction in risk of recurrence or death in the adjuvant treatment in melanoma. Blockade of CTLA-4 by ipilimumab has demonstrated anti-tumor activity in other malignancies, including lung cancer, prostate cancer, and renal cell carcinoma (RCC). Ipilimumab is also approved and in clinical development in combination with nivolumab. The combination was associated with a greater benefit in melanoma compared to each single agent and is currently under evaluation in several malignancies, including non-small cell lung cancer (NSCLC). The activation of a pre-existing but attenuated immune response to cancer by checkpoint blockade is associated with an adverse event (AE) profile that is inherent to immune activation. Ipilimumab treatment-related AEs (TRAEs) can involve multiple organ systems (digestive, skin, and endocrine) and can require cessation of drug and treatment with corticosteroids. The combination regimen is associated with an increased incidence of AEs compared to nivolumab monotherapy but a similar overall AE profile. Strategies to reduce the frequency and severity of ipilimumab-associated irAEs while preserving anti-tumor activity could improve the benefit-risk of ipilimumab-containing treatment regimens.

BMS-986249 is an anti-CTLA-4 Probody™ (PROBODY is a trademark of CytomX Therapeutics, Inc.) mAb. The Probody is made by the addition of 44 amino acids to the N-terminus of both light chains of the human anti-CTLA-4 antibody (Ab) ipilimumab. BMS-986249 contains a masking peptide with a cleavable linker containing protease cleavable sites for specific enzymes that are more prevalent and/or active in tumors than in peripheral tissues. Probody therapeutics are prodrug forms of mAb-based therapeutics. Similar to prodrug strategies that have been successfully applied to small-molecule pharmaceuticals, the premise of the “Probody technology” is to create mAbs that are administered in a form that has significantly reduced ability to bind to a mAb’s cognate antigen and maintains this form while in circulation and when encountering normal healthy tissue. The Probody therapeutic is designed to be activated by proteolytic cleavage at specific sites in the Probody sequence upon encountering proteases predominantly present in the tumor microenvironment. In this way, Probody therapeutics have the potential to minimize toxicities due to limited interaction of the administered (“prodrug”) form of the drug with its target in healthy tissues and to maintain efficacy due to interaction of protease-activated drug with its target in

tumors. By widening the therapeutic window, Probody therapeutics are expected to be most useful for therapies whose clinical utility is limited by significant on-target toxicities caused by antibody binding to targets outside of the tumor. This serves as the basis for BMS-986249, the Probody version of ipilimumab.

The properties of BMS-986249 ipilimumab Probody mAb are summarized below:

- Decreased binding to human CTLA-4 protein (masking efficiency [ME] of 50X)
- Comparable binding to CTLA-4 protein after protease cleavage
- At least equivalent anti-tumor activity to ipilimumab in mouse tumor models
- Decreased peripheral activity compared to ipilimumab based on activation of extratumoral regulatory T cells (Tregs)

Based on this unique mechanism of action, this study will evaluate the safety and preliminary efficacy of BMS-986249 alone and in combination with nivolumab.

3.2 Background

A detailed description of the chemistry, pharmacology, efficacy, and safety of BMS-986249 is provided in the Investigator's Brochure (IB).

3.2.1 BMS-986249

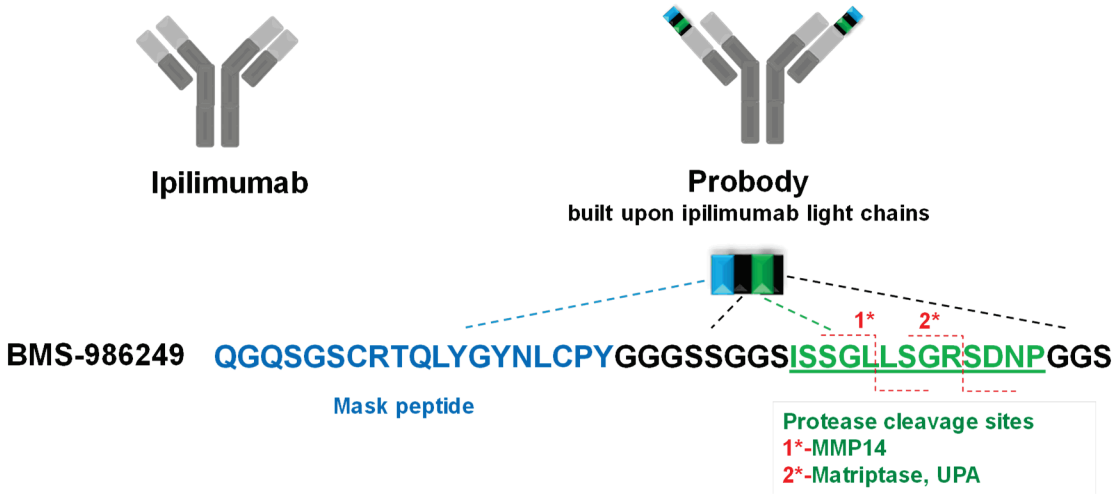
Developing a second generation anti-CTLA–4 Ab that reduces the risk of autoimmune side effects has the potential to greatly improve the benefit-risk profile of anti-CTLA–4 therapy by either improving the safety profile with maintenance of comparable efficacy and/or maintaining the safety but at a higher dose that drives increased efficacy. This is especially important given that the combination therapy of ipilimumab and nivolumab in participants with metastatic melanoma has demonstrated improved progression-free survival (PFS) compared to monotherapy with either Ab,[1] but with an increase in Grade 3-4 AEs that have led to treatment discontinuations. Nevertheless, the added benefit has prompted testing of this combination in multiple tumor types such as RCC, NSCLC, small cell lung cancer (SCLC), colorectal cancer (CRC) (microsatellite instability high [MSI-H]), and glioblastoma multiforme. Tolerability of the combination may depend on tumor type and, in some cases, be improved by changes in the dose or regimen of the combination.[2]

The Probody approach developed by CytomX offers an appealing strategy to address the systemic toxicity associated with anti-CTLA–4 Ab therapy. This system takes advantage of the increased protease activity present in tumors to cleave a proform or "Probody" of an Ab and convert it into an active Ab. Probody generation requires the addition of a masking peptide with a cleavable linker containing protease sites for specific enzymes that are more prevalent and/or active in tumors. The specific mask is derived from an in vitro panning approach where peptides that block antigen recognition by the Ab are identified. The linker is preferentially cleaved enzymatically at the tumor site owing to increased protease activity in the tumor microenvironment relative to those activities in normal tissue (periphery). This preferential binding and activity should result in an improved

therapeutic index as compared to the parental ipilimumab, which can bind its target throughout the body.

The Probody version of ipilimumab is shown in Figure 3.2.1-1. Briefly, the Probody mAb consists of the ipilimumab light chain with an amino terminal addition of a linker sequence containing matric metalloproteinase (MMP) and serine protease sites followed by a flexible serine-glycine linker before a masking peptide that binds to the antigen binding domain of the Ab. If the Probody mAb can maintain activity at the tumor site and reduce peripheral systemic exposure to drug, this should result in an improved therapeutic index as compared to ipilimumab. This hypothesis does rely on the assumption that the anti-tumor activity of ipilimumab is only mediated by target binding at the tumor site or the tumor draining lymph node and does not require binding to CTLA-4 on T cells in peripheral lymphoid organs. A second assumption is that peripheral and not tumor target binding leads to the AEs seen after ipilimumab treatment.

Figure 3.2.1-1: Schematic of BMS-986249



Abbreviations: MMP14 = matrix metalloproteinase-14; UPA = urokinase-type plasminogen activator.

3.2.1.1 Generation of an Anti-human CTLA-4 Probody mAb

Lead Antibody Selection

Since ipilimumab has already been approved for the treatment of human tumors, this anti-CTLA- 4 Ab has been chosen as the basis for a Probody version with reduced target binding capabilities outside of the tumor site. The Sponsor has partnered with CytomX to use their Probody mAb approach, which takes advantage of increased protease activity in tumor tissues to remove a masking peptide and reveal the antigen binding site of the Ab.

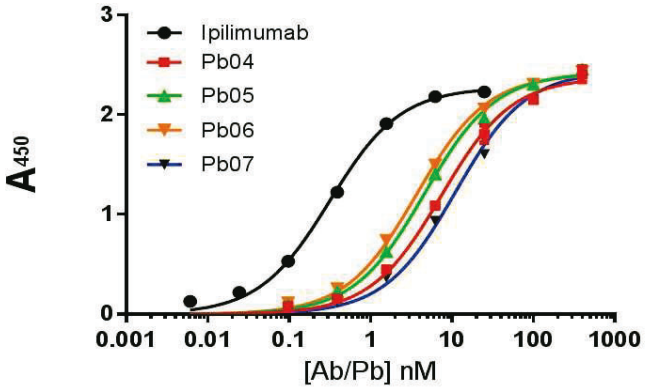
The Probody Approach: Masking Peptide and Cleavable Linker

In the Probody mAb approach, 2 parameters are critical to determining the efficacy and safety of the Probody mAb in comparison to the unaltered parental Ab. The first is the masking peptide that binds to the antigen binding site of the Ab and reduces antigen binding. Masking peptides with

varying affinities for the Ab can be produced and tested for binding to the target, CTLA-4. ME is calculated based on comparing the binding of the masked Ab to the parental Ab to antigen. This can be done either by enzyme-linked immunosorbent assay (ELISA) or by staining target expressing cells. MEs are then determined as the fold change in the half-maximal effective concentration (EC50) of the Probody mAb compared to the parental Ab, with higher MEs representing lower affinity for target. Based on CytomX's experience, probodies with MEs of 20-50X were initially selected for testing.

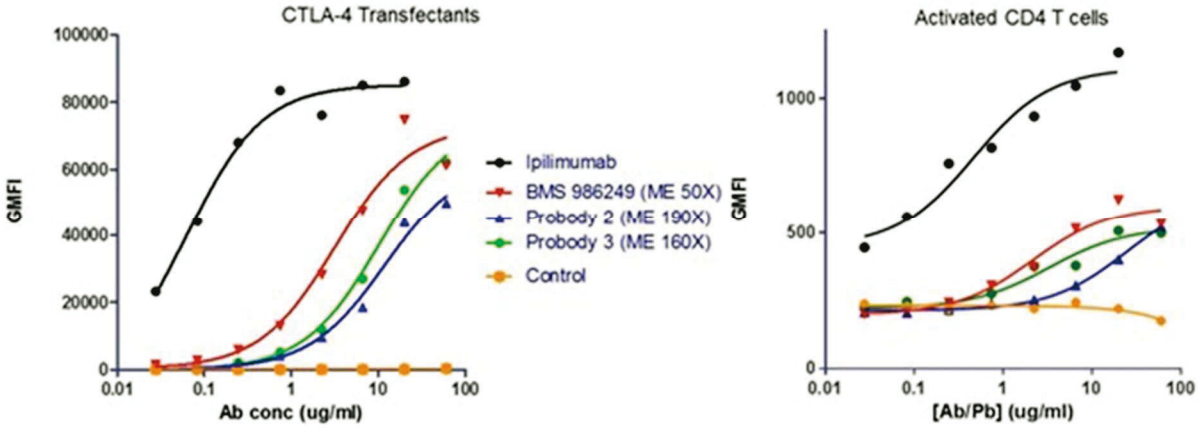
Two sets of assays have been used to define the decrease in target binding of the masked anti-CTLA–4 Ab compared to the parental Ab. First, ELISA was used to measure the affinity of anti- CTLA–4 probodies for protein (Figure 3.2.1.1-1). Binding to CTLA-4 expressed on cells was also tested and showed significantly reduced binding. Cells used for these assays include 58$\alpha^{-}\beta^{-}$/CD3ζ cells, which overexpress CTLA-4 as well as endogenous CTLA-4 expressed by activated cluster of differentiation 4 (CD4) cells (Figure 3.2.1.1-2). Although the absolute value of the shift in EC50 may vary depending on assay, the ranking of probodies is broadly conserved.

Figure 3.2.1.1-1: Binding of Ipilimumab Probodies to CTLA-4 by ELISA



Abbreviations: Ab = antibody; CTLA-4 = cytotoxic T lymphocyte-associated protein 4; ELISA = enzyme-linked immunoassay; Pb = Probody mAb.

Figure 3.2.1.1-2: Binding of Ipilimumab Probody mAbs to Overexpressed and Endogenous CTLA-4 by FACS



Abbreviations: Ab = antibody; CD4 = cluster of differentiation 4; CTLA-4 = cytotoxic T lymphocyte-associated protein 4; FACS = fluorescence-activated cell sorting; GMFI = geometric mean fluorescence intensity; mAb = monoclonal antibody; ME = masking efficiency ; Pb = Probody.

The linker containing specific protease sites is also an important determinant of efficacy and safety. Linkers that are more easily cleaved by specific proteases or cleaved by a broader range of proteases are expected to have higher efficacy, but may also result in higher cleavage systemically, which would result in a lower safety margin. Three linkers were considered for the CTLA-4 Probody mAb, one with specificity for MMPs (885), one with specificity for serine proteases (2787), and a hybrid linker that incorporates specificity for both MMPs and serine proteases (1490). Due to unexpected stability issues with the 1490 sequence, this was later mutated to 1490 DNP, which has very similar protease cleavage activity (Table 3.2.1.1-1).

Table 3.2.1.1-1: KCAT/KM Values for Protease Linker Sequence

	Matriptase	UPA	MMP14	MMP9	MMP7	MMP2
2787	1.0E+05	5.4E+03				
885			1.6E+04	3.2E+04	1.2E+03	5.8E+04
1490	2.5E+03	7.0E+02	1.2E+04			
1490DNP	1.9E+03	8.4E+01	7.6E+03	9.0E+02		

Abbreviations: MMPx = matrix metalloproteinase-[number]; UPA = urokinase-type plasminogen activator.
Blank cells signify not tested.
Cleavage was measured by capillary electrophoresis Units on the numbers are Moles-1Sec-1.

To confirm that reduction of antigen binding was sufficient to reduce functional activity of the Probody mAb, BMS-986249 was tested in the in vitro staphylococcal enterotoxin B (SEB) assay. In this assay, the superantigen SEB is added to human peripheral blood mononuclear cell (PBMC) and induces T cell activation and cytokine release. Ipilimumab has been shown to increase interleukin 2 (IL-2) secretion in this assay in a dose-dependent manner. In comparison to parental ipilimumab, BMS-986249 treatment significantly reduced secretion of IL-2 in response to SEB. Depending on the donor, BMS-986249 either showed reduced or complete loss of IL-2 secretion compared to ipilimumab.[3] This reduction was expected since the tumor proteases required for cleavage were not active in the assay.

3.2.1.2 BMS-986249 Nonclinical Pharmacology

BMS-986249 binds CTLA-4 with a 41-fold higher (ie, less potent) EC50 than ipilimumab when the masking peptide is intact. This reduction in binding affinity also translates to a reduction in functional activity. In a human T cell functional assay using SEB to stimulate IL-2 production, ipilimumab induced higher levels of IL-2 compared to the prodrug version. Antibody-dependent cell-mediated cytotoxicity (ADCC) induced by BMS-986249 in a reporter assay was decreased compared to ipilimumab.

The in vivo activity of BMS-986249 has also been studied using CTLA-4 knock-in (KI) mice that express the extracellular domain of human CTLA-4 in the place of mouse CTLA-4.[4] Human CTLA-4 binds to mouse CD80 and CD86 similarly to mouse CTLA-4, and these mice have been shown to behave similar to wild-type mice with no signs of autoimmunity. In the MC38 mouse syngeneic tumor model, dose titrations of both ipilimumab and BMS-986249 inhibited tumor growth to a similar extent, 97% and 95% at the highest dose level, respectively, and resulted in similar numbers of complete tumor regressions, 10/16 for ipilimumab and 13/16 for BMS-986249. Immune monitoring of T cell populations indicated that BMS-986249 reduced Tregs similarly to ipilimumab, with a 67% and 61% reduction, respectively. Systemic pharmacodynamic markers of ipilimumab activity, such as increased Ki-67 and inducible T cell costimulator (ICOS) levels on T cell subsets in the spleen were significantly reduced in BMS-986249–treated animals compared to ipilimumab. Therefore, BMS-986249 has been shown to maintain anti-tumor activity and tumoral pharmacodynamic effects while reducing systemic pharmacodynamic effects.

In vitro and in vivo data indicate that BMS-986249 should have reduced activity outside of the tumor site compared to ipilimumab while preserving its anti-tumor efficacy, supporting the development of this Ab for the treatment of cancer.

3.2.1.3 BMS-986249 Nonclinical Pharmacokinetics

The PK of BMS-986249, a Probody mAb of ipilimumab (Yervoy™), was evaluated in mice and cynomolgus monkeys. After an intravenous (IV) dose of BMS-986249 in mice (5-mg/kg single dose) or monkeys (5-mg/kg single dose and 10- and 50-mg/kg weekly doses for 4-weeks), BMS-986249-related exposure was measured as intact BMS-986249, its mono- and dual-cleavage products, and total Ab. BMS-986249 exhibited typical Ab PK characteristics: low total body plasma clearance of 25 and 9.7 to 10 mL/d/kg, limited volume of distribution at steady state (Vss) of 147 and 80 to 95 mL/kg, and long apparent elimination half-lives (T-HALF) of 4.2 and 6.7 to

7.6 days in mice and monkeys, respectively. In both species, the T-HALF of the intact Probody mAb was shorter than the T-HALF of the total Ab (21 and 17 to 18 days, respectively), consistent with the intact Probody mAb being slowly converted to mono- and dual-cleaved products. In monkeys, BMS-986249 and its mono- and dual-cleavage products and total Ab exhibited a dose-proportional increase in exposure between 10- and 50-mg/kg doses. The intact Probody mAb was 53% converted to the fully active Ab in mice and 30% to 34% in monkeys. BMS-986249 was immunogenic in monkeys; anti-drug Ab (ADA) formation was observed in some of the monkeys in both dose groups. The ADA response returned to baseline after Day 29 in all monkeys except for 1 monkey in the 10-mg/kg dose group and 2 monkeys in the 50-mg/kg dose group. In addition, the ADA did not appear to impact the exposures of BMS-986249, except for 1 monkey in the 10-mg/kg dose group.

The human efficacious dose of BMS-986249 is projected to be 240 mg, based on the comparable exposure-efficacy relationship observed for BMS-986249 and ipilimumab in human CTLA-4 KI mice bearing the MC38 tumor, combined with the projected human PK parameters. Assuming the Probody mAb cleavage in the MC38 tumor is the same as the cleavage in human tumors, the efficacious dose of BMS-986249 in order to achieve the same clinical efficacy as ipilimumab will be the same as the clinical approved ipilimumab monotherapy dose of 3 mg/kg, which is also being tested in various combination therapies with nivolumab. The optimal dosing regimen of BMS-986249 will be determined in the clinic.

3.2.1.4 BMS-986249 Nonclinical Toxicology

In a 1-month toxicity study in monkeys (n = 5/sex/group) at weekly IV doses of 10 or 50 mg/kg BMS-986249 or 10 or 50 mg/kg ipilimumab,[5] BMS-986249 T cell activation/pharmacodynamic responses were reduced relative to the corresponding dose-matched ipilimumab group in both a dose and time-dependent manner correlating with a delayed conversion of BMS-986249 to active dual-clipped ipilimumab. BMS-986249 was clinically well tolerated at doses up to 50 mg/kg and, in general, resulted in reduced toxicity compared to ipilimumab at corresponding doses. At 50 mg/kg ipilimumab, 1 monkey was euthanized early within 4 weeks of the recovery period (Day 55) due to a progressively deteriorating clinical condition, and skeletal muscle degeneration and necrosis secondary to inflammation. The predominant BMS-986249- and ipilimumab-related microscopic finding was generally dose-related lymphohistiocytic inflammation within a variety of tissues at both doses, but with higher incidence and wider tissue distribution of inflammatory changes in the ipilimumab groups compared to BMS-986249.

Based on the lack of clinical signs, and minimal to moderate histopathological changes in target organs, the highest non-severely toxic dose (HNSTD) for BMS-986249 was considered to be 50 mg/kg (mean total area under the concentration-time curve from time zero to 168 hours [AUC(0-168h)] = [redacted] (µg•h/mL). In contrast, based on mortality, and pathologic effects at 50 mg/kg (mean total area under the curve [AUC][AUC(0-168h)=[redacted] (µg•h/mL)], and minimal effects at 10 mg/kg, the HNSTD for ipilimumab was considered to be 10 mg/kg (mean total AUC[0-168h] = 44,600 (µg•h/mL).

The BMS-986249 HNSTD corresponds to exposure (area under the concentration-time curve [AUC]) multiples of approximately 51-fold and 5.1× the projected exposures at the proposed starting first in human (FIH) dose (3 mg/kg IV, AUC[4-week] [redacted] (µg•h/mL) and highest projected dose for the FIH study (30 mg/kg IV, AUC[4-week] [redacted] (µg•h/mL), respectively.

Because BMS-986249 has an identical binding region sequence to ipilimumab, the cytokine release studies performed with ipilimumab were utilized to support BMS-986249.[6,7,8,9] Ipilimumab induced minimal proliferation (ie, mean peak stimulation index [SI] of 12) and minimal selective cytokine release (ie, IL-2, tumor necrosis factor alpha [TNF-α], IL-6, IL-8; mean peak SI ranging from 2 to 6) in PBMC from individual donors using an immobilized assay format. By comparison, the positive control anti-CD28 Ab induced profound proliferation (ie, mean peak SI of 139) and elicited a release of several cytokines (ie, interferon [IFN, IFN-δ], TNF-α, IL-2, IL-4, IL-5, IL-6, and IL-8) in all donors at a relatively high magnitude (mean peak SI ranging from 4 to 137). No substantial cytokine release from human PBMC was observed with ipilimumab using a soluble assay format.[8] These findings are in agreement with clinical data indicating that ipilimumab generally does not elicit adverse cytokine release in humans.[9]

Overall, BMS-986249 has demonstrated acceptable pharmacologic, nonclinical PK, pharmacodynamic, and risk profiles to support initiation of a FIH clinical study in participants with cancer.

3.2.1.5 BMS-986249 Clinical Pharmacokinetics

Preliminary PK analysis from the Part 1A monotherapy cohorts suggest lower systemic plasma exposure of the active dual-cleaved Probody species (ipilimumab equivalent) compared to preclinical simulations and historical ipilimumab data. Overall, the systemic dual-cleaved Probody species represented approximately 3.7% to 5.9% of total circulating antibody following the first dose of BMS-986249.

Preliminary analysis of the first dosing interval of 240 mg BMS-986249 monotherapy demonstrated the plasma peak concentration (Cmax1 ≈ [redacted] µg/mL) was 5-fold lower as compared to preclinical simulations (Cmax1 ≈ [redacted] µg/mL), with an exposure of 1.7% as compared to historical 3 mg/kg ipilimumab data (Cmax1 ≈ [redacted] µg/mL). Similarly, preliminary analysis of the first dosing interval of 800 mg BMS-986249 monotherapy indicated peak plasma exposure was 2.5% (Cmax1 ≈ [redacted] µg/mL) compared to historical [redacted] mg/kg ipilimumab data (Cmax1 ≈ [redacted] µg/mL).

Preliminary PK analysis suggests that following the first dose across the doses investigated in Part 1A, the majority of the systemic circulating antibody species are the intact Probody, with the mono-cleaved Probody species representing approximately [redacted] to [redacted] of total antibody. Consistent with the in vivo protease-mediated cleavage process, both mono- and dual-cleaved Probody species appeared to be formed gradually with time, supporting the investigation of longer dosing intervals (eg, every 8 week [Q8W] regimens). With limited data, initial assessment of Part 1B suggests co-administration of nivolumab did not significantly impact the BMS-986249 PK profile. Preliminary assessment of tumoral BMS-986249 exposures based on a single on-treatment biopsy across the different doses in Part 1 suggests a more efficient cleavage process with mono-

and dual-cleaved BMS-986249 species representing an average of approximately 45% and 10% of total Ab, respectively. Additional information on the preliminary PK results of BMS-986249 can be found in the IB.[10]

3.2.1.6 Clinical Safety Summary

As of the date of this protocol, the overall safety experience with BMS-986249 as either a monotherapy or in combination with nivolumab is under active investigation and currently emerging. BMS-986249 monotherapy in Part 1A has been administered every 4 weeks (Q4W) at doses of 240 mg, 800 mg, 1,600 mg, and 2,400 mg. In addition, 1,600 mg BMS-986249 has also been administered Q8W. Doses of 240 mg BMS-986249 in combination with 480 mg nivolumab, 800 mg BMS-986249 in combination with 480 mg nivolumab, and 1,200 mg BMS-986249 in combination with 480 mg nivolumab have been administered Q4W in Part 1B. In addition, 800 mg BMS-986249, 1,200 mg BMS-986249, and 1,600 mg BMS-986249 have also been administered Q8W in combination with 480 mg nivolumab administered Q4W. The maximum tolerated dose (MTD) of BMS-986249 as a monotherapy or in combination with nivolumab has not been reached. Overall, the safety profile of BMS-986249 as a single agent and in combination with nivolumab is clinically manageable and consistent with the established safety profile of the active form, ipilimumab. Of note, there may be a possibility of an increased risk of encephalitis associated with BMS-986249 (refer to Section 7.5.2 and Appendix 9).

Upon preliminary evaluation of the available safety profile in Part 1, an increased number of TRAEs was observed with increasing dose of BMS-986249 administered Q4W alone and in combination with nivolumab. When BMS-986249 was administered at the alternative dosing schedule of Q8W a lower number of TRAEs were reported.

Additional details on the safety of BMS-986249 are summarized in the BMS-986249 IB.[10]

3.2.2 Nivolumab

Nivolumab is a fully human, immunoglobulin (Ig) G4 (kappa) isotype mAb that binds to PD-1 with nanomolar affinity (dissociation constant, 3.06 nM) and a high degree of specificity. Nivolumab blocks binding of PD-1 to its ligands, programmed death ligand-1 (PD-L1) and programmed death ligand-2 (PD-L2). Nonclinical in vitro testing of nivolumab demonstrated that binding to PD-1 results in enhanced T cell proliferation and release of IFN-γ in vitro in mixed lymphocyte reaction and cytomegalovirus assays.

The nonclinical safety of nivolumab was evaluated in a comprehensive toxicology program in mice and monkeys and was submitted as part of Biologics License Application 125527.[11] Details of the in vitro and in vivo nonclinical pharmacology studies conducted to support the development of nivolumab can be found in Section 4.1 of the nivolumab IB.[12]

While nivolumab was well tolerated in cynomolgus monkeys, there is a potential for enhanced toxicity when combined with other immunostimulatory agents. However, nonclinical studies with nivolumab did not predict clinically relevant adverse effects (eg, no evidence of immune-mediated adverse effects was observed in nonclinical toxicology studies with nivolumab). Therefore, combination nonclinical toxicology studies with BMS-986249 and nivolumab have not been

conducted and are not required by the International Council for Harmonisation S9 Note for Guidance on Nonclinical Evaluation for Anticancer Pharmaceuticals.[13] The safety of the combination will be carefully monitored in the planned clinical trial.

The overall safety experience with nivolumab, as either monotherapy or in combination with other therapeutics, is based on experience in approximately 23,507 participants.[12] Nivolumab has been approved by the United States (US) Food and Drug Administration (FDA) for the treatment of unresectable or metastatic melanoma (as a single agent and in combination with ipilimumab), melanoma with lymph node involvement or metastatic disease after complete resection in the adjuvant setting, metastatic NSCLC after progression on or after platinum-based chemotherapy, metastatic or recurrent NSCLC with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations as first-line treatment (in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy), metastatic NSCLC expressing PD-L1 ≥ 1%, metastatic SCLC with progression after platinum-based chemotherapy and at least 1 other line of therapy, advanced RCC previously treated with anti-angiogenic therapy, previously untreated advanced RCC with intermediate or poor risk (in combination with ipilimumab), recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) with disease progression on or after a platinum-based therapy, classical Hodgkin's lymphoma that has relapsed or progressed, locally advanced or metastatic urothelial carcinoma, MSI-H or mismatch repair deficient (dMMR) metastatic CRC (as a single agent and in combination with ipilimumab), sorafenib-treated hepatocellular carcinoma (HCC) (as a single agent and in combination with ipilimumab), unresectable advanced, recurrent, or metastatic esophageal squamous cell carcinoma after fluoropyrimidine- and platinum-based chemotherapy, and previously untreated unresectable malignant pleural mesothelioma.[12]

For nivolumab monotherapy, the safety profile is similar across tumor types. The only exception is pulmonary inflammation AEs, which may be numerically greater in participants with NSCLC. In NSCLC participants, it can be difficult to distinguish between nivolumab-related and unrelated causes of pulmonary symptoms and radiographic changes. There is no relationship between the incidence, severity, or causality of AEs and the nivolumab dose level. Additional details on the safety profile of nivolumab, including results from other clinical studies, are summarized in the nivolumab IB.[12]

3.2.2.1 Clinical Pharmacokinetics of Nivolumab

Single-dose PK of nivolumab was evaluated in 39 participants with multiple tumor types in CA209001 in the dose range of 0.3 to 10 mg/kg. The median time of maximum observed concentration (Tmax) across dose levels ranged from 1.6 to 3.1 hours with individual values ranging from 0.9 to 7 hours. The PK of nivolumab was linear in the range of 0.3 to 10 mg/kg with dose-proportional increase in maximum observed concentration (Cmax) and AUC(INF). Geometric mean clearance after a single IV dose ranged from 0.13 to 0.19 mL/h/kg, while mean volume of distribution of terminal phase (Vz) varied between 83 to 113 mL/kg across doses. The mean terminal T-HALF of nivolumab was 17 to 25 days, consistent with half-life of endogenous IgG4, indicating that the elimination mechanism of nivolumab may be similar to IgG4. Both

elimination and distribution of nivolumab appeared to be independent of dose within the dose range studied.

The multiple dose PK of nivolumab given every 2 weeks (Q2W) in participants with multiple tumor types was determined from the CA209003 study as well as population PK (PPK) analyses using data from 909 participants across nivolumab studies. Multiple-dose PK of nivolumab following Q2W dosing was linear with dose proportional increase in Cmax and AUC(TAU) in the studied range of 0.1 to 10 mg/kg. The geometric mean of terminal T-HALF was 26.7 days and the typical clearance was 8.7 mL/h, which are consistent with those of full human immunoglobulin antibodies.

A dose of 480 mg nivolumab Q4W is currently under active clinical evaluation across multiple tumor types. Using a PPK model, 480 mg nivolumab Q4W is predicted to provide average steady-state concentrations similar to 3 mg/kg nivolumab Q2W. A dose of 480 mg nivolumab Q4W is predicted to provide a greater (approximately 40%) peak steady state concentration (Cmaxss) and lower (approximately 20%) trough steady state concentrations (Cminss). Nivolumab has been shown to be safe and well tolerated up to doses of 10 mg/kg Q2W and has not demonstrated a clear dose response or exposure-response safety relationship. Based on these safety findings, the predicted Cmaxss at 480 mg Q4W is not considered to put participants at increased risk for AEs. The approved doses of 3 mg/kg Q2W and 240 mg Q2W have shown survival benefit across multiple tumor types compared to respective standards of care. Nivolumab exposure was not a predictor of survival in exposure response efficacy analyses conducted for multiple tumor types. The Cminss values following 480 mg nivolumab Q4W are predicted to be in the range of those on the flat part of the exposure-response efficacy curves and are not expected to impact efficacy.

As of Jun-2017, approximately 310 participants in the nivolumab clinical development programs have received at least 1 dose of 480 mg nivolumab Q4W, either as the starting therapy or as maintenance treatment following 240 mg nivolumab Q2W. The Sponsor has a clinical safety program that monitors symptoms potentially related to infusion-related reactions reported on the day of infusion and the following day. For the approximately 310 participants treated with 30-minute infusions of 480 mg nivolumab, there have been no reports of any symptoms that may potentially be linked to infusion reactions on the day of infusion or the following day. There have been no new safety signals identified during routine clinical and pharmacovigilance monitoring of these studies. Clinical evaluation of this dose regimen is ongoing; as such, summaries of safety information, PK, and immunogenicity are not currently available. A dose of 480 mg nivolumab Q4W infused over 30 minutes was FDA-approved in Mar 2018 for the majority of the approved indications. The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has also recommended adding the option of a 4-week dosing schedule to the label for nivolumab for the treatment of patients with advanced melanoma and previously treated RCC.

Additional details are provided in the current version of the nivolumab IB.[12]

3.2.3 Ipilimumab

Ipilimumab (BMS-734016, MDX010, and MDX-CTLA-4) is a fully human monoclonal IgG1κ specific for human CTLA-4, CD152. CTLA-4 is expressed on a subset of activated T cells on which it acts as a negative regulator of T cell activity. Ipilimumab is a mAb that binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T cell activation and proliferation, including the activation and proliferation of tumor infiltrating T-effector cells. Inhibition of CTLA-4 signaling can also reduce Treg function, which may contribute to a general increase in T cell responsiveness, including the anti-tumor response. Ipilimumab has been administered to more than 28,686 participants (total number of participants enrolled in ipilimumab studies) in several cancer types in completed and ongoing studies, as well as a compassionate use program. Ipilimumab has been approved for use in over 47 countries including the US (Mar-2011), the European Union (Jul-2011), and Australia (Jul-2011).

The focus of the monotherapy clinical program has been in melanoma, with advanced melanoma and adjuvant melanoma being the most comprehensively studied indications. Ipilimumab is being investigated in combination with other modalities such as chemotherapy, radiation therapy, and other immunotherapies in multiple tumor types.

In melanoma, 2 completed Phase 3 studies (MDX010-20 and CA184024) demonstrated a clinically meaningful and statistically significant survival benefit in pretreated advanced melanoma and previously untreated advanced melanoma, respectively.

The safety profile of ipilimumab is generally consistent across studies, with a) the majority of AEs being inflammatory in nature, which is consistent with the proposed mechanism of action of ipilimumab; b) the same types of such immune-mediated AEs in the gastrointestinal (GI) tract, skin, liver, and endocrine system being reported; and c) most of these events being manageable with immune suppressive therapies.

In participants with advanced melanoma who received 3 mg/kg ipilimumab monotherapy in a Phase 3 study (MDX010-20), the most frequently reported adverse reactions (≥ 10% of participants) were diarrhea, rash, pruritus, fatigue, nausea, vomiting, decreased appetite, and abdominal pain. The majority of AEs were mild to moderate (Grade 1-2), and treatment was discontinued for adverse reactions in 10% of participants.

Long-term survival benefit of treatment with 3 mg/kg ipilimumab was demonstrated through a pooled analysis of overall survival (OS) data from clinical trials in participants with previously treated and treatment naive advanced melanoma (N = 965). The Kaplan-Meier OS curve revealed a plateau beginning around year 3 (OS rate = 21% [95% confidence interval (CI): 17 to 24]) that extended up to 10 years in some participants.

Dose-dependent toxicity as well as relative efficacy of ipilimumab 3 mg/kg versus 10 mg/kg were established in a Phase 3 study in advanced melanoma (CA184169). Ipilimumab resulted in a median OS of 15.70 months in participants treated with 10 mg/kg and 11.53 months in participants treated with 3 mg/kg. Ipilimumab 10 mg/kg demonstrated statistically significant improvement in OS (primary efficacy endpoint) compared with 3 mg/kg ipilimumab (hazard ratio [HR] = 0.84,

95% CI: 0.70, 0.99; P-value = 0.0400). Best objective response rate (ORR) was 15.3% (95% CI: 11.8, 19.5) for 10 mg/kg and 12.2% (95% CI: 9.0, 16.0) for 3 mg/kg.[14]

Ipilimumab monotherapy prolongs survival in patients with pretreated and previously untreated advanced melanoma and has demonstrated anti-tumor activity in other malignancies, including lung cancer, prostate cancer, and RCC.[15]

Additional details on the safety profile and clinical benefit of ipilimumab alone and in combination with nivolumab, including results from clinical studies in melanoma, prostate, lung, kidney, bladder, or breast tumors are summarized in the ipilimumab and nivolumab IBs.[12, 15]

3.2.4 Nivolumab Combined with Ipilimumab

Multiple clinical studies have evaluated nivolumab combined with ipilimumab at different doses and schedules. The following information describes the results of initial early phase clinical studies that were the basis for the nivolumab and ipilimumab combination regimens that have been explored in late phase clinical development.

In the Phase 1 study CA209004, ascending doses of nivolumab have been studied concomitantly with ascending doses of ipilimumab in participants with unresectable or metastatic melanoma. In each arm in this multi-arm study, ipilimumab was administered once every 3 weeks (Q3W) for 4 doses with nivolumab administered once Q3W for 8 doses. Starting at Week 24, ipilimumab and nivolumab were administered once every 12 weeks (Q12W) for 8 doses. The 3 initial dose-escalation cohorts consisted of Cohort 1 (0.3 mg/kg nivolumab in combination with 3 mg/kg ipilimumab; n=14), Cohort 2 (1.0 g/kg nivolumab in combination with 3 mg/kg ipilimumab; n=17) and Cohort 3 (3.0 mg/kg nivolumab in combination with 3 mg/kg ipilimumab; n=6). Later, the study was amended to include Cohort 2a which evaluated 3 mg/kg nivolumab in combination with 1 mg/kg ipilimumab (n=16). The primary objective was to assess safety/tolerability; the secondary objective was to assess preliminary efficacy.

Of the 52 participants evaluable for response as of the 15-Feb-2013 clinical cut-off in CA209004, 21 participants (40%) had an objective response by modified World Health Organization (mWHO) criteria. In an additional 2 participants (4%) there was an unconfirmed objective response. In Cohort 1 (0.1 mg/kg nivolumab in combination with 3 mg/kg ipilimumab), 3 out of 14 evaluable participants had an objective response by mWHO (21%), including 1 complete response (CR) and 2 partial responses (PRs).[16] In Cohort 2 (1 mg/kg nivolumab in combination with 3 mg/kg ipilimumab), 9 out of 17 (53%) evaluable participants had an objective response by mWHO, including 3 CRs (18%) and 6 PRs (35%). In Cohort 2a (3 mg/kg nivolumab in combination with 1 mg/kg ipilimumab), 6 out of 15 (40%) response evaluable participants had an objective response by mWHO, including 1 CR (7%) and 5 PRs (33%). In Cohort 3 (3 mg/kg nivolumab in combination with 3 mg/kg ipilimumab), 3 out of 6 (50%) evaluable participants had an objective response by mWHO, all 3 of which were PRs (50%).

Preliminary analysis revealed 16 of the 52 evaluable participants (31%) had > 80% reduction in the size of target tumor lesions by the Week 12 evaluation. This is compared to < 2% for 3 mg/kg

ipilimumab monotherapy based on CA184020 (N=540) and < 3% for nivolumab monotherapy based on CA209003 (N=94, 0.1-10 mg/kg).

The following dose limiting toxicities (DLTs) were observed: in Cohort 1, Grade 3 elevated aspartate aminotransferase (AST)/alanine aminotransferase (ALT) (1 participant); in Cohort 2, Grade 3 uveitis (1 participant) and Grade 3 elevated AST/ALT (1 participant) and in Cohort 3, Grade 4 elevated lipase (2 participants) and Grade 3 elevated lipase (1 participant). Based on these data, Cohort 2 was identified as the MTD and Cohort 3 exceeded the MTD.

A total of 53 melanoma participants were treated with nivolumab combined with ipilimumab in CA209004 across Cohorts 1, 2, 2a, and 3. At least 1 AE regardless of causality has been reported in 98% of participants treated. The most common (reported at > 10% incidence) TRAEs (any Grade 93%; Grade 3-4 53%:) are rash (55%; 4%), pruritus (47%; 0%), vitiligo (11%; 0%), fatigue (38%; 0%), pyrexia (21%, 0%), diarrhea (34%; 6%), nausea (21%, 0%), vomiting (11%, 2%), ALT increased (21%; 11%), AST increased (21%; 13%), lipase increased (19%; 13%), amylase increased (15%, 6%), headache (11%, 0%), and cough (13%, 0%).

The majority of AEs leading to discontinuation (regardless of causality) were Grade 3-4 (reported in 11 of 53 participants, 21%). Grade 3 events included lipase increased, ALT increased, AST increased, troponin I increased, colitis, diverticular perforation, pancreatitis, tachycardia, renal failure acute, choroiditis, autoimmune disorder, and pneumonitis. One participant each discontinued due to Grade 4 events of blood creatinine increased and AST increased. No drug-related deaths were reported.[16]

The combination of nivolumab with ipilimumab is being studied in the Phase 1 study CA209016. Participants with metastatic RCC (mRCC) (Karnofsky performance status ≥ 80%; untreated or any number of prior therapies) were randomized to receive 3 mg/kg nivolumab in combination with 1 mg/kg ipilimumab (arm N3 + I1) or 1 mg/kg nivolumab in combination with 3 mg/kg ipilimumab (arm N1 + I3) IV Q3W for 4 doses followed by 3 mg/kg nivolumab IV Q2W until progression/toxicity. The primary objective was to assess safety/tolerability; secondary objective was to assess anti-tumor activity.

Participants were randomized to N3 + I1 (n = 47) and N1 + I3 (n = 47). Approximately half (n = 46; 51%) had prior systemic therapy (N3 + I1: 22; N1 + I3: 26).

After a median follow-up of 22.3 months, the confirmed ORR per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) was 40.4% (n = 47) in both Arms N3 + I1 and N1 + I3; 42.1% (n = 8) and 36.8% (n = 7) had an ongoing response, with a median duration of response (DOR) of 88.7 weeks (95% CI: 37.14, NA) and 85.9 weeks (95% CI: 35.14, not available), respectively. Median PFS was 7.7 months (95% CI: 3.71, 14.29) and 9.4 months (95% CI: 5.62, 18.63) in Arms N3 + I1 and N1 + I3, respectively. OS at 12 months was 80.9% and 85.0% in Arms N3 + I1 and N1 + I3, respectively, and at 24 months was 67.3% and 69.6%, respectively.

The safety of nivolumab combined with ipilimumab was assessed in study CA209016. TRAEs were seen in 88/94 pts (94%), including 43/47 (92%) in N3 + I1 and 45/47 (96%) in N1 + I3. The most frequently reported drug-related AEs in N3 + I1 included fatigue (66%), cough (53.2%), and

arthralgia (51.1%); the majority were Grade 1-2. The most frequently reported drug-related AEs in N1 + I3 included fatigue (74.5%), nausea (55.3%), and diarrhea (53.2%). The majority were Grade 1-2.

TRAEs leading to discontinuation (31.9% versus 10.6%), and treatment-related serious adverse events (SAEs) (34% versus 23.4%) occurred more commonly in participants in the N1 + I3 arm than in the N3 + I1 arm, respectively.[17]

CA209012 was a multi-arm Phase 1b trial evaluating the safety and tolerability of nivolumab in participants with chemotherapy-naïve advanced NSCLC, as either a monotherapy or in combination with other agents including ipilimumab, at different doses and schedules. The primary endpoint of the study was safety with secondary endpoints of ORR per RECIST v1.1 and 24-week PFS. Participants were assigned to receive 3 mg/kg nivolumab Q2W in combination with 1 mg/kg ipilimumab Q12W (n=38), 3 mg/kg nivolumab Q2W in combination with 1 mg/kg ipilimumab every 6 weeks (Q6W) (n=39) and 3 mg/kg nivolumab Q2W (n=52). The confirmed ORR was 47% (N3 Q2W + I1 Q12W), 39% (N3 Q2W + I1 Q6W) and 23% (N3 Q2W). The median DOR was not reached in any of these groups.

The rate of TRAEs in the Q12W (82%) and Q6W (72%) arms were comparable to monotherapy (72%). In the study, Grade 3-4 AEs were 37%, 33%, and 19% for the Q12W, Q6W, and nivolumab monotherapy arms, respectively. Grade 3-4 TRAEs led to discontinuation in 5% and 8% of participants in the Q12W and Q6W cohorts, respectively, and were similar to nivolumab monotherapy. There were no treatment-related deaths. The treatment-related select AEs in participants administered the optimized dosing schedule (3 mg/kg of nivolumab Q2W in combination with 1 mg/kg of ipilimumab Q6W) were skin-related (36%), GI (23%), endocrine (20%), and pulmonary (5%) and there were ≤ 5% Grade 3-4 TRAEs per category.[18]

3.3 Benefit/Risk Assessment

Patients who have advanced solid tumors have a poor prognosis and few curative options.

Immunotherapy with ipilimumab or nivolumab has demonstrated clinical activity in patients with melanoma or advanced NSCLC, RCC, SCCHN, HCC, and other tumors. TRAEs include those associated with autoimmune activation, such as colitis, pneumonitis, thyroiditis, hepatitis, and adrenal insufficiency.

There is no prior human experience with BMS-986249; therefore, clinical benefit has not been established in patients with advanced cancer. However, nonclinical models are suggestive of at least similar anti-tumor activity that has been observed with ipilimumab.

In the absence of previous clinical studies with BMS-986249, the initial evaluation of risk is based primarily on the potential effects based on the proposed mechanism of action as well as on information from nonclinical studies with BMS-986249 in monkeys (Section 3.2.1) and clinical evidence from ipilimumab therapy.

The nonclinical Good Laboratory Practice (GLP) toxicology assessment of BMS-986249 has demonstrated a dose-related toxicity profile of irAEs and cytokine release potential compatible with the expected mechanism of action (see Section 3.2.1).

For the combination of BMS-986249 and nivolumab, as observed with ipilimumab and nivolumab combination therapy, it is possible that a higher incidence of irAEs may occur. The safety profile of nivolumab monotherapy and the combination of ipilimumab and nivolumab are characterized based on experience with more than 23,507 participants as either monotherapy or in combination therapy. The frequency and types of immune-mediated adverse reactions are similar across multiple types of tumors and are described in the Reference Safety Information in the current nivolumab and ipilimumab IBs.[12,15] Unanticipated side effect events may also occur.

The proposed clinical studies of BMS-986249 have been designed to minimize the overall risk to participants; measures will include the following:

- Continuous safety assessments will be utilized by the investigators and Sponsor to determine whether additional safety measures, or termination of the study is required at any time. In addition, AEs and SAEs will be reviewed on an ongoing basis by the Medical Monitor (or designee) and Global Pharmacovigilance and Epidemiology (GPVE) representatives to monitor for any safety signals or trends. As BMS-986249 is an experimental agent, it is possible that unforeseen, unknown, or unanticipated reactions may occur. However, based on the nonclinical safety profile of BMS-986249 built into the planned starting dose of 240 mg (equivalent to approximately 3 mg/kg), the potential safety risks are expected to be minimized.
- Doses above 800 mg (equivalent to approximately 10 mg/kg) will only be evaluated if lower doses are deemed tolerable and if the PK profile of BMS-986249 appears consistent with the expected effects of a Probody mAb, specifically, if the systemic exposure to the cleaved prodrug (ie, ipilimumab) and peripheral pharmacodynamic effects are reduced.
- The administration will occur at infusion centers with medical monitoring and the capability to manage infusion reactions or anaphylaxis. The protocol provides a treatment algorithm for infusion reactions (see Section 7.5.5). In addition to conventional safety measures for infusion of biologic agents, all participants will undergo observation and assessment for signs of infusion reaction for a 60-minute period after the completion of the infusion for the first 3 doses for each participant.
- Furthermore, to assess for potential effects of lymphocyte activation, a sentinel participant will be monitored for 5 days at each dose level. The sentinel participant approach is used to closely monitor early-onset safety events in the monotherapy and combination therapy arms because the doses are escalated in a staggered manner.
- Management algorithms for ipilimumab/nivolumab-induced AEs involving GI, renal, pulmonary, hepatic, endocrinopathy, skin, cardiac, and neurologic systems are included in the protocol (see Appendix 9).
- Participants who develop irAEs may require prolonged treatment with high-dose corticosteroids and other immunosuppressive agents. This could increase the risk of opportunistic infections. The irAE management algorithms in the protocol recommend antibiotic prophylaxis against opportunistic infections in such situations.

- Complete blood counts and chemistry (including liver enzyme) tests will be carried out prior to administration of study therapy and on a weekly basis during the first 8 weeks of treatment in monotherapy and the first 8 weeks of the combination between BMS-986249 and nivolumab. In addition, complete physical examinations (PEs) will be conducted on Day 1 of each new cycle, along with weekly symptom-directed targeted PEs during the first 8 weeks of treatment. Due to the potential risk of exaggerated inflammatory response, participants with autoimmune disorders, chronic viral infections, or who are at risk for flare of autoimmunity will be excluded.
- The mandated biopsies pose limited risk to the participant and include discomfort, pain, and bleeding. Section 9.8.2 gives guidance on lesions that are appropriate for a research biopsy, and participants who are not able to undergo a biopsy with an acceptable risk can participate in some situations and upon agreement with the study director/Medical Monitor. Because of the need for development of predictive biomarkers for participants treated with BMS-986249 in future studies or the clinical setting, the limited risk of a research biopsy in selected (low risk) participants is considered appropriate in an early-phase research setting.
- The amount of blood sampling poses limited risk to the participant and includes discomfort, pain, and bleeding. The amount of total blood is reduced to the minimal quantity required to address the need of safety monitoring, standard of care, PK/ADA, and biomarker needs and is below the recommended daily limits for each treatment day.

In conclusion, the potential direct benefit to participants who participate in this study is that both single-agent and combined therapies with these investigational agents may result in a greater proportion of participants with stabilization of disease, ORR, PFS, OS, or increased DOR than those observed with standard therapy or other investigational immunotherapy.

The potential for direct benefit described above warrants evaluating BMS-986249 both as a single agent and in combination with nivolumab in this Phase 1/2 clinical study with risk mitigation described above.

More detailed information about the known and expected benefits and risks and reasonably anticipated AEs of BMS-986249 may be found in the IB.

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints: The Dose Escalation Phase (Part 1)

Objectives	Endpoints
Primary	
• To characterize the safety, tolerability, and DLTs and to determine the MTD/RP2D of BMS-986249 administered as monotherapy and in combination with nivolumab in participants with advanced solid tumors (Parts 1A and 1B)	• Incidence of AEs, SAEs, AEs meeting protocol-defined DLT criteria, AEs leading to discontinuation, death, and laboratory abnormalities

Table 4-1: Objectives and Endpoints: The Dose Escalation Phase (Part 1)

Objectives	Endpoints
Secondary	
• To characterize the PK of BMS-986249 when administered alone and in combination with nivolumab	• Summary measures of PK parameters of BMS-986249
• To assess the preliminary anti-tumor activity of BMS-986249 alone and in combination with nivolumab in advanced solid tumors (Parts 1A and 1B) using RECIST v1.1 or PCWG3 (for prostate cancer)	• ORR, DOR, PFS, and TTR per RECIST v1.1 or PCWG3 (for prostate cancer)
Exploratory	
[redacted]	
• To explore the associations between PK of BMS-986249 and nivolumab, safety, efficacy, and clinical biomarkers such as, but not limited to T cell-specific genes	• Association measures between BMS-986249 PK levels, select outcomes, and biomarkers of interest
[redacted]	
• To characterize the immunogenicity of BMS-986249 and nivolumab	• Incidence of ADA to nivolumab and BMS-986249
• To assess the potential effect of BMS-986249 when administered as monotherapy on the QTc interval	• Summary measures of ECG parameters and changes in QTcF (ΔQTcF) from baseline

Abbreviations: ADA = anti-drug antibody; AE = adverse event; DLT = dose-limiting toxicity; DOR = duration of response; ECG = electrocardiogram; MTD = maximum tolerated dose; ORR = Objective Response Rate; PCWG3 = Prostate Cancer Working Group 3; PFS = progression-free survival; PK = pharmacokinetics; QTc = QT interval corrected; QTcF = QT interval corrected for heart rate using Fridericia's formula; RECIST = Response Evaluation Criteria in Solid Tumors; RP2D = recommended Phase 2 dose of BMS-986249; SAE = serious adverse events; TTR = time to response.

Table 4-2: Objectives and Endpoints: The Dose Expansion Phase in Melanoma (Part 2A)

Objectives	Endpoints
Primary	
• To evaluate the preliminary safety and tolerability of BMS-986249 in combination with nivolumab (Arm C and Arm F) relative to ipilimumab in combination with nivolumab (Arm D) in participants with previously untreated, unresectable or metastatic melanoma	• Incidence of treatment-related Grade 3-5 AEs within 24 weeks
• To evaluate the preliminary efficacy of BMS-986249 in combination with nivolumab (Arm C and Arm F) relative to historic nivolumab monotherapy data in participants with previously untreated, unresectable or metastatic melanoma	• ORR as assessed by investigator using RECIST v1.1
Secondary	
• To assess the anti-tumor activity of BMS-986249 in combination with nivolumab (Arm C and Arm F) and ipilimumab in combination with nivolumab (Arm D) in participants with previously untreated, unresectable or metastatic melanoma	• ORR, DOR, PFS, and TTR as assessed by investigator using RECIST v1.1
• To assess the safety and tolerability of BMS-986249 in combination with nivolumab (Arm C and Arm F), and ipilimumab in combination with nivolumab (Arm D) in participants with previously untreated, unresectable or metastatic melanoma	• Incidence of AEs, SAEs, AEs leading to discontinuation, death, and laboratory abnormalities
• To characterize the PK of BMS-986249 when administered in combination with nivolumab	• Summary measures of PK parameters of BMS-986249 in combination with nivolumab
• To evaluate time to deterioration (TTD) in Quality of Life (QoL) and physical functioning	• TTD as defined by a minimally important decrease from baseline ≥10 points on the EORTC QLQ-C30 global health status/quality of life subscale (items 29 & 30) and Physical Functioning Scale (items 1 to 5)
Exploratory	
[redacted]	
• To explore the associations between PK of BMS-986249, ipilimumab and nivolumab, safety, efficacy, and clinical biomarkers such as, but not limited to T cell-specific genes	• Association measures between BMS986249, ipilimumab, and nivolumab PK levels, select outcomes, and biomarkers of interest
[redacted]	

Table 4-2: Objectives and Endpoints: The Dose Expansion Phase in Melanoma (Part 2A)

Objectives	Endpoints
• To characterize the immunogenicity of BMS-986249, ipilimumab and nivolumab	• Incidence of ADA to ipilimumab, nivolumab, and BMS-986249
• To explore OS of BMS-986249 in combination with nivolumab (Arm C and Arm F), and ipilimumab in combination with nivolumab (Arm D)	• OS rate at 1 and 2 years
• To evaluate changes in QoL, health status, and patient reported tolerability	• Mean scores and post-baseline score changes for all EORTC QLQ-C30 subscales, EQ-5D-3L utility index and VAS, and n (%) of endorsing participants by arm and time point for FACIT GP5 item and PRO-CTCAE items

Abbreviations: ADA = anti-drug antibody; AE = adverse event; DOR = duration of response; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; EQ-5D-3L = European Quality of Life – 5 Dimension – 3 Level Questionnaire; FACIT GP5 = Functional Assessment of Chronic Illness Therapy General Physical item 5; ORR = Objective Response Rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; PRO-CTCAE = Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; QoL = quality of life; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event;; TTD = time to deterioration; TTR = time to response; VAS = visual analogue scale.

Table 4-3: Objectives and Endpoints: The Dose Expansion Phase in Additional Tumors (Part 2B)

Objectives	Endpoints
Primary	
• To evaluate the preliminary safety and tolerability of BMS-986249 in combination with nivolumab in participants with previously treated HCC, CRPC, and TNBC	• Incidence of treatment-related Grade 3-5 AEs within 24 weeks
Secondary	
• To assess the preliminary anti-tumor activity of BMS-986249 in combination with nivolumab in participants with previously treated HCC, CRPC, and TNBC	• ORR, DOR, PFS, and TTR as assessed by investigator per RECIST v1.1 or PCWG3 (for prostate cancer). PSA response rate for prostate cancer
• To characterize the safety and tolerability of BMS-986249 in combination with nivolumab in participants with previously treated HCC, CRPC, and TNBC	• Incidence of AEs, SAEs, AEs leading to discontinuation, death, and laboratory abnormalities
• To characterize the PK of BMS-986249 when administered in combination with nivolumab in participants with previously treated HCC, CRPC, and TNBC	• Summary measures of PK parameters of BMS-986249 in combination with nivolumab

Table 4-3: Objectives and Endpoints: The Dose Expansion Phase in Additional Tumors (Part 2B)

Objectives	Endpoints
Exploratory	
[redacted]	[redacted]
• To explore the associations between PK of BMS-986249 and nivolumab, safety, efficacy, and clinical biomarkers such as, but not limited to T cell-specific genes	• Association measures between BMS-986249 and nivolumab PK levels, select outcomes, and biomarkers of interest
[redacted]	[redacted]
• To characterize the immunogenicity of BMS-986249 and nivolumab	• Incidence of ADA to nivolumab and BMS-986249
• To explore OS	• OS rate at 1 and 2 years
• To evaluate changes in QoL, health status, and patient reported tolerability	• Mean scores and post-baseline score changes for all EORTC QLQ-C30 subscales, EQ-5D-3L utility index and VAS, and n (%) of endorsing participants by arm and time point for FACIT GP5 item and PRO-CTCAE items

Abbreviations: ADA = anti-drug antibody; AE = adverse event; CRPC = castration-resistant prostate cancer; DOR = duration of response; EQ-5D-3L = European Quality of Life – 5 Dimension – 3 Level Questionnaire; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; FACIT GP5 = functional assessment of chronic illness therapy general physical item 5; HCC = hepatocellular carcinoma; ORR = objective response rate; OS = overall survival; PCWG3 = Prostate Cancer Working Group 3; PFS = progression-free survival; PK = pharmacokinetics; PRO-CTCAE = patient reported outcomes version for Common Terminology Criteria for Adverse Events; PSA = prostate-specific antigen; QoL = quality of life; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse events; TNBC = triple-negative breast cancer; TTR = time to response; VAS = visual analogue scale.

Table 4-4: Primary Estimands Part 2A

Objectives	Endpoints
Primary	Primary
To evaluate the preliminary safety and tolerability of BMS-986249 in combination with nivolumab (Arm C and Arm F) relative to ipilimumab in combination with nivolumab (Arm D) in participants with previously untreated, unresectable or metastatic melanoma	Incidence of treatment-related Grade 3-5 AEs within 24 weeks

Table 4-4: Primary Estimands Part 2A

Objectives	Endpoints
Main Estimand for the Primary Objective Treatment: 1200 mg BMS-986249 IV Q8W + 480 mg nivolumab IV Q4W (Arm C); 3 mg/kg ipilimumab Q3W + 1 mg/kg nivolumab IV Q3W for 4 doses followed three weeks later by 480 mg nivolumab IV Q4W(Arm D); 600 mg BMS-986249 IV Q4W +480 mg nivolumab IV Q4W (Arm F) Population: All treated participants Variable: Treatment Related AE with CTCAE Grade 3 or higher that occurred within 24 weeks from first dose Intercurrent events: early discontinuation of study Treatment Policy: Patients that discontinue treatment early will have a 100 days post last dose safety follow-up. AEs occurring after this safety follow-up window will not be included in the analysis, even if they occurred within the 24 weeks from first dose. Intercurrent event: initiation of subsequent anti-cancer therapy While on treatment: Patients that initiate an anti-cancer subsequent therapy will be discontinued from study but will be followed up for safety events 100 days from last dose. Safety events regardless of whether they occur before or after subsequent therapy will be include in the analysis. AEs occurring past 100 days safety follow-up will not be included in the analysis, even if they occurred within the 24 weeks from first dose. Intercurrent event: death and withdrew While on treatment: Patients who die or withdraw consent before reaching the 24 weeks landmark will be included in the analysis and their Grade 3 to 5 treatment related AEs will be include in the summary. Population level summary: Grade 3 to 5 treatment related adverse event incidence rate, comparison of Arm C vs Arm D and Arm F vs Arm D with estimated difference and odd ratio and 80% confidence interval using Cochran Mantel Haenszel methodology adjusting for stratification factors will be computed. Adjusted and unadjusted chi square test will be performed and p-values will be provided.	
Objective	**Endpoint**
Primary	Primary
To evaluate the preliminary efficacy of BMS-986249 in combination with nivolumab (Arm C and Arm F) relative to historic nivolumab monotherapy data in participants with previously untreated, unresectable or metastatic melanoma	ORR as assessed by investigator using RECIST v1.1
Main Estimand for the Primary Objective Treatment: 1200 mg BMS-986249 IV Q8W + 480 mg nivolumab IV Q4W (Arm C); 3 mg/kg ipilimumab Q3W + 1 mg/kg nivolumab IV Q3W for 4 doses followed three weeks later by 480 mg nivolumab IV Q4W(Arm D); 600 mg BMS-986249 IV Q4W + 480 mg nivolumab IV Q4W (Arm F) Population: All treated participants with evaluable baseline tumor assessment per RECIST v1.1 Variable: BOR, defined as the best response, as determined by investigator, per RECIST 1.1 Intercurrent events: early discontinuation of study Treatment policy (all post-baseline tumor assessment regardless of on-treatment status will contribute to BOR determination) Intercurrent event: initiation of subsequent anti-cancer therapy While on treatment (all post-baseline tumor assessment up to initiation of subsequent anticancer therapy will contribute to BOR determination)	

Table 4-4: Primary Estimands Part 2A

Objectives	Endpoints
Population level summary: ORR, defined as the number of randomized participants who achieve a BOR of confirmed CR or confirmed PR based on investigator assessments (using RECIST 1.1) divided by the number of all response-evaluable participants in each treatment group, with two sided 60% confidence interval Estimated odd ratio and 60% confidence interval using Cochran Mantel Haenszel methodology adjusting for stratification factors will be computed. Adjusted and unadjusted chi square test will be performed and p-value will be provided. The difference in ORR (adjusted and unadjusted) will also be provided.	

Abbreviations: AE = adverse event; BOR = best overall response; CR = complete response; CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous; ORR = objective response rate; PR = partial response; Q3W = every 3 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks; RECIST= Response Evaluation Criteria in Solid Tumors.

Table 4-5: Primary Estimands Part 2B

Objective	Endpoint
Primary	Primary
To evaluate the preliminary safety and tolerability of BMS 986249 in combination with nivolumab in participants with previously treated HCC, CRPC, and TNBC	Incidence of treatment-related Grade 3-5 AEs within 24 weeks

Main Estimand for the Primary Objective

Treatment: 1200 mg BMS-986249 IV Q8W +480 mg nivolumab IV Q4W

Population: All treated participants in Part 2B

Variable: Treatment Related AE with CTCAE Grade 3 or higher that occurred within 24 weeks from first dose

Intercurrent events: early discontinuation of study

Treatment Policy: Patients that discontinue treatment early will have a 100 days post last dose safety follow-up. AEs occurring after this safety follow-up window will not be included in the analysis, even if they occurred within the 24 weeks from first dose.

Intercurrent event: initiation of subsequent anti-cancer therapy

While on treatment: Patients that initiate an anti-cancer subsequent therapy will be discontinued from study but will be followed-up for safety events 100 days from last dose. Safety events regardless of whether they occur before or after subsequent therapy will be include in the analysis. AEs occurring past 100 days safety follow-up will not be included in the analysis, even if they occurred within the 24 weeks from first dose.

Intercurrent event: death and lost of consent

While on treatment: Patients who die or withdrew consent before reaching the 24 weeks landmark will be included in the analysis and their Grade 3 to 5 treatment related AEs will be included in the summary.

Population level summary: Grade 3 to 5 treatment related adverse event incidence rate

Abbreviations: AE = adverse event; CRPC = castration-resistant prostate cancer; CTCAE = Common Terminology Criteria for Adverse Events; HCC = hepatocellular carcinoma; IV = intravenous; Q4W = every 4 weeks; Q8W = every 8 weeks; TNBC = triple-negative breast cancer.

5 STUDY DESIGN

5.1 Overall Design

This is a Phase 1/2, open-label study of BMS-986249 administered as a single agent and in combination with nivolumab in participants with advanced solid tumors. The study is composed of 2 parts: dose escalation and dose expansion.

Part 1: The Dose Escalation Phase is where the dose of BMS-986249 will be given alone (Part 1A) or in combination with nivolumab (Part 1B). The Part 1A monotherapy dose escalation will evaluate different doses of BMS-986249 starting at 240 mg followed by 800, 1,600, and 2,400 mg (flat doses, Q4W). If during the monotherapy Dose Escalation Phase (Part 1A) it appears that a dose is associated with an unacceptable frequency of toxicities, then a conditional dose (eg, intermediate dose or alternative administration schedule [eg, Q8W, see Appendix 12]) may be evaluated in the study after clinical evaluation of the available safety, PK, and [redacted] data. Alternative dose schedules will be initiated and documented by a note to file or administrative letter following discussions and agreement between the investigators and Medical Monitor (or designee).

The BMS-986249 Monotherapy Dose Escalation (Part 1A) will escalate the dose of BMS-986249 to determine a safe and efficacious dose. The study will first evaluate the safety and tolerability of monotherapy BMS-986249 Q4W, based on DLTs using a Bayesian Logistic Regression Model (BLRM) employing the escalation with overdose control (EWOC) principle. [redacted]

The Safety Evaluation of Combination Doses of BMS-986249 with Nivolumab (Part 1B) will evaluate the safety and tolerability of doses of BMS-986249 in combination with nivolumab. Part 1B will begin only when data (safety and PK) on BMS-986429 at 240 mg (equivalent to approximately 3 mg/kg) and 800 mg (equivalent to approximately 10 mg/kg) are available from the monotherapy dose-escalation cohort (Part 1A). In Part 1B, the dose of BMS-986429 will be escalated, whereas the dose of nivolumab will be fixed at 480 mg Q4W. However, if an MTD is identified, then additional cohorts with lower doses of nivolumab and then potential higher doses of BMS-986249 may be studied as outlined in the study schematic (Figure 5.1-1). Alternative administration schedules of BMS-986249 (eg, Q8W, see Appendix 12 and Figure 5.1-1) may also be explored after clinical evaluation of available safety, PK, and [redacted] data. Alternative dose schedules will be initiated and documented by a note to file or administrative letter following discussions and agreement between the investigators and Medical Monitor (or designee).

To better estimate the preliminary safety profile and PK of any cohort in Part 1A or 1B, additional participants may be enrolled to cohorts deemed tolerable per the BLRM method.

Part 2: The BMS-986249 Cohort Expansion Combination Therapy Phase will open upon an overall assessment of available preliminary safety, PK, and [redacted] data from Part 1A and Part 1B. The different dose levels selected for Part 2 will not exceed the highest dose level assessed and deemed tolerable in Part 1. Part 2 will expand a specific patient population to assess the anti-tumor activity, safety, and tolerability of BMS-986249 in combination with nivolumab. PK,

[redacted], and patient-reported outcome (PRO) information of BMS-986249 in combination with nivolumab will also be evaluated.

The BMS-986249 in Combination with Nivolumab Randomized Cohort Expansion in Melanoma (Part 2A) will include participants with previously untreated, unresectable or metastatic melanoma. Part 2A participants will be stratified by PD-L1 status (≥ 1% tumor cell surface expression versus < 1% tumor cell expression/indeterminate) and American Joint Committee on Cancer Version 7 (AJCC) M-stage (M0/M1a/M1b versus M1c), and initially randomized 1:1:1:1:1 between 5 treatment arms:

- Arm A: 240 mg BMS-986249 in combination with 360 mg nivolumab administered IV Q3W for 4 doses (Combination Therapy Phase) as a co-administration, followed by 480 mg nivolumab monotherapy administered IV over approximately 30 minutes Q4W (Maintenance Phase), which will begin 3 weeks after the last combination dose.
- Arm B: 800 mg BMS-986249 administered IV Q8W in combination with 480 mg nivolumab administered IV Q4W. Co-administration will continue on cycles where both study treatments are scheduled, while nivolumab will be administered IV over approximately 30 minutes when scheduled as a monotherapy.
- Arm C: 1,200 mg BMS-986249 administered IV Q8W in combination with 480 mg nivolumab administered IV Q4W. Co-administration will continue on cycles where both study treatments are scheduled, while nivolumab will be administered IV over approximately 30 minutes when scheduled as a monotherapy.
- Arm D: 3 mg/kg ipilimumab in combination with 1 mg/kg nivolumab administered IV Q3W for 4 doses (Combination Therapy Phase), followed by 480 mg nivolumab monotherapy administered IV over approximately 30 minutes Q4W (Maintenance Phase), which will begin 3 weeks after the last combination dose. Nivolumab and ipilimumab will be administered sequentially as 2 separate IV infusions. Nivolumab will be given first, over approximately 30 minutes, followed by ipilimumab over approximately 30 minutes, beginning approximately 30 minutes after completion of the infusion of nivolumab.
- Arm E: 480 mg nivolumab monotherapy administered IV over approximately 30 minutes Q4W.

- Addendum Per Revised Protocol 07: Part 2A Arm A, Arm B, and Arm E are discontinued for further enrollment/randomization. The modification of enrollment/randomization in Part 2A is not a consequence of changes in the safety or tolerability profile or benefit/risk assessment of BMS-986249 (see Section 5.5.4). Currently active participants in these arms will continue treatment as assigned and may remain on treatment until protocol-defined discontinuation criteria have been met. In accordance with Revised Protocol 07, participants in Part 2A will be randomized across the study approximately 1:1:1 between 3 treatment arms:
  - Arm C: described above
  - Arm D: described above
  - Arm F: 600 mg BMS-986249 administered IV Q4W in combination with 480 mg nivolumab administered IV Q4W as a co-administration.

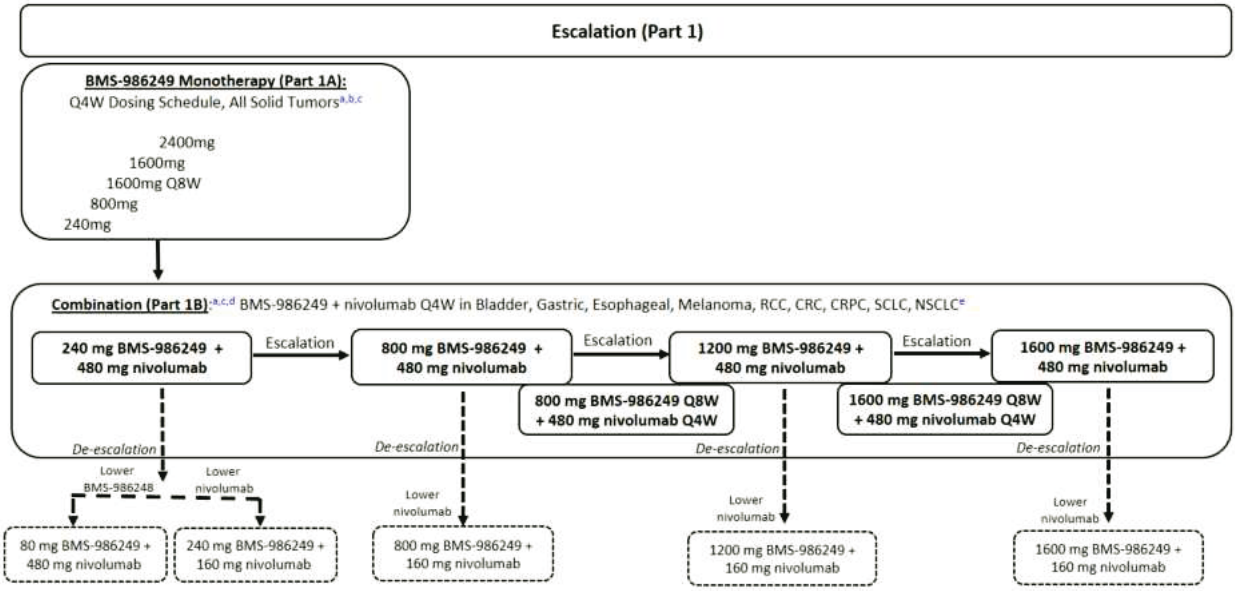
The BMS-986249 in Combination with Nivolumab Additional Tumor Cohort Expansion (Part 2B) will be comprised of signal seeking expansion cohorts including advanced or intermediate HCC participants previously treated with prior anti-PD-(L)1 therapy (Cohort 1), metastatic castration-resistant prostate cancer (mCRPC) participants treated with a prior taxane-containing chemotherapy regimen (Cohort 2), and unresectable locally advanced or metastatic TNBC participants treated with a prior chemotherapy-based treatment (Cohort 3). In each Part 2B single-arm tumor-specific expansion cohort, participants will receive 1,200 mg BMS-986249 administered IV Q8W in combination with 480 mg nivolumab administered IV Q4W. Co-administration will continue on cycles where both study treatments are scheduled, while nivolumab will be administered IV over approximately 30 minutes when scheduled as a monotherapy. The duration of study participation will be approximately 4 years (treatment of up to 2 years and follow-up of up to 2 years).

Addendum per Protocol Amendment 09: The duration of study participation will be approximately 2 years and 3 months (treatment of up to 2 years and Follow-up Period of 100 days post EOT).

At the Sponsor's discretion, scans will be submitted to an imaging core laboratory and may be reviewed by blinded independent central review (BICR) at a later date or at any time during the study.

The study design schematic is presented in Figure 5.1-1 (Part 1) and Figure 5.1-2 (Part 2). A detailed schematic for study-period and participant flow is presented in Figure 5.1-3.

Figure 5.1-1: Study Design Schematic - Part 1, the Dose Escalation Phase



Abbreviations: BMS = Bristol Myers Squibb; CRC = colorectal cancer; CRPC = castration-resistant prostate cancer; CTLA-4 = cytotoxic T lymphocyte-associated protein 4; DLT = dose-limiting toxicity; NSCLC = non-small cell lung cancer; PD-1 = programmed cell death protein 1; PD-L1 = programmed death ligand-1; Q4W = every 4 weeks; Q8W = every 8 weeks; RCC = renal cell carcinoma; SCLC = small cell lung cancer.

[a] Alternative dosing schedules (eg, Q8W) may occur after evaluation of available safety, PK, and [redacted] data, and upon discussion and agreement between the investigators and Medical Monitor (or designee), refer to Appendix 12.

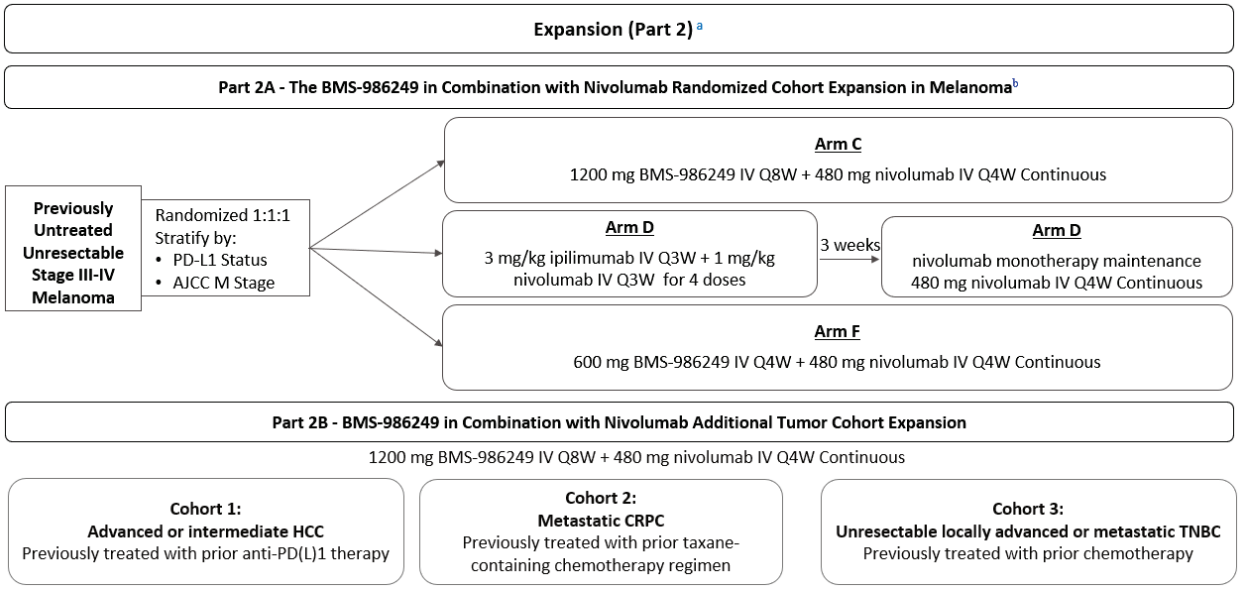
[b] Participants in the monotherapy arm must be anti-CTLA-4-naive. Prior anti-PD-1 or anti-PD-L1 exposure is allowed in the monotherapy arm, but at time of enrollment, participants must be at least 5 half-lives (approximately 100 days) from last dose of PD-1/PD-L1 therapy.

[c] Intra-participant dose escalation/reduction of BMS-986249 or nivolumab is not permitted.

[d] Part 1B will not start until demonstration of acceptable safety in at least 2 cohorts from Part 1A has occurred. Subsequently, treatment in both parts will occur in parallel.

[e] Part 1B participants with NSCLC will only be evaluated in a cohort once the DLT evaluation for that cohort has been completed.

Figure 5.1-2: Study Design Schematic - Part 2, the BMS-986249 Cohort Expansion Combination Therapy Phase

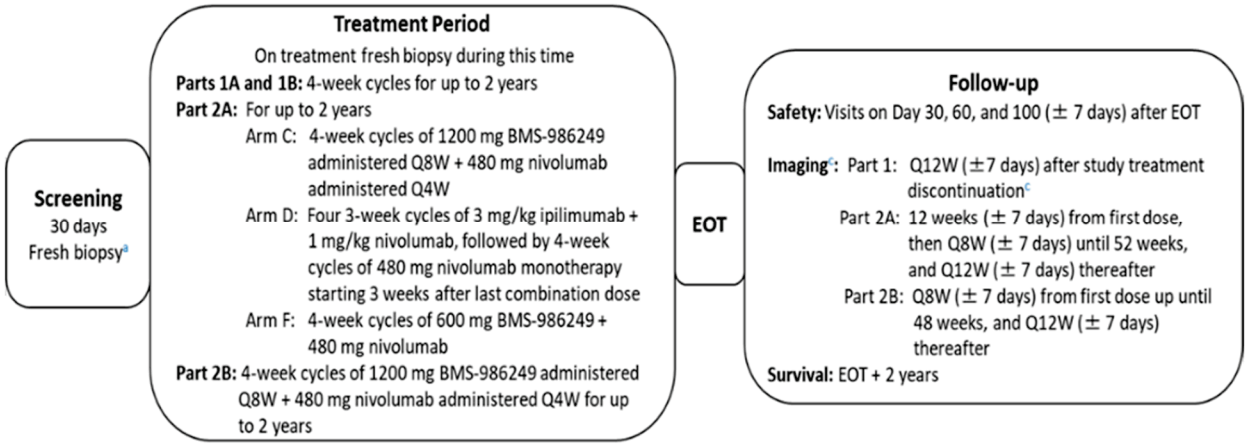


Abbreviations: AJCC = American Joint Committee on Cancer; CRPC = castration-resistant prostate cancer; HCC = hepatocellular carcinoma; IV = intravenous; PD-L1 = programmed death ligand-1; Q3W = every 3 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks; TNBC = triple-negative breast cancer.

[a] Will only open upon evaluation of available data from Parts 1A and 1B.

[b] Per Revised Protocol 07, Part 2A Arm A, Arm B, and Arm E were closed to enrollment and are not displayed. Part 2A Arm A, 240 mg BMS-986249 IV Q3W in combination with 360 mg nivolumab IV Q3W for 4 doses followed by nivolumab monotherapy Maintenance Phase of 480 mg nivolumab IV Q4W continuous. Part 2A Arm B, 800 mg BMS-986249 IV Q8W in combination with 480 mg nivolumab IV Q4W continuous. Part 2A Arm E, 480 mg nivolumab IV Q4W continuous.

Figure 5.1-3: Study Period and Participant Flow



Abbreviations: BMS = Bristol Myers Squibb; EOT = end of treatment, Q4W = every 4 weeks; Q8W = every 8 weeks; Q12W = every 12 weeks.

[a] May be required, refer to Section 2

[b] With Revised Protocol 07, Part 2A Arm A, Arm B, and Arm E closed to enrollment and are not displayed. Part 2A Arm A, 240 mg BMS-986249 IV Q3W in combination with 360 mg nivolumab IV Q3W followed by nivolumab monotherapy Maintenance Phase of 480 mg nivolumab IV Q4W continuous. Part 2A Arm B, 800 mg BMS-986249 IV Q8W in combination with 480 mg nivolumab IV Q4W continuous. Part 2A Arm E, 480 mg nivolumab IV Q4W continuous.

[c] During follow-up for up to 2 years after EOT, or until death, or initiation of another anti-cancer treatment, whichever occurs first. Refer to Section 2 and Section 9.1.1.

5.1.1 Screening Period

The screening period will be up to 30 days and begins by establishing the participant's initial eligibility and signing of the informed consent form (ICF). The screening assessments are shown in Table 2-1. If a participant exceeds the 30-day screening period due to a study-related procedure (eg, scheduling of a tumor biopsy or waiting for a study-related laboratory value), the participant must be re-consented and will require a new participant identification number. In this situation, the fewest number of procedures from the initial screening should be repeated to qualify the participant, while maintaining participant safety and eligibility. For Part 2A participants awaiting PD-L1 results, the screening window may be extended past the 30-day period upon discussion with the Medical Monitor (or designee). However, if screening extends over a prolonged period, baseline procedures, such as tumor assessments and labs, may need to be repeated so that they fall within the acceptable protocol-specified window. Within a given disease type, participants meeting all eligibility criteria will be enrolled in the study according to the part and treatment arm availability.

5.1.2 Treatment Period

The initial dosing regimen of BMS-986249 was selected as Q4W, with an additional dosing regimen of Q8W subsequently explored. All participants will be treated for up to 2 years. Continuous safety evaluation and tumor assessment occurring in Part 1, Part 2A, and Part 2B will

guide the decision to treat a participant with additional cycles of study therapy if the participant has confirmed clinical benefit (up to a maximum of 2 years).

Weekly study visits will be performed up to the first 12 weeks after the first dose of study treatment for the BMS-986249 Monotherapy Escalation (Part 1A), Safety Evaluation of Combination Doses of BMS-986249 with Nivolumab (Part 1B), BMS-986249 in Combination with Nivolumab Randomized Cohort Expansion in Melanoma (Part 2A), and BMS-986249 in Combination with Nivolumab Additional Tumor Cohort Expansion (Part 2B), followed by study visits Q4W thereafter. See Section 9.5 for further details.

For the BMS-986249 Monotherapy Escalation (Part 1A), BMS-986249 will initially be infused over approximately 30 minutes for the 240 mg dose. Infusion times for subsequent dose concentrations will vary to adjust for the different drug protein concentrations.

For the Safety Evaluation of Combination Doses of BMS-986249 with Nivolumab (Part 1B), both study treatments will be administered as a co-administration through the same IV bag. Initial dosing will be 240 mg BMS-986249 in combination with 480 mg nivolumab co-administration infused over approximately 120 minutes. Infusion times will vary with subsequent co-administration doses to adjust for the different drug protein concentrations. If an alternative dosing schedule is evaluated, co-administration will continue on cycles where both study treatments are scheduled, while nivolumab will be administered IV over approximately 30 minutes when scheduled as a monotherapy.

In the BMS-986249 in Combination with Nivolumab Randomized Cohort Expansion in Melanoma (Part 2A) dose administration will vary with treatment arm. See Section 5.1.

In the BMS-986249 in Combination with Nivolumab Additional Tumor Cohort Expansion (Part 2B), across all tumor-specific cohorts 1,200 mg BMS-986249 will be administered IV Q8W, while 480 mg nivolumab will be administered IV Q4W. Co-administration will continue on cycles where both study treatments are scheduled, while nivolumab will be administered IV over approximately 30 minutes when scheduled as a monotherapy.

BMS-986249 infusions, as a monotherapy or co-administration, will require a 60-minute observation period after the completion of the infusion for the first 3 doses for each participant.

See Table 7.1.1-1 for a complete list of dose selection and timing. Refer to the Pharmacy Manual for additional treatment administration, timing, and infusion details for BMS-986249, ipilimumab, and nivolumab.

5.1.2.1 BMS-986249 Monotherapy Escalation (Part 1A)

Approximately 45 evaluable participants are expected to be treated during the BMS-986249 monotherapy dose escalation (Part 1A) of the study guided by BLRM. Each participant will be administered IV doses of BMS-986249 in planned flat doses of 240, 800, 1,600, and 2,400 mg. Each dose is initially to be administered Q4W for a total of 2 years. Prior to declaring the MTD, and in consultation with investigators, the Sponsor has the option to expand any dose level previously established to be tolerable in order to obtain additional experience or to investigate dose

levels intermediate to those defined in the protocol. Planned dose levels may be modified (eg, alternative administration schedule, see Appendix 12), or intermediate dose levels added, based upon evaluation of available safety, PK, and [redacted] data.

Sentinel Participant

During the Dose Escalation Phase, a staggered dosing (sentinel participant) approach will be used. The first participant to be treated at C1D1 of each dose level will be observed for 5 days, before additional participants (ie, Participant 2 onward in that cohort) receive study treatments in the same dose level.

Initially, 3 participants will be enrolled at the start of each cohort, in accordance with the sentinel participant approach cited above. However, to allow for any unforeseen discontinuations (such as disease progression) before the 5-week DLT period (35 days) is completed, an extra participant may be enrolled in each dose-escalation cohort. Therefore, there may be a total of 4 participants (3 + 1) at the start of each cohort, provided that the fourth participant is able to start dosing within approximately 1 week of the third participant in the same dose-escalation cohort. Additional information on DLTs can be found in Section 7.5.1.

5.1.2.2 Safety Evaluation of Combination Doses of BMS-986249 with Nivolumab (Part 1B)

The Safety Evaluation of Combination Doses of BMS-986249 with Nivolumab (Part 1B) will be initiated in a staggered manner relative to the BMS-986249 monotherapy cohort once safety and preliminary PK data are provided from the first 2 monotherapy cohorts. The safety will be defined from BLRM and an overall assessment of available safety, PK, [redacted] and efficacy data of the BMS-986249 Monotherapy Dose Escalation (Part 1A). In each cohort, a flat dose of both BMS-986249 and nivolumab will be initially administered Q4W.

Subsequent dose selection of the combination will be based on evaluating the recommendation from BLRM and an overall assessment of available safety, PK, and [redacted] data. The dose regimens to be selected are shown in the study design schematic in Figure 5.1-1.

At no time will the dose of BMS-986249 in the Safety Evaluation of Combination Doses of BMS-986249 with Nivolumab (Part 1B) exceed the highest tolerated dose in the BMS-986249 Monotherapy Dose Escalation (Part 1A). Dose escalation in each cohort, within the constraints cited above, will be enrolled in parallel (see details in Section 7.2). Additional information on DLTs can be found in Section 7.5.1.

Sentinel Participant

During Part 1B, a staggered dosing (sentinel participant) approach will be used. The first participant to be treated at C1D1 of each dose level will be observed for 5 days, before additional participants (ie, Participant 2 onward in that cohort) receive study treatments in the same dose level.

Initially, 3 participants will be enrolled at the start of each cohort, in accordance with the sentinel participant approach cited above. However, to allow for any unforeseen discontinuations (such as disease progression) before the 5-week DLT period (35 days) is completed, an extra participant

may be enrolled in each dose-escalation cohort. Therefore, there may be a total of 4 participants (3 + 1) at the start of each cohort, provided that the fourth participant is able to start dosing within approximately 1 week of the third participant in the same dose-escalation cohort. Additional information on DLTs can be found in Section 7.5.1.

5.1.2.3 Dose Escalation Decisions for the BMS-986249 Monotherapy Escalation (Part 1A) and the Safety Evaluation of Combination Doses of BMS-986249 with Nivolumab (Part 1B)

The Dose Escalation Phase of the study will evaluate the safety and tolerability of BMS-986249, given alone or in combination with nivolumab, based on DLTs, using a BLRM (for the BMS-986249 Monotherapy Escalation [Part 1A] and for the Safety Evaluation of Combination Doses of BMS-986249 with Nivolumab [Part 1B]).

The DLT period will be 5 weeks, based primarily on prior safety knowledge for the active moiety (ipilimumab) of the BMS-986249 prodrug, and clinical PK data (Section 3.2.1.5).

The safety profile of ipilimumab as a monotherapy and in combination with nivolumab is generally consistent across studies, with a) the majority of AEs being inflammatory in nature, which is consistent with the proposed mechanism of action of ipilimumab; b) the same types of such select AEs in the GI tract, skin, liver, and endocrine system being reported; and c) most of these events being manageable with immune suppressive therapies. Analysis of ipilimumab TRAEs with onset in the initial 5 weeks, demonstrated a well-characterized safety profile consistent with the types of AEs occurring with longer duration that is generally manageable with established treatment algorithms. Treatment risk with BMS-986249 should therefore be recognized and managed with a 5-week DLT period. Clinical assessment will continue to take into consideration the entirety of available data (including AEs that occur outside the 5-week DLT period) from all treated participants when assessing the safety of a dose level and determining dosing for the next cohort.

During the Dose Escalation Phase (Part 1), a set of approximately 3 participants will be treated at each specified dose level. Cohort tolerability assessment and subsequent dose recommendation will occur when at least 2 evaluable participants within a cohort have completed a 5-week DLT period. Any toxicities that occur beyond the DLT period will be accounted for in making dose level decisions and/or dose level modifications. Additional information on DLTs can be found in Section 7.5.1.

If the potential DLT occurring in the third evaluable participant regarding the specific dose level does not influence the dose recommendation by BLRM, the next dose level may proceed without waiting for the third participant to complete the corresponding DLT observation period, after discussion and agreement between the Sponsor and investigators. Continuous reassessment of dose recommendation, by BLRM in the BMS-986249 monotherapy dose escalation (Part 1A) and in the Safety Evaluation of Combination Doses of BMS-986249 with Nivolumab (Part 1B), will be carried out for each dose level. The dose regimens to be selected are shown in the study design schematic in Figure 5.1-1.

During the Dose Escalation Phase (Part 1), planned dose levels may be modified (eg, alternative administration schedule, see Appendix 12 and Figure 5.1-1), or intermediate dose levels added,

based upon evaluation of available safety and PK/[redacted] data. Once the tolerability (during the DLT evaluation) of a dose level has been established, additional participants may be added at that dose level to better characterize the safety, PK, and [redacted] profiles.

5.1.2.4 The BMS-986249 Cohort Expansion Combination Therapy (Part 2)

The purpose of the cohort expansions is to gather preliminary efficacy information in specific populations regarding BMS-986249 in combination with nivolumab. In addition, safety, tolerability, PK, and [redacted] information will be evaluated. Further, patient-reported quality of life, symptoms, and treatment tolerability will be assessed using the EORTC QLQ-C30, EQ-5D-3L, FACIT GP5, and PRO-CTCAE (see Section 9.9).

The BMS-986249 in Combination with Nivolumab Randomized Cohort Expansion in Melanoma (Part 2A) will evaluate the efficacy and safety of BMS-986249 in combination with nivolumab relative to ipilimumab combined with nivolumab, and historical nivolumab monotherapy data, in a cohort of participants with previously untreated, unresectable or metastatic melanoma. See Section 5.1 and Figure 5.1-2.

The BMS-986249 in Combination with Nivolumab Additional Tumor Cohort Expansion (Part 2B) will evaluate the safety and tolerability of BMS-986249 in combination with nivolumab through single-arm expansion cohorts in previously treated advanced or intermediate HCC, metastatic CRPC, and unresectable locally advanced or metastatic TNBC.

Preliminary reviews of the data in Part 1 and Part 2 will occur prior to the final data base lock, in order to assess the initial safety, PK, and [redacted] signal. The earliest assessment of the efficacy signal for a Part 2A arm and/or Part 2B tumor cohort may be performed after approximately 15 to 20 participants are randomized into the arm/cohort and complete the first tumor scan (at about 8 to 12 weeks after start of treatment). The evaluation of this preliminary data will assist in further planning for the study, including the option to discontinue treatment arm(s) or de-escalate individual Part 2 arm/cohort dose levels, if supported by the data. The study is expected to continue as planned during this evaluation, until the interpretation of the data is complete. Any changes to the design based on such evaluation may be implemented via a protocol amendment, unless already anticipated and planned for by the current protocol.

Continuous evaluation of toxicity events in the Part 2 BMS-986249 Cohort Expansions will be performed throughout enrollment for all expansion cohorts. Upon clinical evaluation of toxicity events, Bayesian posterior probability may be used to trigger decision-making. Specifically, if the probability is equal or higher to 95% that the aggregate rate of treatment-related toxicities meeting DLT criteria in BMS-986249 is higher than the defined threshold of interest [redacted], a decision to interrupt further enrollment may be discussed with investigators.

If an arm/cohort is determined to have excess toxicity, the BMS-986249 dose/schedule previously evaluated may be replaced with a de-escalated dose/schedule of 800 mg BMS-986249 Q8W in combination with 480 mg nivolumab Q4W based on review of the available data and in consultation and agreement between Investigators and Sponsor via an administrative letter or note to file. If an arm/cohort is determined to have excess toxicity, and an alternative dose/schedule

(not defined above) is considered, a revised protocol reflecting the new dose level will be submitted prior to enrollment, unless already anticipated and planned for by the current protocol.

Part 2 participants will be allowed to continue study treatment until the first occurrence of any of the following:

- Completion of the maximum 2 calendar years of study therapy
- Progressive disease (PD) defined by RECIST v1.1 (Appendix 5) or PCWG3 for prostate cancer (Appendix 6) unless participants meet criteria for treatment beyond progression (Section 8.1.1)
- Clinical deterioration suggesting that no further benefit from treatment is likely
- Intolerability to therapy
- Participant meets criteria for discontinuation of study treatment as shown in Section 8.1

5.1.3 Treatment Beyond Progression

Tumor progression and response endpoints will be assessed using RECIST v1.1 criteria for solid tumors (Appendix 5) or PCWG 3 for prostate cancer (Appendix 6). Treatment beyond progression may be allowed in selected participants with initial RECIST v1.1 (or PCWG 3 for prostate) defined PD after discussion and agreement with the Medical Monitor (or designee), if the benefit-risk assessment favors continued administration of study treatment (eg, participants are continuing to experience clinical benefit as assessed by the investigator, tolerating treatment, and meeting other criteria; see Section 8.1.1).

Participants must be re-consented with an ICF addendum or similar document to continue treatment beyond progression. Treatment beyond progression will require continued tumor assessments.

5.1.4 Window Visits

A ± 2 day window is permitted to accommodate study participants and schedules during and between cycle visit days for all treatment visits, except for Cycle 1 Day 1.

5.1.5 Follow-up

5.1.5.1 Safety Follow-up Period

Upon completion of study therapy (or up to a maximum of 2 years, if applicable) or once the decision is made to discontinue the participant from treatment, that is, at end of treatment (EOT), all participants will enter a Safety Follow-up Period.

For participants who will complete all scheduled cycles of therapy, the EOT visit will be the same visit as the last scheduled and completed on-treatment visit and will be the start of the Safety Follow-up Period. For participants who will not complete all scheduled cycles of therapy, the EOT visit will be the most recent on-treatment visit (with all available safety and response data) and will not need to be repeated. Accordingly, for these participants, this visit will be considered the start of the Safety Follow-up Period.

After the EOT visit, follow-up study visits should occur at Days 30, 60, and 100 (±7 days) for all study participants. Safety reporting of AEs and SAEs should take place from date of informed consent through 100 days post EOT.

All participants should complete the 3 clinical safety follow-up visits regardless of whether new anti-cancer therapy is started, except those participants who withdraw consent for study participation.

5.1.5.2 Imaging Follow-up Period

At the time of study treatment discontinuation, participants will continue to have radiologic and clinical tumor assessments per Section 2.

The duration of the Imaging Follow-up Period will be for a total of 2 years following EOT, or until death, or initiation of another anti-cancer treatment, whichever occurs first. Radiological assessments for participants who have ongoing clinical benefit may continue to be collected after participants complete the Survival Follow-up Period of the study. Participants who have disease progression after an initial course of study therapy will be evaluated beyond the EOT visit and will be allowed to receive other tumor-directed therapy as required.

Addendum per Protocol Amendment 09: The duration of the Imaging Follow-up Period will be 100 days post EOT or until death, or initiation of another anti-cancer treatment, whichever occurs first. Radiological assessments for participants who have ongoing clinical benefit may continue to be collected after participants complete the Survival Follow-up Period of the study. Participants who have disease progression after an initial course of study therapy will be evaluated beyond the EOT visit and will be allowed to receive other tumor-directed therapy as required. The initiation of another anti-cancer treatment will indicate the end of the Imaging Follow-up Period.

5.1.5.3 Survival Follow-up Period

In parallel with the Safety Follow-up Period, all participants will start the Survival Follow-up Period.

Participants will be followed by telephone Q12W (from EOT) for 2 years or until death, loss to follow-up, withdrawal of consent, or conclusion of the study, whichever comes first. For Part 2 participants, EQ-5D-3L data will be collected by telephone or email during the Survival Follow-up Period. Participants will have both the Imaging Follow-up Period and Survival Follow-up Period occur simultaneously. The duration of this follow-up is up to 2 years after EOT, although a longer follow-up period could be considered in selected cases if an efficacy signal is apparent. Subsequent therapies will also be recorded in this Survival Follow-up Period.

Addendum per Protocol Amendment 09: Since further formal OS analyses will not be conducted, the maximum study duration will be through 100 days post EOT. Participants who are in the follow-up period past 100 days after EOT should be discontinued from the study. Participants will be followed by telephone (from EOT) through 100 days post EOT or until death, loss to follow-up, withdrawal of consent, or conclusion of the study, whichever comes first. For Part 2 participants, EQ-5D-3L data will be collected by telephone or email during the Survival Follow-up Period. Participants will have both the Imaging Follow-up Period and Survival Follow-up Period occur

simultaneously. The duration of this follow-up will be through 100 days post EOT. Subsequent therapies will also be recorded in this Survival Follow-up Period.

5.1.6 Data Monitoring Committee and Other External Committees

Relative to the exploratory nature of this Phase 1/2 study and the robust experience that already exists around use of ipilimumab (which is a surrogate for BMS-986249), a Data Monitoring Committee is not needed for this study. In addition to the comprehensive safety monitoring plan outlined below, the following key points were considered for this decision:

- This is an open-label study.
- The eligibility criteria exclude participants with disease characteristics that could predispose to higher risk of morbidity (eg, history of interstitial lung disease, recent history of thrombosis).
- Exclusion of participants with known autoimmunity also applies because they could be at risk for exacerbation of their condition by the administration of therapies that relieve immune suppression such as BMS-986249 and nivolumab.
- Participants will be observed frequently for clinical evaluation and blood counts during dose escalation.
- Well-defined discontinuation criteria are established in the protocol for individual participants for both safety and treatment futility with clear criteria for treatment discontinuation, dose delay, and toxicity management.

BMS has in place a multi-layered process for ensuring patient safety through close collaboration of study site investigators, the BMS study team, and the BMS GPVE led Medical Surveillance Team (MST). This collaborative process constitutes the Data Safety Monitoring Plan for the study as detailed below:

Study safety is evaluated continuously by representatives of BMS GPVE, who operate independently from the clinical team and monitor safety across all BMS protocols. AEs are monitored continuously by GPVE. Signal detection is performed at least monthly and ad hoc throughout the study by the MST composed, at a minimum, of the GPVE medical safety assessment physician (Chairman of the MST) and GPVE single case review physician, the study Medical Monitor(s) (or designee), the study biostatistician, and epidemiologist. The MST monitors actual or potential issues related to patient safety that could result in a significant change in the medical benefit-risk balance associated with the use of study treatments. Furthermore, investigators will be kept updated of important safety information, such as DLTs, during teleconferences between investigators and the BMS clinical team, which will be held at least Q4W during dose escalation and at least monthly during cohort expansion. If appropriate, select safety issues may be escalated to a senior level, multidisciplinary, BMS-wide Medical Review Group for further evaluation and action.

To support safety oversight, BMS has established ongoing processes for collection, review, analysis, and submission of individual AE reports and their aggregate analyses. Because this is an open-label study, the Medical Monitor and the investigators will have access to all data necessary for safety evaluation.

All participants in this study represent individuals with high unmet medical need because the prognosis for advanced/metastatic solid tumors is generally very poor.

5.2 Number of Participants

- Part 1A Monotherapy Escalation: The total sample size is up to approximately 45 evaluable participants.
- Part 1B Combination Escalation: The total sample size is up to approximately 60 evaluable participants.
- Part 2A Expansion in Melanoma: The total sample size is up to approximately 200 evaluable participants with approximately 60 evaluable participants each treated in Arm C, Arm D, and Arm F, respectively. Prior to Revised Protocol 07, up to approximately 20 evaluable participants may have been enrolled across Arms A, B, and E, collectively. (See Section 10.1.2.)
- Part 2B Additional Tumor Cohort Expansion: The total sample size is up to approximately 120 evaluable participants with approximately 40 evaluable participants per tumor type cohort.

5.3 End of Study Definition

The start of the study is defined as the first visit for the first participant screened. Similarly, the end of the study is defined as the last visit or scheduled procedure shown in Section 2 for the last participant. Primary study completion is defined as the final date on which data for the primary endpoint are expected to be collected.

5.4 Scientific Rationale for Study Design

BMS-986249 is being investigated in humans with advanced solid tumors either as monotherapy or in combination with nivolumab.

5.4.1 Rationale for the BMS-986249 Monotherapy Dose Escalation (Part 1A) and the Safety Evaluation of Combination Doses of BMS-986249 with Nivolumab (Part 1B) Design

The projected human efficacious dose of BMS-986249 is based on the comparable exposure-efficacy relationship observed for BMS-986249 and ipilimumab in nonclinical models. The human efficacious dose of BMS-986249 is projected to be 3 mg/kg (240 mg flat dose), the same as ipilimumab's approved clinical monotherapy dose. The safety of ipilimumab has been extensively characterized in more than 28,686 participants with different cancer types (refer to the ipilimumab IB for further details[15]). In nonclinical experiments, BMS-986249 was well tolerated at doses up to 50 mg/kg, with evidence of pharmacodynamic effects at all doses. Thus, this study will evaluate dose escalation of BMS-986249 at planned flat doses of 800, 1,600, and 2,400 mg. Additional de-escalation doses may be tested.

Furthermore, the study plans to evaluate different dose escalations of BMS-986249 in combination with nivolumab. The combination study design and the doses are based on the results of safety data from clinical trials evaluating nivolumab and ipilimumab combinations (CheckMate 067[1],

012,[20] and 016[19]). The study will evaluate BMS-986249 in combination with 480 mg nivolumab (flat dose) as outlined in the study design schematic in Figure 5.1-1.

Modifying the ipilimumab structure with a Probody mAb has the potential to offer decreased systemic absorption, which may translate into better tolerability but similar efficacy with ipilimumab. Furthermore, the PK data will be evaluated to ensure that there is evidence of decreased systemic absorption.

Given that BMS-986249 shares the structure and properties of ipilimumab, the population in this study includes participants naive to checkpoint inhibitors in order to minimize bias when evaluating safety and efficacy.

5.4.2 Rationale for the Combination of BMS-986249 and Nivolumab

Studies have shown that tumors co-opt some specific immune-checkpoint pathways to engender immune resistance, particularly against T cells that are specific for tumor antigens. Co-engagement of multiple immune receptors on activated T cells (combination immunotherapy) may result in better outcomes as compared with engagement of a single immune receptor.

This assumption is currently being tested in multiple combination regimens with various agents. However, the only combination with proven clinical activity is that of ipilimumab and nivolumab.

CTLA-4 and PD-1 induce tumor evasion from the immune system through complementary but distinct mechanisms. Nivolumab interferes with the interaction of PD-1 with its ligands PD-L1 and PD-L2, allowing for activation and proliferation of exhausted or anergic T-effector cell in the tumor. Ipilimumab interferes with the interaction of CTLA-4 with CD80 (B7-1) and CD86 (B7-2) molecules expressed on antigen-presenting cells, allowing for T cell activation through engagement of the co-stimulatory receptor CD28 that binds to these same B7 ligands.

The combination of ipilimumab and nivolumab is approved in the US for the treatment of advanced melanoma. Information regarding safety and efficacy can be found in the nivolumab IB.[12] The combination of nivolumab and ipilimumab is currently under evaluation in various doses, schedules of administration, and other tumor types. Results of the combination studies showed promising activity with higher but tolerable toxicity compared with studies on ipilimumab or nivolumab alone. Different doses and schedules of administration were evaluated with different outcomes in terms of safety, tolerability, and efficacy depending on tumor type.

Based on the described synergy between ipilimumab and nivolumab, the current study will evaluate the safety, tolerability, and efficacy of the combination of BMS-986249 with nivolumab, with the rationale that BMS-986249 may yield a more tolerable treatment in combination with nivolumab. This may provide the opportunity and translate the combination in a more effective regimen for a large number of patients in different tumor types.

Furthermore, ipilimumab and nivolumab in combination therapy in participants with NSCLC is poorly tolerated, as demonstrated by the results in CheckMate CA209012.[20] To minimize the introduction of bias, participants with NSCLC will not be included in the cohort during the DLT evaluation period. Since there is evidence of efficacy of the combination in NSCLC, once the DLT

and the MTD are identified, participants with NSCLC will be evaluated to determine the safety and preliminary efficacy of the combination therapy.

5.4.3 Rationale for Tumor Selection for Part 1B

Preliminary tumor types (eg, RCC, NSCLC, melanoma, gastric cancer, and bladder cancer) and additional tumor types [eg, SCLC, CRC, CRPC, and esophageal cancer] were selected in Part 1B to evaluate the safety and tolerability of BMS-986249 in combination with nivolumab based on the following rationale:

- Previously demonstrated safety profile of ipilimumab in combination with nivolumab in patients with melanoma, RCC, NSCLC, urothelial carcinoma, SCLC, gastric cancer, gastroesophageal junction cancer, adenocarcinoma of the lower esophagus, and CRC.
- Previously demonstrated anti-tumor immune responses of ipilimumab alone and in combination with nivolumab in patients with melanoma, SCLC, NSCLC, RCC, CRPC, and gastric cancer.

Non-clinical data suggests that BMS-986249 maintains activity at the tumor site and reduces peripheral systemic exposure to CTLA-4 blockade compared to ipilimumab. Hence, BMS-986249 may potentially improve the therapeutic index previously seen with ipilimumab treatment in the aforementioned tumor types.

5.4.4 Rationale for Treatment Duration

The optimal duration of immunotherapy is an important question and continues to be investigated. Evaluation of continuous ipilimumab therapy beyond the recommended regimen of 12 weeks of ipilimumab (4 doses Q3W) is currently ongoing, and results are not yet available. Re-induction or maintenance therapy Q12W with ipilimumab has been tested in some study participants. Overall, the safety profile observed in these participants was consistent with the safety profile observed in participants in the induction phase. There were no unexpected toxicities due to re-induction or maintenance. The most common TRAEs during re-induction or maintenance affected the GI tract and skin and were Grade 1-2 in severity.[15] Data from animal models suggest that prolonged therapy might be beneficial.

In Study CA209153, participants with previously treated advanced NSCLC who completed 1 year of nivolumab therapy were randomized to either continue or stop treatment, with the option of retreatment upon progression. Among 163 participants still on treatment at 1 year and without progression, those who were randomized to continue nivolumab had significant improvement in PFS compared to those who were randomized to stop treatment, with median PFS (post-randomization) not reached versus 10.3 months, respectively; HR=0.42 (95% CI, 0.25 to 0.71). With a median follow-up of 14.9 months post-randomization, there also was a trend for participants on continued treatment to live longer (OS HR = 0.63 [95% CI: 0.33, 1.20]). Of note, the PFS curves in both groups plateau approximately 1 year after randomization (ie, 2 years after treatment initiation), suggesting that there may be minimal benefit in extending treatment beyond a total of 2 years.[21]

Moreover, accumulating data suggest that 2 years of PD-1 checkpoint inhibitor treatment may be sufficient for long-term benefit. In Study CA209003, a dose-escalation cohort expansion trial evaluating the safety and clinical activity of nivolumab in participants with previously treated advanced solid tumors (including 129 participants with NSCLC), specified a maximum treatment duration of 2 years. Among 16 participants with NSCLC who discontinued nivolumab after completing 2 years of treatment, 12 participants were alive > 5 years and remained progression -free without any subsequent therapy. In the CA209003 NSCLC cohort, the OS curve begins to plateau after 2 years, with an OS rate of 25% at 2 years and 18% at 3 years.[22] These survival outcomes are similar to Phase 3 studies in previously treated NSCLC, in which nivolumab treatment was continued until progression or unacceptable toxicity (2 year OS rates of 23% and 29%, and 3 year OS rates of 16%-18% for squamous and non-squamous NSCLC respectively).[23]

Taken together, the data suggest shorter duration of nivolumab of only 1 year was associated with increased risk of progression in previously treated participants with NSCLC, suggesting that treatment beyond 1 year is likely needed. Also, treatment beyond 2 years is unlikely to confer additional clinically meaningful benefit and that the risk of progression after discontinuing treatment at 2 years is low.

Collectively, these data suggest that there is minimal, if any, benefit derived from continuing immuno-oncology (I-O) treatment beyond 2 years in advanced tumors. However, even though immunotherapy is well tolerated, participants will be at risk for additional toxicity with longer term treatment. Therefore in Study CA030001, treatment with BMS-986249 and nivolumab will be extended for up to 2 years.

5.4.5 Rationale for Treatment Beyond Progression

Immunotherapeutic agents produce atypical clinical response patterns that are not usually observed with conventional chemotherapy. Accumulating clinical evidence indicates that some participants treated with immune system stimulating agents may develop disease progression by the conventional response criteria before demonstrating clinical objective responses and/or stable disease (SD).

Two distinct non-conventional patterns have been reported: 1) a reduction in target tumor burden despite the appearance of new lesion(s) and 2) a transient increase in target tumor burden in an initial phase, followed by subsequent tumor shrinkage.

These phenomena were observed in the BMS Phase 2 study (Study CA209003) of nivolumab in participants with solid tumors. Two hypotheses potentially explain these phenomena. First, enhanced inflammation within tumors could lead to an increase in tumor size, which would appear as enlarged index lesions and as newly visible small non-index lesions. Over time, both the malignant and inflammatory portions of the mass may then decrease, leading to overt signs of clinical improvement. Alternatively, in some individuals, the kinetics of tumor growth may initially outpace anti-tumor immune activity. With sufficient time, the anti-tumor activity will dominate and become clinically apparent. Therefore, it is important to avoid premature discontinuation of the study treatment that might induce a non-conventional response pattern in some participants.

The decision to continue treatment beyond investigator-assessed progression should be discussed with the Medical Monitor (or designee) and documented in the study records. The assessment of clinical benefit should take into account whether the participant is clinically deteriorating and unlikely to receive further benefit from continued treatment.

5.4.6 Rationale for Selecting Melanoma in Part 2A Expansion

Considerable progress in the treatment of metastatic melanoma has been made in the past 10 years with the approval of immune checkpoint–blocking antibodies. The safety and efficacy of individual checkpoint inhibition was first established with the anti-CTLA-4 ipilimumab, in advanced melanoma (See Section 3.2.3). Subsequently, the anti-PD-1 nivolumab, was shown to be safe and effective in multiple advanced tumor types including advanced melanoma (See Section 3.2.2). A multitude of trials in various advanced cancers have evaluated the combination of these 2 agents (See Section 3.2.4).

The most mature of these trials are in advanced melanoma participants. Studies CA209067 and CA209069 demonstrated a greater efficacy with the ipilimumab and nivolumab combination than either ipilimumab or nivolumab as a monotherapy. However, 3 mg/kg ipilimumab in combination with 1 mg/kg nivolumab, also demonstrated increased toxicity compared to either single agent. Given BMS-986249 is a Probody of ipilimumab, combination with nivolumab may be more tolerable, and may translate to a more effective treatment regimen for a larger number of metastatic melanoma participants than either ipilimumab in combination with nivolumab or nivolumab monotherapy.

5.4.7 Rationale for Part 2A Expansion Reference Arms

Evaluating the efficacy of a combination with solely experimental arms can be difficult due to many confounding factors, particularly if part of the combination has known anti-tumor activity. In addition, given the rapidly changing oncology treatment landscape, historical control data may not be fully representative of the current patient population. Hence, Arm D (ipilimumab in combination with nivolumab) and Arm E (nivolumab monotherapy) were initially included as reference arms to better evaluate the safety, efficacy, [redacted], and contribution of components of BMS-986249 when combined with nivolumab as described further below.

5.4.7.1 Rationale for Ipilimumab and Nivolumab Combination Therapy as a Reference

The combination of ipilimumab and nivolumab has been approved in the US, European Union, Australia, and additional regions for the treatment of metastatic melanoma. In study CA209067, 3 mg/kg ipilimumab in combination with 1 mg/kg nivolumab demonstrated a response rate of 58%, numerically higher than either single agent. In trial CA209069, the same combination dose achieved a response rate of 61%, significantly greater than that of ipilimumab alone. While the efficacy of the combination was improved, the incidence of serious adverse reactions, adverse reactions leading to permanent discontinuation or dosing delays, any grade drug-related select AEs, and Grade 3-4 AEs was higher in the combination arm of each study than in the respective monotherapy arms (see Table 5.4.7.1-1).[24,25]

Table 5.4.7.1-1: CA209067 Safety Result Summary

Safety Result	Nivolumab (N=313)	Nivolumab in Combination with Ipilimumab Regimen (N=313)	Ipilimumab (N=311)
TRAEs - Any grade	257 (82.1%)	299 (95.5%)	268 (86.2%)
TRAEs - Grade 3-4	51 (16.3%)	172 (55.0%)	85 (27.3%)
Drug-related select AEs - Any grade	25 (8.0%)	150 (47.9%)	69 (22.2%)
Drug-related select AEs - Grade 3-4	18 (5.8%)	112 (35.8%)	51 (16.4%)
Drug-related AEs leading to discontinuation	24 (7.7%)	114 (36.4%)	46 (14.8%)

Abbreviations: AE = adverse event; TRAE = treatment-related adverse event.

The combination of ipilimumab and nivolumab (Arm D) was chosen as a reference arm in Part 2A because the combination contains the parental antibody (ipilimumab) of BMS-986249. As an anti-CTLA-4 Probody, BMS-986249 is hypothesized to have preferential activity in the tumor microenvironment relative to normal tissue. BMS-986249 may then result in a reduction of the systemic irAEs seen after treatment with ipilimumab in combination with nivolumab, while maintaining anti-tumor activity. Including ipilimumab in combination with nivolumab will therefore allow for a more complete assessment of the therapeutic index of BMS-986249 in combination with nivolumab.

The dose and schedule of 3 mg/kg ipilimumab in combination with 1 mg/kg nivolumab administered IV Q3W for 4 doses (Combination Therapy Phase), followed by 480 mg nivolumab monotherapy administered IV Q4W (Maintenance Phase), beginning 3 weeks after the last combination dose, is based on the approved recommended dose in advanced melanoma.[26]

5.4.7.2 Rationale for Nivolumab Monotherapy as a Reference

In 2 distinct Phase 3 trials, nivolumab monotherapy demonstrated clinical benefit in participants with previously untreated unresectable or metastatic melanoma.[12] In the Phase 3 trial, CA209066, 3 mg/kg nivolumab monotherapy demonstrated an ORR of 40%, significantly greater than that of dacarbazine alone (14%).[27] In study CA209067, 3 mg/kg nivolumab monotherapy achieved an ORR of 45%, this was numerically lower than ipilimumab in combination with nivolumab, but significantly greater than that of ipilimumab alone. This pattern of response rate was consistent regardless of PD-L1 expression levels (see Table 5.4.7.2-1).[12]

Table 5.4.7.2-1: CA209067 ORR Result Summary by PD-L1 Expression

	nivolumab (N=316)	nivolumab in combination with ipilimumab regimen (N=314)	ipilimumab (N=315)
Objective Response	141 (45%)	185 (59%)	60 (19%)
ORR by tumour PD-L1 expression < 1%	35%, n=41/117	55%, n=68/123	19%, n=21/113
ORR by tumour PD-L1 expression ≥ 1%	55%, n=94/171	65%, n=101/155	19%, n=31/164

Abbreviations: ORR = objective response rate; PD-L1 = programmed death ligand-1.

In both CA209066 and CA209067, the incidence of AEs was lowest in the nivolumab group, most AEs were low-grade (Grade 1-2) with relatively few drug-related high-grade AEs (Grade 3-4, 15% in CA209066 and 16% in CA209067, see Table 5.4.7.1-1). In addition, the safety profile was consistent with that seen in other tumor types.[24,27] These data resulted in nivolumab being approved for use by the U.S. FDA in 2014, Marketing Authorization in Europe in 2015, and additional regions for the treatment of metastatic melanoma.[12]

Nivolumab monotherapy was initially chosen as a reference arm in Part 2A because it may have allowed for a contemporaneous assessment of the contribution of components and therapeutic index of BMS-986249 in combination with nivolumab.

The dose and schedule of 480 mg nivolumab administered IV Q4W is based on the approved recommended dose in advanced melanoma.[26]

Nivolumab monotherapy has demonstrated a generally consistent safety profile as a single agent. However, the safety profile of nivolumab in combination therapy varies, and both the frequency and severity of TRAEs may be greater than that observed with monotherapy. Across melanoma studies, nivolumab monotherapy has demonstrated anti-tumor activity; however, outcomes analysis of CA209067 with a minimum follow-up of 60 months demonstrated median OS was more than 60.0 months (median not reached) in the ipilimumab in combination with nivolumab group versus 36.9 months in the nivolumab monotherapy group.[28] In addition, the mean treatment-free survival for ipilimumab in combination with nivolumab-treated participants was 19.7 months of the 60-month period versus 9.9 months in the nivolumab group (difference 9.8 months; 95% CI, 6.7–12.8).[29]

With emergent data, provider and patient treatment preferences are affected by a number of factors including efficacy measures, AE profiles, and individual patient characteristics (eg, age, tumor burden, brain metastasis).[30] Hence, potential participants able to randomize into an ipilimumab in combination with nivolumab or nivolumab reference arm may not accurately reflect the broader metastatic melanoma patient population. Upon consideration of the evolving melanoma treatment

landscape and emergent data from CA209067, no further enrollment/randomization will occur into Part 2A Arm E with Revised Protocol 07.

5.4.8 Rationale for Part 2A Stratification by M-Staging and PD-L1 Status

In order to minimize the potential for imbalances across treatment arms, participants will be stratified by PD-L1 expression (≥ 1% tumor cell surface expression versus < 1% tumor cell expression/indeterminate), and the AJCC M stage (M0/M1a/M1b versus M1c) in Part 2A. Prognostic implications of M-Staging are well established.[31] Among patients treated with nivolumab monotherapy and the combination of ipilimumab and nivolumab, higher response rates have been observed in patients with PD-L1 tumor expression ≥ 1%, thus stratification in this study will ensure better balance in baseline characteristics and will minimize bias in terms of response across treatment groups.[32,33] While both BRAF positive and BRAF wild-type participants are eligible, BRAF status is not a stratification factor.

5.4.9 Rationale for Selecting HCC, CRPC, and TNBC in Part 2B Expansion

HCC is a highly lethal cancer, resulting as a third leading cause of cancer-related deaths globally.[34] Immunotherapeutic compounds, such as anti-PD-1, anti-PD-L1, and anti-CTLA-4 agents, either as monotherapy or as combination therapy, have shown benefit when used in different lines of treatment for unresectable HCC. In CA209040, nivolumab 1 mg/kg and ipilimumab 3 mg/kg Q3W combination therapy demonstrated promising efficacy and received accelerated approval by the FDA with 33% ORR in the second-line post-sorafenib setting. With this combination, however, 95% of participants experienced any-grade TRAEs (53% Grade 3-4 TRAEs) and 29% of the participants discontinued treatment due to study treatment toxicity, suggesting a need for a regimen with an improved safety and tolerability profile.[35] Additionally, the use of anti-PD-(L)1 agents in combination with anti-angiogenics (ie, anti-vascular endothelial growth factor [VEGF]) has become the standard of care in the unresectable HCC setting not amenable for curative surgery or locoregional therapy. However, the inhibition of the VEGF receptor and signaling pathway in HCC has shown concerning toxicity, such as hypertension and gastroesophageal variceal bleeding. Thus, safer alternative regimens that will allow better clinical outcomes are still needed.[36,37] Given BMS-986249 is a Probody of ipilimumab, participants with HCC may benefit from treatment with BMS-98649 in combination with nivolumab.

mCRPC is defined as participants with confirmed castrate levels of testosterone following orchiectomy or treatment with androgen deprivation therapy (ADT), and the presence of novel distant soft tissue or bony metastases by the National Comprehensive Cancer Network criteria. In the initial analysis of the Phase 3 CA184043 trial evaluating mCRPC participants in the post-docetaxel setting, ipilimumab 10 mg/kg with bone-directed radiotherapy compared with placebo with bone-directed radiotherapy demonstrated a significant improvement in PFS (median 4 months ipilimumab versus 3 months placebo, HR 0.70, 95% CI 0.61-0.82), a high proportion of participants with a confirmed > 50% prostate-specific antigen (PSA) decline (13.1% ipilimumab versus 5.2% placebo, 95% CI NA), and non-statistically significant benefit in OS (median 11.2 months ipilimumab versus 9.95 months placebo, p = 0.053). The pre-planned final long-term survival analysis (median follow-up of 50 months) showed OS favored the ipilimumab group with

survival rates being 2 to 3 times higher than radiotherapy alone at 3 years and beyond.[38] Preclinical CRPC tumor models indicate that the combination of PD-1 and CTLA-4 receptor blockade may improve anti-tumor activity. Combination therapy of ipilimumab and nivolumab was evaluated in CA209650 where durable objective responses in a subset of mCRPC participants was observed (10% ORR with all responders exhibiting durable responses at time of data cutoff).[39] However, more than 75% of mCRPC participants in the post-chemotherapy setting were not able to receive the full 4 planned cycles of the combination dose, 3 mg/kg ipilimumab with 1 mg/kg nivolumab Q4W (53% Grade 3-4 TRAEs), suggesting tolerability of the combination regimen may be a concern for participants with mCRPC.[39] Given BMS-986249 is a Probody of ipilimumab, participants with CRPC may benefit from treatment with BMS-986249 in combination with nivolumab.[39]

TNBC is defined by the absence of estrogen receptor (ER) and progesterone receptor expression, and lack of amplification of the human epidermal growth factor receptor 2 (HER2)/Neu (ErbB2) gene and/or HER2 protein overexpression. TNBC is considered to be the most immunogenic breast cancer (BC) subtype, as reflected by higher rates of tumor-infiltrating lymphocytes, higher rates of PD-L1 expression, as well as higher rates of immunogenic gene signatures' upregulation.[40,41,42] To date, PD-L1 inhibition in combination with chemotherapy has demonstrated clinical activity in the advanced or metastatic setting with a modestly extended DOR compared to chemotherapy, though clinical benefit appears to be limited to participants who are PD-L1 positive.[43,44] As described in Sections 3.2.3 and 3.2.4, ipilimumab alone and in combination with nivolumab has been assessed in a number of tumors and has been shown to generate clinically meaningful and durable responses irrespective of PD-L1 status. CTLA-4 is expressed at the cell membrane of a subgroup of TNBC tumors and may regulate key signal transducers in tumor cells.[45,46] The combination of PD-L1 and CTLA-4 inhibition has been assessed in a number of different BC preclinical models, which indicate potential synergistic anti-tumor activity.[47] In a BC gene 1 (BRCA1)-deficient TNBC preclinical model, cisplatin treatment combined with dual anti-PD-1 and anti-CTLA-4 treatment substantially augmented anti-tumor immunity, resulting in an avid systemic and intra-tumoral immune response.[47] Indeed, in CA209032, combination of nivolumab and ipilimumab improved clinical activity (median OS of 10.6 months) but increased toxicity events (44% Grade 3-4 TRAEs) in heavily pre-treated participants with metastatic TNBC, as compared to nivolumab monotherapy.[48] In the neoadjuvant setting, a single dose of ipilimumab and cryoablation and/or nivolumab was demonstrated to be safe and tolerable where all participants underwent surgery without delay, and all participants in the ipilimumab and cryoablation group remaining recurrence free at time of data cutoff with median follow-up of 66 months. The addition of nivolumab to ipilimumab and cryoablation resulted in a higher expression of activation markers on peripheral T cells and downregulation of suppressor cells.[49] The Phase 2 DART (SWOG S1609, Cohort 36) study, assessed nivolumab 240 mg combined with ipilimumab 1 mg/kg Q6W among 17 participants with pre-treated metastatic metaplastic BC that were predominantly TNBC with a median of 2 lines prior therapy. ORR of 18% was demonstrated with ongoing responses in all 3 participants at time of clinical data cutoff. 24% experienced

Grade 3-4 TRAEs and 0% discontinuing treatment due to study treatment toxicity.[50] Therefore, preclinical and clinical evidence suggests the combination of anti-PD-L1 and anti-CTLA-4 may provide a new treatment option for patients with TNBC. Given BMS-986249 is a Probody of ipilimumab, combination with nivolumab may translate to a clinically meaningful treatment regimen for TNBC participants.

5.4.10 Rationale for Quality of Life Evaluation

The evaluation of PROs is an increasingly important aspect of clinical efficacy in oncology trials. Such data provide an understanding of the impact of treatment from the participant's perspective and offer insights into patient experience that may not be captured through physician reporting. Additionally, generic health-related quality of life measures provide data needed for calculating utility values to inform health economic models.

The EORTC QLQ-C30 will be used to assess changes in functioning, symptoms, and QoL over time, the EQ-5D-3L will be used to assess general health status, the FACIT GP5 (single item) will be used to assess the overall bother of side effects, and the PRO-CTCAE will be used to assess the severity, frequency, and interference of side effects. These questionnaires will be used in Part 2A and Part 2B.

5.5 Justification for Dose

5.5.1 BMS-986249 Rationale for Starting Dose in Humans

The FIH starting dose of BMS-986249 is selected to be 240 mg (equivalent to approximately 3 mg/kg) Q4W, assuming a median body weight of 80 kg. This starting dose is the same as the approved ipilimumab monotherapy dose in melanoma participants, but with a less frequent schedule (Q4W versus the approved Q3W dosing regimen for ipilimumab). The starting dose selection is supported by the reduced toxicities and systemic pharmacodynamic responses of BMS-986249 compared to ipilimumab in nonclinical pharmacology and toxicology studies. In addition, BMS-986249, as a Probody mAb of ipilimumab, is expected to have the same type of irAEs as those of ipilimumab, which have been well defined in the clinic. The safety risk of BMS-986249 at the starting dose, therefore, can be well managed based on the ipilimumab risk evaluation and mitigation strategy (REMS) guidelines approved by FDA.

It is expected that BMS-986249 exhibits the same type of irAEs as ipilimumab, irAEs that can be clinically monitored and treated. The nonclinical toxicology and pharmacology assessment of BMS-986249 demonstrated decreased systemic immune-activating pharmacodynamic responses and toxicities in cynomolgus monkeys but similar anti-tumor efficacy in a MC38 mouse tumor model in comparison with ipilimumab. Human PK projection suggests that BMS-986249 will slowly convert to the fully active species in systemic circulation with a steady-state exposure approximately [redacted] of that of ipilimumab, further indicating less systemic toxicities of BMS-986249 than of ipilimumab at the same dose level. Taken together, the approved ipilimumab monotherapy dose of 3 mg/kg in melanoma participants is suggested as the starting dose of BMS-986249 to offer efficacy benefits and likely reduced toxicity to the FIH trial participants.

5.5.1.1 Starting Dose Selection Supported by BMS-986249 Nonclinical Pharmacology

In nonclinical pharmacology and toxicology studies, BMS-986249 demonstrated reduced in vitro activities, in vivo systemic active drug exposure, and pharmacodynamic responses, yet maintained comparable anti-tumor activity in mouse MC38 tumor model. The key differences between BMS-986249 and ipilimumab are summarized below.

- BMS-986249 binds human CTLA-4 expressed on 58 α-β-CTLA-4/CD3 cells with a 41-fold higher EC50 than ipilimumab (22 nM versus 0.5 nM). The reduced binding affinity of BMS-986249 translates to a 2-fold reduction of activities in SEB human T cell functional assay as well as Fcγ receptor-mediated ADCC assay.
- PK of BMS-986249 in mice and cynomolgus monkeys suggests that the intact Probody mAb is slowly converted to mono- and dual-cleaved species in vivo. The projected systemic exposure of the dual-cleaved Probody mAb, which is equally active as ipilimumab, is 38% of ipilimumab exposure when BMS-986249 is administered at the same dose as ipilimumab in participants.
- In human CTLA-4 knock-in mice bearing MC38 tumors, ipilimumab led to dose-dependent immune activation such as increased Ki-67 and ICOS levels on T cell subsets in the spleen; whereas BMS-986249 only showed the immune activation pharmacodynamic effects in the highest dose group (10 mg/kg), with the activation 2-fold lower than that of ipilimumab at the same dose. In contrast to the reduced pharmacodynamic effects in spleen, BMS-986249 maintained anti-tumor activity comparable to that of ipilimumab.
- In a GLP 1-month repeat-dose toxicity study in cynomolgus monkeys, BMS-986249 exhibited lower systemic T cell activation/pharmacodynamic responses when compared to ipilimumab in a dose- and time-dependent manner, corresponding with a slow conversion of BMS-986249 to its active forms. The magnitude of pharmacodynamic activity for each dose was 50 mg/kg/week ipilimumab > 10 mg/kg/week ipilimumab = 50 mg/kg/week BMS-986249 > 10 mg/kg/week BMS-986249.

Assuming that the reduced in vitro activities, in vivo systemic active drug exposure, and pharmacodynamic responses of BMS-986249 relative to ipilimumab in nonclinical studies translate to participants with cancer, BMS-986249 at the starting dose of 3 mg/kg may provide similar efficacy to ipilimumab at the same dose level but with reduced systemic active drug exposure and reduced pharmacodynamic responses that may be responsible for irAEs.

5.5.1.2 Starting Dose Selection Supported by the HNSTD in Monkeys

In the 1-month repeat-dose toxicity study in cynomolgus monkeys, BMS-986249 demonstrated overall decreased toxicities when compared to ipilimumab at same doses (10 and 50 mg/kg/week), and no new toxicities of BMS-986249 were observed compared to ipilimumab. As a result, the highest tested dose of 50 mg/kg/week was considered as the HNSTD, 5-fold higher than the ipilimumab HNSTD at 10 mg/kg. The FIH starting dose of BMS-986249 from the HNSTD-based toxicology approach was 8 mg/kg after applying a safety factor of 6-fold. As a result, the selected

BMS-986249 starting dose of 3 mg/kg is nearly 3-fold lower and, thus, is more conservative than the starting dose derived from the toxicology approach.

5.5.1.3 Starting Dose Selection Based on Ipilimumab Clinical Safety Data[51]

The AEs of ipilimumab in cancer patients are mostly irAEs, which have been well defined in terms of their incidence, severity, time to onset, and resolution. In participants with advanced melanoma, the irAEs of ipilimumab at 3 mg/kg Q3W for 4 cycles occurred in approximately 60% to 65% of the participants. These AEs were mostly Grade 1-2 and affected primarily the skin (in 43% to 45% of participants) and GI tract (in 29% to 32% of participants), followed by the liver and endocrine system (in 6% to 8% of participants). The vast majority of these irAEs occurred within 12 weeks of initial dosing, with a median time of Grade 2-4 irAEs occurring at 4.6 weeks.[52] In addition, low incidence of infusion-related reaction (IRR) of ipilimumab was also reported in 2.2% and 4.3% of participants treated at 3 and 10 mg/kg infused over 90 minutes and can be treated with premedication of diphenhydramine.[56] Management of irAEs attributed to ipilimumab treatment have been well established in the REMS Guidelines approved by FDA.[53]

BMS-986249 is expected to have the same type but reduced irAEs compared with ipilimumab based on the Probody mAb mechanism, which has been demonstrated in the nonclinical pharmacology and GLP toxicology studies. The efficacious dose of BMS-986249 is projected to be 3 mg/kg, same as the ipilimumab approved clinical dose. Therefore, an FIH starting dose of BMS-986249 at 240 mg (equivalent to approximately 3 mg/kg) may achieve anti-tumor efficacy similar to that of ipilimumab and reduced toxicities in participants that can be well managed based on ipilimumab REMS guidelines.

5.5.1.4 Rationale for Flat Dosing

A flat dose (ie, in mg) of BMS-986249 will be used in this study instead of a body size-based (ie, body weight or body surface area) dose. Therapeutic mAb doses have been routinely calculated on a body size basis. This practice assumes that dosing by body size significantly reduces variability in therapeutic mAb exposure.[54] However, recent analyses of marketed and experimental mAbs have demonstrated that body size-based dosing did not always offer advantages over flat dosing in reducing exposure variability. Many mAbs are target-specific with a relatively large therapeutic window that increases the tolerability of exposure variability. Additionally, patient-specific, disease-specific, and physiologic characteristics often contribute to exposure variability, resulting in a generally smaller contribution of body size. Therefore, the dosing paradigm for mAbs should be assessed in the context of all of these unique characteristics.

With either dosing strategy, bias with respect to exposure is expected to occur in the extremes of the body weight distribution. In general, body size-based dosing could result in higher mAb concentrations in the heaviest patients (eg, 90th percentile), whereas flat dosing could lead to higher mAb concentrations in the lightest patients (eg, 10th percentile). Body weight distribution data from a clinical trial database of over 2,500 adults with solid or hematologic cancers suggest a log-normal distribution of body weight with median, 10th, and 90th percentiles of 78, 56, and 112 kg, respectively.[55]

In addition to the above rationale, flat dosing offers practical advantages over body size-based dosing, including a convenient approach with respect to pharmacy preparation and clinical administration, and is also more likely to reduce the potential for dosing errors related to body size-based calculations.[54] Because the magnitude of the impact of body size on the human PK of BMS-986249 is not yet determined, the PK and safety data from the Phase 1/2a study will be evaluated to validate the flat dosing approach. If appropriate, based on the entirety of the preliminary data, the Sponsor will consider a revision of the flat dosing strategy.

BMS-986249 will initially be administered Q4W. This dosing frequency is supported by the projected human T-HALF for BMS-986249 of 15 days. In addition, it complements the Q4W dosing regimen planned in Part 1B, Combination Doses of BMS-986249 with Nivolumab, thereby simplifying study logistics for both participants and investigators. An alternative dosing schedule may implemented upon evaluation of all available safety, PK, and [redacted] data. Alternative dose schedules in Part 1 that may be explored include Q8W (see Appendix 12 for potential alternative schedules of activities and PK/ADA), which will be initiated and documented by a note to file or administrative letter following discussions and agreement between the Investigators and Medical Monitor (or designee). If a cohort with a more frequent schedule of administration is explored, the dose level will be based on the PK data obtained from the Q4W dosing schedule, and will not exceed the highest dose level assessed and deemed tolerable.

5.5.2 Rationale for Ipilimumab and Nivolumab 30-minute Infusions

Ipilimumab is currently approved for IV administration over 90 minutes. Recently, Momtaz et al. retrospectively reviewed computerized pharmacy records at their institution of all patients with metastatic solid tumor malignancies who received at least 1 dose of 3 or 10 mg/kg ipilimumab over 90 minutes between 01-Apr-2008 and 30-Jun-2013.[56] They found a low incidence of IRRs: 2.2% and 4.3% for ipilimumab at 3- and 10-mg/kg doses, respectively (P=0.22, Fisher's exact test).[56] This finding led the investigators to prospectively evaluate 3 mg/kg ipilimumab administered IV over 30 minutes. In the first 120 patients evaluated, the incidence of IRR was 5.8%, and the few reactions that were observed occurred at the second dose of ipilimumab.[56] Two out of the 7 IRRs did not occur during the infusion. In addition, 6 out of the 7 IRRs were Grade 2, and in no case were the IRRs dose limiting. The investigators concluded that the incidence of IRRs in patients receiving 3 mg/kg ipilimumab IV over 30 minutes was acceptably low although slightly higher than that of the standard 90-minute infusion.[56] The IRRs were managed according to institutional guidelines that included premedication with diphenhydramine and/or corticosteroids. It was concluded that 3 mg/kg ipilimumab can be safely infused over 30 minutes considering the acceptable and manageable low incidence of IRRs.[56] In addition, after an IRR, patients can safely receive additional doses of ipilimumab with premedication.[56]

Nivolumab is currently approved for IV administration over 30 minutes for select indications. The impact of infusion time on nivolumab safety was assessed in a substudy conducted as part of an ongoing community based trial (ie, CheckMate 153) in participants with previously treated advanced or metastatic NSCLC.[57] In the substudy, 322 participants received 3 mg/kg nivolumab

IV Q2W as a 30-minute infusion, and 355 participants received the same nivolumab regimen as a 60-minute infusion.

Overall, the safety profiles between the 30- and 60-minute infusion groups were similar. TRAEs, of any grade were reported in 53% and 51% of participants who were given 30- or 60-minute infusions, respectively. Grade 3-4 TRAEs were reported in 12% of participants in each infusion group. Among select AEs of any cause, Grade 3-4 events were comparable between infusion groups in the pulmonary (3% and 2%), hepatic (2% and 3%), and GI (2% and 2%) categories. Hypersensitivity/infusion reactions of any cause were reported in 8 (2%) and 5 (1%) participants administered 30- and 60-minute infusions, respectively. The incidence of Grade 3-4 hypersensitivity/infusion reactions was < 1% in each infusion group. Hypersensitivity/infusion reactions were managed either through dosing interruptions (8 participants given 30-minute infusions and 3 participants given 60-minute infusions), discontinuations (1 participant given a 30-minute infusion and 2 participants given 60-minute infusions), or administration of systemic corticosteroids (3 participants given 30-minute infusions and 1 participant given a 60-minute infusion). In addition, PPK modelling demonstrated similar predicted Cmax after the first nivolumab dose and at steady state in both infusion groups, suggesting that a 30-minute infusion does not pose an increased safety risk due to an increase in nivolumab Cmax.

In conclusion, ipilimumab and nivolumab can be safely administered as 30-minute infusions, with a low incidence of irAEs. Given these findings, 30-minute infusions are being implemented across the ipilimumab and nivolumab development programs, including the FIH study CA030001.

5.5.3 Rationale for BMS-986249 and Nivolumab Co-administration

Depending on the dosing and schedule, BMS-986249 in combination with nivolumab may be co-administered over approximately 60, 120, or 180 minutes through the same IV bag. See Table 7.1.1-1 for a list of dose selection and timing and the pharmacy manual for additional information. Co-administration will allow for increased convenience for participants, doctors, nursing staff, other health-care staff members, and pharmacists. Key advantages of co-administration of this combination are as follows:

- Participants potentially benefit from 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 participant

Although co-administration may result in overlapping Tmax for BMS-986249 and nivolumab, the PK and exposure of BMS-986249 and nivolumab will be the same as when administered sequentially. Therefore, sequential versus co-administration is not expected to impact the overall safety profile.

5.5.4 Rationale for Evaluating Different Dose Levels and Schedules of BMS-986249 in Combination with Nivolumab in Part 2A

Multiple clinical studies have evaluated ipilimumab combined with nivolumab at different doses and schedules. Clinical trial experience suggests that the tolerability of the ipilimumab and nivolumab combination may be improved by changes in dose and regimen. Indeed the combination of ipilimumab and nivolumab has been currently FDA approved at 4 different dosing regimens; 1) 3 mg/kg ipilimumab and 1 mg/kg nivolumab Q3W for 4 doses in participants with unresectable or metastatic melanoma and in patients with HCC who have been previously treated with sorafenib, 2) 1 mg/kg ipilimumab and 3 mg/kg nivolumab Q3W for 4 doses in patients with intermediate or poor risk, previously untreated advanced RCC and in patients with MSI-H or dMMR metastatic CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, 3) 1 mg/kg ipilimumab Q6W and 3 mg/kg nivolumab Q2W in adult patients with metastatic NSCLC expressing PD-L1 (≥ 1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, and 4) 1 mg/kg ipilimumab Q6W and 360 mg nivolumab Q3W in adult patients with unresectable malignant pleural mesothelioma, and in combination with 2 cycles of chemotherapy Q3W for adult patients with metastatic or recurrent NSCLC with no EGFR or ALK genomic tumor aberrations as first-line treatment.[11] Furthermore, as described in Section 3.2.4, a number of early clinical studies demonstrated the rate of Grade 3-4 TRAEs varied with the dosing schedule of the ipilimumab and nivolumab combination.

As summarized in Section 3.2.1.6 and consistent with the ipilimumab experience, the tolerability of BMS-986249 may also be dose and schedule dependent. Specifically, an increased number of TRAEs was observed with higher doses of BMS-986249 administered Q4W alone or in combination with nivolumab and a lower number of TRAEs were reported when administered at the alternative dosing schedule of Q8W. Hence, based on the preliminary safety, PK, and [redacted] data available from Part 1 (Dose Escalation Phase), 3 different BMS-986249 dose/schedule regimens were initially selected for investigation in Part 2A (Section 5.1).

Additional review of the available Part 1 data was recently undertaken. Analyses included assessment of cleaved Probody species following various BMS-986249 doses and schedules, preliminary quantitative modeling and simulations of exposure and safety (Grade 3+ TRAE) relationships, and preliminary evaluation of available target lesion response data. These analyses resulted in the decision to close enrollment into Part 2A Arms A and B, and add Part 2A Arm F. Specifically for Arm A (BMS-986249 240 mg Q3W in combination with nivolumab 360 mg Q3W for 4 doses followed by nivolumab 480 mg Q4W), the induction-only regimen of BMS-986249 does not fit the desired continuous CTLA-4 inhibition afforded by the greater tolerability with Probody technology. Furthermore, limited preliminary analysis suggests clinical activity at all Part 1B doses/schedules evaluated; however, preliminary analysis also suggests higher administered doses of BMS-986249 may increase the best overall response in the individual tumor target lesions. Available clinical safety observations from Part 1, as well as preliminary model-based predictions suggest good tolerability with Arm B (BMS-986249 800 mg Q8W in combination with nivolumab 480 mg Q4W) and Arm C (BMS-986249 1,200 mg Q8W in combination with nivolumab 480 mg Q4W). Consequently, Arm B may not represent a

differentiated regimen from Arm C. Predictions based on the preliminary exposure-safety analysis for Arm F (BMS-986249 600 mg Q4W in combination with nivolumab 480 mg Q4W) and Part 1 Q4W dose escalation data suggest an acceptable safety profile. Furthermore, given the dose and administration schedule, Arm F is expected to provide similar average exposures to that of Arm C (1,200 mg BMS-986249 Q8W), while maintaining significantly higher trough concentrations, which may help maximize the therapeutic potential of BMS-986249. This approach therefore provides an opportunity to understand exposure measures underlining pharmacological activities and further informs the exposure-response relationship.

Importantly, none of the doses/schedules selected for Part 2A exceed the highest dose level equivalent assessed and deemed tolerable in Part 1B (Safety Evaluation of Combination Doses of BMS-986249 with Nivolumab) and modification to Part 2A treatment arms was not based on any change in the BMS-986249 safety or tolerability profile, or measures of clinical activity.

5.5.5 Rationale for Q3W dosing of BMS-986249 and Nivolumab in Part 2A Arm A

As summarized in Sections 3.2.3 and 3.2.4, different studies of ipilimumab as a monotherapy and in combination with nivolumab have demonstrated different outcomes of safety, tolerability, and efficacy based on dose and administration schedule. Because BMS-986249 is a Probody of ipilimumab, Part 2A Arm A was designed to utilize the ipilimumab in combination with nivolumab approved Q3W schedule to minimize the potential confounding impact of administration schedule. The Q3W dose of Arm A will be 240 mg and does not exceed the highest dose level equivalent assessed and deemed tolerable of BMS-986249 in combination with nivolumab in Part 1B.

PK, safety, and efficacy data indicate that the safety and efficacy profile of 360 mg nivolumab Q3W and 480 mg nivolumab Q4W will be similar to that of 3 mg/kg nivolumab Q2W (see additional details in Section 3.2.2.1 and the nivolumab IB). Given the above data, 360 mg nivolumab Q3W was selected for Part 2A Arm A (BMS-986249 and nivolumab Combination Therapy Phase), based on equivalent nivolumab average exposure to the 480 mg Q4W administration evaluated in Part 1B. As described above, additional review of the available Part 1 data suggests a longer dosing interval may be more aligned with the BMS-986249 exposure profile; in addition, the Probody technology may enable a more tolerable safety profile enabling continuous administration, hence as of Revised Protocol 07, no further enrollment/randomization will occur into Part 2A Arm A.

5.5.6 Rationale for Dose Selection in Part 2B

BMS-986249 1,200 mg Q8W in combination with nivolumab 480 mg Q4W is selected to be further investigated in Part 2B, based on review of the preliminary safety, PK, and clinical activity data available from Part 1 (Dose Escalation Phase). Preliminary analysis of target lesion response data suggests increased clinical activity with higher administered doses of BMS-986249 alone or in combination with nivolumab. Preliminary PPK analysis of BMS-986249 supports the potential to deliver increased anti-CTLA-4 in combination with full dose nivolumab (480 mg Q4W or 3 mg/kg based on average body weight of 80 kg), which may translate into greater therapeutic activities beyond that achieved with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg.

Importantly, available clinical safety observations and preliminary model-based predictions suggest a manageable safety profile with good tolerability with the selected dose. Additionally, as summarized in Section 3.2.1.6 and consistent with the ipilimumab experience, when a longer dosing interval for BMS-986249 was evaluated (Q8W compared to Q4W) a lower incidence of TRAEs was observed. The Q8W dosing of BMS-986249 is further supported by the de novo gradual formation of the cleaved Probody species over time, which may mitigate the greater exposure fluctuations (peak-to-trough ratio) typically associated with prolonged dosing intervals. Limited and preliminary data analysis for Part 2A (Dose Expansion Phase in Melanoma) further supports the observations seen in Part 1. Additional information on the preliminary clinical results of BMS-986249 can be found in the IB.[10]

6 STUDY POPULATION

For entry into the study, the following criteria MUST be met prior to dosing on Day 1. No exceptions will be granted. This study permits the re-enrollment of a participant who has discontinued the study as a pretreatment failure. If re-enrolled, the participant must be re-consented and meet all inclusion/exclusion criteria.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1 Inclusion Criteria

1) **Signed Written Informed Consent**
   a) The participant must sign the ICF prior to the performance of any study-related procedures that are not considered part of standard of care.
   b) The participant must sign the consent for tumor biopsy samples (see Section 9.8.2 for details).
2) **Type of Participants and Target Disease Characteristics**
   a) Participants must be at least 18 years old and have histologic or cytologic confirmation of a solid tumor that is advanced (metastatic, recurrent, and/or unresectable) with measurable disease per RECIST v1.1 (Appendix 5) or metastatic disease documented by either bone lesions on radionuclide bone scan and/or soft tissue lesions on CT/MRI per PCWG3 criteria for prostate cancer (Appendix 6) and have at least 1 soft-tissue tumor lesion accessible for biopsy. For Part 2B participants with HCC, intermediate disease is allowed.
   b) Eastern Cooperative Oncology Group Performance Status of 0 or 1 (Appendix 7)
   c) The BMS-986249 Monotherapy Dose Escalation (Part 1A):
      i) All solid tumor histologies, except for participants with primary central nervous system (CNS) tumors or tumors with CNS metastases as the only site of active disease, will be permitted during the Dose Escalation Phase.
      ii) Participants must have received, and then progressed, relapsed, or been intolerant to, at least 1 standard treatment regimen in the advanced or metastatic setting according to tumor type, if such a therapy exists.
         1) BC participants must have received or been intolerant to, all approved standard systemic treatments that have shown a documented benefit in OS per product label.

iii) Participants in the monotherapy arm must be anti-CTLA-4-naive. Prior anti-PD-1 or anti-PD-L1 exposure is allowed in the monotherapy arm, but at time of first study treatment, participants must be at least 5 half-lives (approximately 100 days) from last dose of PD-1/PD-L1 therapy.

d) The Combination Dose Escalation of BMS-986249 with Nivolumab (Part 1B):

i) Participants with biopsy-proven SCLC, CRC, CRPC, RCC, bladder cancer, gastric cancer (including gastro-esophageal junction), esophageal cancer, and melanoma will be permitted during dose escalation, except for participants with tumors with CNS metastases as the only site of active disease.

Participants with NSCLC will also be permitted in this portion of the study but not as part of the initial DLT assessment; instead, NSCLC participants will be evaluated only as part of adding additional participants to a previously tested cohort.

ii) *Participants with Gastric, Esophageal, or Urothelial cancer:*

1) Gastric and esophageal cancer participants must have received, and then progressed, relapsed, or been intolerant to, at least 1 standard treatment regimen in the advanced or metastatic setting, if such a therapy exists.

2) Urothelial carcinoma participants must have received, and then progressed, relapsed, been intolerant to, or ineligible for, at least 1 platinum-containing chemotherapy regimen.

iii) *Participants with NSCLC:*

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

2) If the tumor is PD-L1 >50% by immunohistochemistry (IHC), they may be treatment-naive.

iv) *All Part 1B participants must be naive to prior anti-CTLA-4 and anti-PD-1 or anti-PD-L1 therapies*.

v) *Participants with CRC:*

1) Participants must have received and then progressed on or after, or have been intolerant or refractory to, at least 1 standard systemic therapy for metastatic and/or unresectable disease (or have progressed within 6 months of adjuvant therapy), including oxaliplatin and irinotecan.

2) Participants must have known MSI-H or dMMR status. KRAS, and BRAF status, if known, should be documented.

3) Participants who have received prior anti-angiogenic therapy (eg, bevacizumab) and/or anti epidermal growth factor receptor therapy (eg, cetuximab or panitumumab) are eligible.

vi) *Participants with SCLC:*

1) Histologically or cytologically documented SCLC, limited or extensive stage disease.

2) Received at least 1 prior platinum-containing chemotherapy regimen.

vii) *Participants with CRPC:*

1) Participants must have at least 1 soft tissue lesion, unrelated to bone, that qualifies as measurable disease per RECIST v1.1.
2) Participants must have received and progressed/been intolerant of (or not be a candidate for) at least 1 and not more than 3 standard therapies and have been considered for all other potentially efficacious therapies.
3) Previous treatment for hormone sensitive prostate cancer does not qualify without subsequent treatment for hormone refractory state.

viii) *Participants with RCC:*

1) Participants 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, and bevacizumab) in the advanced or metastatic setting. Prior cytokine therapy (eg, IL-2, IFN-α), vaccine therapy, or treatment with cytotoxics is allowed.
2) Participants must have received no more than 3 total prior systemic treatment regimens in the advanced or metastatic setting and must have evidence of progression on or after the last treatment regimen received and within 6 months prior to study enrollment.

e) The BMS-986249 in combination with Nivolumab Randomized Cohort Expansion in Melanoma (Part 2A):

i) Histologically confirmed melanoma (per AJCC staging system) that is unresectable or metastatic (Refer to Appendix 11).
   1) Participants with ocular melanoma are excluded.

ii) No prior systemic anti-cancer therapy for unresectable or metastatic melanoma.
   1) Prior adjuvant or neoadjuvant melanoma therapy is permitted if it was completed at least 6 weeks prior to randomization, and all related AEs have either returned to baseline or stabilized.
      a) Anti-PD-(L)1 therapy with at least 6 months between the last dose and date of recurrence is allowed.
   2) Participants must be naive to treatment with an anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, or any other antibody or drug targeting T cell co-stimulation or checkpoint pathways.

iii) In order to be randomized, a participant must have quantifiable PD-L1 expression (≥ 1% or < 1% tumor cell membrane staining) or be classified as PD-L1 indeterminate. Tumor PD-L1 expression will be centrally assessed prior to patient randomization. (Refer to Table 2-1, Section 9.8.2, and the Laboratory Manual).

iv) Known BRAF V600 mutation status as determined by local institutional standard or participant consent to BRAF V600 mutation testing per local institutional standards during the Screening Period, the results of which must be reported within 3 months of randomization. All BRAF statuses (BRAF wild-type or BRAF 600 mutation positive) are eligible.

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

f) The BMS-986249 in combination with Nivolumab Additional Tumor Cohort Expansion (Part 2B):

i) *Cohort 1:Participants with HCC*

1) Participants must have a diagnosis of HCC based on histological confirmation.
   a) Participants with only a radiological diagnosis of HCC may be enrolled for screening in the study but histological confirmation is mandatory prior to the start of study therapy.
   b) Known fibrolamellar HCC, sarcomatoid HCC, or combined hepatocellular cholangiocarcinoma are excluded.
2) Participants must have advanced or intermediate HCC not eligible for curative surgical and/or locoregional therapies.
3) Participants must have received and progressed on or after, or been intolerant to, a prior anti-PD-(L)1 therapy when administered as either a monotherapy or as part of a combination in the advanced or intermediate setting.
   a) No more than 1 intervening therapy is allowed but not required between prior anti-PD-(L)1 containing regimen and enrollment.
   b) Participants must not have received prior anti-CTLA-4 therapy.
4) Participants with macrovascular invasion are allowed to enroll.
5) Participants with extrahepatic spread are allowed to enroll.
6) Child-Pugh score of 5 or 6 (ie, Child-Pugh A; Appendix 13).
7) Participants are eligible to enroll if they have non-viral HCC, or if they have hepatitis B virus (HBV)-HCC, or hepatitis C virus (HCV)-HCC defined as follows:
   a) HBV-HCC: Resolved HBV infection (as evidenced by detectable HBV surface antibody, detectable HBV core Ab, undetectable HBV deoxyribonucleic acid [DNA], and undetectable HBV surface antigen) or chronic HBV infection (as evidenced by detectable HBV surface antigen or HBV DNA). Participants with chronic HBV infection must have HBV DNA < 500 IU/mL and must be on antiviral therapy.
   b) HCV-HCC: Active or resolved HCV infection as evidenced by detectable HCV ribonucleic acid (RNA) or HCV Ab.
   c) Participants with active co-infection with both HBV and HCV (as evidenced by detectable HBV surface antigen or HBV DNA and HCV RNA) or hepatitis D infection in participants with hepatitis B are excluded.
8) Participants with prior hepatic encephalopathy are excluded.
9) Participants with clinically significant ascites as defined by prior ascites that required treatment and requires ongoing prophylaxis or current ascites requiring treatment are excluded.
10) Participants with presence of portal hypertension with history of bleeding due to esophageal or gastric varices within the past 3 months prior to enrollment are excluded.

ii) *Cohort 2: Participants with CRPC*

1) Participants must have a histologically confirmed adenocarcinoma of the prostate without small cell features and with current evidence of metastatic disease documented by either bone lesions on radionuclide bone scan and/or soft tissue lesions on computed tomography (CT)/magnetic resonance imaging (MRI). Metastases may be in regional lymph nodes (N1 per current AJCC staging criteria) and/or distant metastases (M1 per current AJCC staging criteria).
   a) Participants whose disease spread is limited to regional pelvic lymph nodes (N1M0) must have a lymph node measuring at least 2 cm in short axis to be considered eligible.
2) Participants must have:
   a) Documented prostate cancer progression as per PCWG3 criteria within 6 months prior to screening, with at least 1 of the following:

      i) PSA progression* defined by a minimum of 2 rising PSA levels with an interval of ≥ 1 week between each determination. The PSA value should be ≥ 2 ug/L (2 ng/mL).

      *Participants who received an anti-androgen must have PSA progression after withdrawal (see below).

      ii) Radiographic disease progression in soft tissue disease based on RECIST v1.1.

      iii) Radiographic disease progression in bone defined as appearance of 2 or more new bone lesions on bone scan.

   b) Received and progressed on or after, or been intolerant to, a taxane-containing regimen and received no more than 2 prior chemotherapy regimens in the metastatic setting.
      (i) If taxane-based chemotherapy was only given in the metastatic castration-sensitive setting, participants must also have progressed following prior treatment with a second generation hormonal therapy.
3) Prior second-generation hormonal manipulations (eg, abiraterone acetate, enzalutamide, apalutamide), ketoconazole, prostate cancer vaccine therapy, radiation therapy (including targeted radioligands), radium-223, anti-androgens (eg, flutamide), chemotherapy, and diethylstilbestrols or other estrogens are allowed up to 28 days prior to study treatment.

   Note: Bicalutamide or nilutamide must be discontinued at least 6 weeks prior to treatment.
   a) Participants with a history of response to an anti-androgen or adrenal androgen production inhibitor and subsequent progression while on that anti-androgen should be assessed for anti-androgen withdrawal response for 4 weeks (6 weeks for bicalutamide or nilutamide), and must demonstrate progression off anti-androgen prior to enrollment.
   b) For participants that have never responded to anti-androgens, observation for anti-androgen withdrawal response is not necessary; however, a 2-week washout period is required prior to start of study therapy.

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

4) Ongoing ADT with a gonadotropin-releasing hormone (GnRH) analogue or bilateral orchiectomy (ie, surgical or medical castration) confirmed by testosterone level ≤ 1.73 nmol/L (50 ng/dL) at the screening visit. Castrate levels of testosterone must be maintained by surgical or medical means (luteinizing hormone-releasing hormone [LHRH]/GnRH analogues) throughout the conduct of the study.

5) Must be naive to treatment with an anti-PD-(L)1, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T cell co-stimulation or checkpoint pathways.

6) **Not Applicable per Protocol Amendment 08:** Participants must not have visceral metastases in liver.

7) Participants with superscan on Technecium-99m radionuclide bone scans are not eligible for the study. Superscan is defined as a bone scan which demonstrates markedly increased skeletal radioisotope uptake relative to soft tissue in association with absent or faint renal activity (absent kidney sign).

iii) *Cohort 3: Participants with TNBC*

1) Males and females with locally recurrent unresectable or metastatic histologically confirmed TNBC as defined by the most recent American Society of Clinical Oncology/College of American Pathologists guidelines.

2) Participants must have previously received at least 1 standard chemotherapy based treatment containing taxane and/or anthracycline for the treatment of TNBC.

a) Participants whose tumors express PD-L1 may have received and progressed on or after an anti-PD-(L)1 inhibitor containing chemotherapeutic regimen, if available.

b) Participants who were not tested or participants who were tested and are negative for PD-L1 must not have received prior anti-PD-(L)1 therapy.

3) Participants are eligible to enroll regardless of PD-L1 status. If PD-L1 status is known, PD-L1 status and PD-L1 assay details should be documented.

4) Participants must not have received prior anti-CTLA-4 therapy.

3) Physical and Laboratory Test Findings

a) Adequate hematologic function for participants as defined by the following:

i) Neutrophils ≥ 1,500/μL.

ii) ***Not applicable per Revised Protocol 04*:** Platelets ≥ 80×10^3/μL (transfusion to achieve this level is not permitted within 2 weeks of first study treatment administration).

iii) ***Not applicable per Revised Protocol 04*:** Hemoglobin ≥ 8 g/dL (transfusion to achieve this level is not permitted within 2 weeks of first study treatment administration).

iv) Platelets ≥ 100×10^3/μL (transfusion to achieve this level is not permitted within 2 weeks of first study treatment administration).

1) For participants with HCC: Platelets ≥ 60×10^3/μL

v) Hemoglobin ≥ 9 g/dL (transfusion to achieve this level is not permitted within 2 weeks of first study treatment administration).

1) For participants with HCC: Hemoglobin ≥ 8.5 g/dL and white blood cells ≥ 2000/μL

vi) WBC ≥ 2000/μL

b) Adequate hepatic function (except for HCC)

i) ALT and AST ≤ 3× upper limit of normal (ULN).

ii) Total bilirubin ≤ 1.5× ULN (except participants with Gilbert's syndrome who must have normal direct bilirubin).

iii) For participants with HCC:

1) Serum albumin ≥ 2.8 g/dL

2) Total bilirubin ≤ 3 mg/dL

3) AST and ALT ≤ 5 x ULN

4) PT/INR ≤ 2.3 or PT ≤ 6 seconds above control

c) Normal thyroid function or stable on hormone supplementation per investigator assessment.

d) Serum creatinine ≤ 1.5× ULN or creatinine clearance (CrCl) ≥ 40 mL/min (measured using the Cockcroft-Gault formula below):

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

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

e) Ability to comply with treatment, PK and [redacted] sample collection, and required study follow-up periods.

4) Age and Reproductive Status

a) Males and females, aged at least 18 years old.

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

c) Women must not be breastfeeding.

d) WOCBP must agree to follow instructions for method(s) of contraception (Appendix 4) for the duration of combination therapy treatment with study treatment BMS-986249 plus 5 half-lives of nivolumab plus 30 days (duration of ovulatory cycle), for a total of 155 days post treatment completion. WOCBP receiving monotherapy treatment with BMS-986249 must agree to follow instructions for method(s) of contraception for the duration of monotherapy treatment with BMS-986249 plus 5 half-lives of BMS-986249 plus 30 days (duration of ovulatory cycle) for total of 105 days post treatment completion. WOCBP receiving nivolumab in combination with ipilimumab agree to follow instructions for methods of contraception for the duration of combination treatment and 5 months after the last dose of study treatment. WOCBP receiving monotherapy nivolumab agree to follow instructions for methods of contraception for the duration of monotherapy treatment and for 5 months after the last dose of study treatment. Local laws and regulations may require use of alternative and/or additional contraception methods. See Appendix 4. All WOCBP

must agree not to donate eggs (ova, oocytes) for the purpose of reproduction throughout the time period mentioned above.

e) WOCBP who are continuously not heterosexually active are also exempt from contraceptive requirements but should still undergo pregnancy testing as described in this section.

f) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception and fetal protection (Appendix 4) during combination treatment with study treatment BMS-986249 and nivolumab, plus 5 half-lives of nivolumab (approximately 125 days), plus 90 days (duration of sperm turnover), for a total of 215 days post treatment completion. Males who are sexually active with WOCBP must agree to follow instructions for methods of contraception during monotherapy treatment with BMS-986249 plus 5 half-lives (approximately 75 days) of BMS-986249 plus 90 days (duration of sperm turnover) for a total of 165 days post treatment completion. Males who are sexually active with WOCBP while receiving nivolumab in combination with ipilimumab must agree to follow instructions for methods of contraception for the duration of combination treatment plus 7 months after the last dose of study treatment. Males who are sexually active with WOCBP while receiving monotherapy nivolumab must agree to follow instructions for methods of contraception for the of monotherapy treatment plus 7 months after the last dose of study treatment. In addition, male participants must be willing to refrain from sperm donation during this time. See Appendix 4.

g) Azoospermic males are exempt from contraceptive requirements unless the potential exists for fetal toxicity due to study treatment being present in seminal fluid, even if the participant has undergone a successful vasectomy or if the partner is pregnant.

h) Women who are not of childbearing potential are exempt from contraceptive requirements. Women participants must have documented proof that they are not of childbearing potential.

Investigators shall counsel WOCBP and male participants who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy and when applicable, the potential of fetal toxicity occurring due to transmission of study treatment, present in seminal fluid, to a developing fetus, even if the participant has undergone a successful vasectomy or if the partner is pregnant. Investigators shall advise on the use of highly effective methods of contraception (Appendix 4), which have a failure rate of < 1% when used consistently and correctly. The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

6.2 Exclusion Criteria

1) Target Disease Exclusions

a) Participants with primary CNS malignancies, tumors with CNS metastases as the only site of disease, or active brain metastases will be excluded. Participants with controlled brain metastases, however, will be allowed to enroll. Controlled brain metastases are defined as no radiographic progression for at least 4 weeks following radiation and/or surgical treatment (or 4 weeks of observation if no intervention is clinically indicated) and no longer

taking steroids for at least 2 weeks prior to first dose of study treatment and with no new or progressive neurological signs and symptoms.

2) Prohibited Treatments

a) Cytotoxic agents, unless at least 4 weeks have elapsed from last dose of prior anti-cancer therapy and initiation of study therapy.

b) Noncytotoxic agents, unless at least 4 weeks or 5 half-lives (whichever is shorter) have elapsed from the last dose of prior anti-cancer therapy and the initiation of study therapy. If 5 half-lives is shorter than 4 weeks, agreement with the Sponsor/Medical Monitor (or designee) is mandatory. See Section 6.1 for additional requirements for prior treatments.

i) ***Not applicable per Revised Protocol 04:*** Continued ADT in men with CRPC after progression on an initial ADT regimen is allowed.

ii) Continued LHRH/GnRH agonist therapy in men with CRPC after progression on an initial ADT regimen is allowed.

iii) Goserelin (or other applicable GnRH agonist therapy) may be administered per institutional guidelines for prevention of premature menopause in premenopausal women.

c) Prior immunotherapy treatments, unless at least 4 weeks or 5 half-lives (whichever is shorter) have elapsed from the last dose of immune therapy and initiation of study therapy. See Section 6.1 for additional requirements for prior immunotherapy treatments.

d) Any botanical preparation (eg, herbal supplements or traditional Chinese medicines) intended to treat the disease under study within 2 weeks prior to treatment. If less than 2 weeks have elapsed from the last botanical supplement and the initiation of study treatment, the participant can be treated at the investigator's discretion and in agreement with the Sponsor/Medical Monitor (or designee).

i) Use of marijuana and its derivatives for treatment of symptoms related to cancer or cancer treatment are permitted if obtained by medical prescription or if its use (even without a medical prescription) has been legalized locally.

e) Participants currently in other interventional trials, including those for coronavirus disease of 2019 (COVID-19), may not participate in BMS clinical trials until the protocol-specific washout period is achieved. If a study participant has received an investigational COVID-19 vaccine or other investigational product designed to treat or prevent COVID-19 prior to screening, enrollment must be delayed until the biologic impact of the vaccine or investigational product is stabilized, as determined by discussion between the investigator and the Medical Monitor (or designee).

3) Medical History and Concurrent Diseases

a) Participants with concomitant second malignancies (except adequately treated nonmelanomatous skin cancers or in situ urothelial, breast, or cervical cancers) are excluded unless a complete remission was achieved at least 2 years prior to study entry, and no additional therapy is required or anticipated to be required during the study period.

i) In Part 2, the BMS-986249 Cohort Expansion Combination Therapy Phase, participants with concurrent malignancies that do not require treatment and are clinically stable and anticipated to be followed in an active surveillance manner for the next 12 months are eligible. Treatment should not be required at timing of consent and not be expected to be needed not only for the concurrent malignancy, but also for

complications caused by it. The investigator should inform the participant that the study treatment is not intended and not expected to be considered as treatment for the concurrent malignancy.

b) Participants with other active malignancy requiring concurrent intervention.

c) Prior organ allograft.

d) Toxicity (except for alopecia) related to prior anti-cancer therapy and/or surgery, unless the toxicity is resolved, returned to baseline or Grade 1, or deemed irreversible.

   i) Any active neuropathy > Grade 2 (National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] v4.03).

e) Participants with the following:

   i) Active, known, or suspected autoimmune disease.

      1) Participants with well-controlled asthma and/or mild allergic rhinitis (seasonal allergies) are eligible.

      2) Participants with the following disease conditions are also eligible:

         (a) Vitiligo

         (b) Type 1 diabetes mellitus

         (c) Residual hypothyroidism due to autoimmune condition only requiring hormone replacement.

         (d) Euthyroid participants with a history of Grave's disease (participants with suspected autoimmune thyroid disorders must be negative for thyroglobulin and thyroid peroxidase antibodies and thyroid stimulating Ig prior to the first dose of study treatment).

         (e) Psoriasis not requiring systemic treatment or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

   ii) History of life-threatening toxicity related to prior immune therapy or any toxicity that resulted in permanent discontinuation from prior immune therapy (eg, anti-CTLA-4 or anti-PD-1/PD-L1 treatment or any other Ab or drug specifically targeting T cell co-stimulation or immune-checkpoint pathways) except those that are unlikely to re-occur with standard countermeasures (eg, hormone replacement after adrenal crisis).

   iii) Conditions requiring systemic treatment with either corticosteroids > 10 mg daily prednisone equivalents or other immunosuppressive medications within 14 days of study treatment administration, except for adrenal replacement steroid doses of > 10 mg daily prednisone equivalent in the absence of active autoimmune disease.

      1) Treatment with a short course of steroids (< 5 days) up to 7 days prior to initiating study treatment is permitted.

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

      1) Myocardial infarction or stroke/transient ischemic attack within the past 6 months.

      2) Uncontrolled angina within the past 3 months.

      3) Any history of clinically significant arrhythmias (such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes).

4) History of other clinically significant heart disease (eg, cardiomyopathy, congestive heart failure with New York Heart Association functional classification III to IV [Appendix 8], pericarditis, or significant pericardial effusion).
5) History of myocarditis, regardless of etiology.
6) Cardiovascular disease-related requirement for daily supplemental oxygen therapy.
7) QT interval corrected for heart rate using Fridericia's formula (QTcF) prolongation > 480 msec, except for right bundle branch block.

v) History of chronic hepatitis (except for HCC) as evidenced by the following:
1) Positive test for hepatitis B surface antigen or any positive test result for HBV indicating presence of the virus.
2) Positive test for qualitative hepatitis C viral load by polymerase chain reaction (PCR).
(a) Participants with positive hepatitis C Ab and negative quantitative hepatitis C by PCR are eligible. History of resolved hepatitis A virus infection is not an exclusion criterion.
(b) Additional testing or substitute testing per institutional guidelines to rule out infection is permitted.

vi) Evidence of active infection that requires systemic antibacterial, antiviral, or antifungal therapy ≤ 7 days prior to the first dose of study treatment (except for viral infections that are presumed to be associated with the underlying tumor type required for study entry).

vii) ***Not applicable per Revised Protocol 04:*** Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).

Note: Testing for HIV must be performed at sites where mandated by local requirements.

viii) Any major surgery within 4 weeks of the first dose of study treatment. Participants must have recovered from the effects of major surgery or significant traumatic injury at least 14 days before the first dose of study treatment.

ix) Participants who have received live/attenuated vaccine within 30 days of first treatment.
1) The use of inactivated seasonal influenza vaccines (eg, Fluzone™) will be permitted on study without restriction

x) Receipt of packed red blood cells or platelet transfusion within 2 weeks of the first dose of study treatment.

xi) Any known or underlying medical, psychiatric condition and/or social reason that, in the opinion of the investigator or Sponsor, could make the administration of study treatment hazardous to the participants or could adversely affect the ability of the participant to comply with or tolerate the study.

xii) Positive test for HIV with an AIDS-defining opportunistic infection within the last year, or a current CD4 count < 350 cells/μL. Participants with HIV are eligible if:

1) They have received antiretroviral therapy (ART) for at least 4 weeks prior to study treatment as clinically indicated.

2) They continue on ART as clinically indicated while enrolled on study.

3) CD4 counts and viral load are monitored per standard of care by a local healthcare provider while enrolled on study.

Note: Testing for HIV must be performed at sites where mandated by local requirements. HIV-positive participants must be excluded where locally mandated (see Appendix 14).

xiii) Interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected treatment-related pulmonary toxicity.

xiv) Previous severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection either suspected or confirmed within 4 weeks prior to screening.

1) Acute symptoms must have resolved and based on investigator assessment in consultation with the Medical Monitor, there are no sequelae that would place the participant at a higher risk of receiving investigational treatment.

f) WOCBP who are pregnant or breastfeeding.

4) Allergies and Adverse Drug Reaction

a) History of allergy to study treatment(s) or any of its components.

b) History of severe hypersensitivity reaction to any mAb.

5) Other Exclusion Criteria

a) Prisoners or participants who are involuntarily incarcerated. (Note: Under certain specific circumstances and only in countries where local regulations permit, a person who has been imprisoned may be included or permitted to continue as a participant. Strict conditions apply, and BMS approval is required).

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

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

6.3 Lifestyle Restrictions

There are no lifestyle restrictions applicable for this study given that the participants will receive the study investigational products (IPs) IV.

6.4 Screen Failures

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

6.4.1 Retesting During Screening Period

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

Retesting of laboratory parameters and/or other assessments during the extended screening period will be permitted (in addition to any parameters that require a confirmatory value).

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

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

Testing for asymptomatic SARS-CoV-2 infection, (eg, by reverse transcriptase polymerase chain reaction (RT-PCR) or viral antigen) is not required. However, some participants may develop suspected or confirmed symptomatic SARS-CoV-2 infection or be discovered to have asymptomatic SARS-CoV-2 infection during the screening period. In such cases, participants may be considered eligible for the study after meeting all inclusion/exclusion criteria related to active infection, and after meeting the following criteria:

- At least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared or positive RT-PCR or viral antigen test result, and
- At least 24 hours have passed since last fever without the use of fever-reducing medications, and
- Acute symptoms (eg, cough, shortness of breath) have resolved, and
- In the opinion of the investigator, there are no COVID-19-related sequelae that may place the participant at a higher risk of receiving investigational treatment, and
- Negative follow-up SARS-CoV-2 RT-PCR or viral antigen test based on institutional, local or regional guidelines

7 TREATMENT

7.1 Treatments Administered

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

An IP, 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 from the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

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

In this protocol, IPs are the following:

- BMS-986249
- Nivolumab
- Ipilimumab

All 3 drugs used in this open-label study qualify as IPs, per previous text, and their description and storage information are described in Table 7.1-1.

Table 7.1-1: Study Treatments for CA030001

Product Description / Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per Label)
BMS-986249-01 for injection	160 mg/vial (40 mg/mL)	IP	Open label	Vial	Store at 2°C to 8°C. Protect from light and freezing
nivolumab (BMS-936558) solution for injection	100 mg/vial (10 mg/mL)	IP	Open label	Vial	Store at 2°C to 8°C. Protect from light and freezing.
ipilimumab (BMS-734016) solution for injection	200 mg/vial (5 mg/mL)	IP	Open label	Vial	Store at 2°C to 8°C. Protect from light and freezing.
ipilimumab (BMS-734016) solution for injection	50 mg/vial (5 mg/mL)	IP	Open label	Vial	Store at 2°C to 8°C. Protect from light and freezing.

Abbreviations: IMP = investigational medicinal product, IP = investigational product.

7.1.1 Schedule of Dose for Each Investigational Product

The dosing schedule for each IP is detailed below in Table 7.1.1-1 for all study parts. Planned dose levels may be modified (eg, change in administration schedule) or intermediate dose levels may be added, based upon evaluation of available safety, PK, and [redacted] data.

All participants will be monitored continuously for AEs while on study treatment. Treatment modifications (eg, dose delay or discontinuation) will be based on specific laboratory and AE criteria, as described in Section 7.5.

Table 7.1.1-1: Selection and Timing of Dose for All Study Parts

Study Treatment[a]	Flat Dose Levels	Frequency of Administration	Route of Administration	Minimal Infusion Time[b] (Minutes)
BMS-986249 monotherapy	240 - 800 mg	Q4W	IV	30
BMS-986249 monotherapy	1,600 mg	Q4W or Q8W	IV	120
BMS-986249 monotherapy	2,400 mg	Q4W	IV	180
BMS-986249 + nivolumab Co-administration	240 mg - 800 mg + 480 mg	Q4W or Q8W	IV	120
BMS-986249 + nivolumab Co-administration	1,200 mg + 480 mg	Q4W or Q8W	IV	120[c]
BMS-986249 + nivolumab Co-administration	1,600 mg + 480 mg	Q4W or Q8W	IV	180
nivolumab monotherapy	480 mg	Q4W	IV	30
BMS-986249 + nivolumab Co-administration (Combination Therapy Phase, Cycles 1-4)	240 mg + 360 mg	Q3W x 4 doses	IV	60
Followed by nivolumab monotherapy[d] (Maintenance Phase, Cycle 5 and beyond)	480 mg	Q4W	IV	30
Ipilimumab + nivolumab[e] (Combination Therapy Phase, Cycles 1-4)	3 mg/kg + 1 mg/kg	Q3W x 4 doses Q3W x 4 doses	IV IV	30 30
Followed by nivolumab monotherapy[d] (Maintenance Phase, Cycle 5 and beyond)	480 mg	Q4W	IV	30

Abbreviations: IV = intravenous; Q3W = every 3 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks.

a Additional dose levels and/or schedules may be explored

b If needed, flush the IV line with an appropriate amount of diluent (eg, 0.9% sodium chloride or 5% dextrose in water) to ensure that the complete dose is administered over the approximate designated infusion time.

c For participants < 35 kg receiving 1,200 mg BMS-986249 in combination with 480 mg nivolumab, the minimum infusion time will be approximately 180 minutes.

d The nivolumab monotherapy Maintenance Phase will begin 3 weeks after the last BMS-986249 or ipilimumab and nivolumab Combination Therapy Phase (Cycles 1-4) dose.

e Ipilimumab and nivolumab will be administered sequentially as 2 separate IV infusions. Nivolumab will be given first, over approximately 30 minutes, followed by ipilimumab over approximately 30 minutes, beginning at least approximately 30 minutes after completion of the infusion of nivolumab.

BMS-986249 infusions, as a monotherapy or co-administration, will require a 60-minute observation period following the first 3 infusions for each participant.

Additional preparation, administration, storage/handling and infusion details for BMS-986249, ipilimumab, and nivolumab are provided in the Pharmacy Manual.

7.2 Method of Treatment Assignment

Participants will be enrolled using an Interactive Response Technology (IRT) system; until this system is activated, enrollment will be manually managed by the Sponsor.

During the screening visit, the investigative site will use the enrollment option of the IRT designated by BMS for assignment of a 5-digit participant number that will be unique across all sites. Enrolled participants, including those not treated, will be assigned sequential participant numbers starting with [redacted] The participant identification number (PID) will ultimately be composed of the site number and participant number. [redacted]. Specific instructions for using the IRT system will be provided to the investigational sites in a separate document.

During dose escalation, all participants will be assigned to Part 1A until the decision is made to escalate to the third dose cohort. Subsequently, treatment in Part 1B will be initiated, and dose escalation in the 2 parts will occur in parallel. Treatment assignments for participants eligible for both Part 1A and Part 1B will prioritize Part 1B through IRT whenever possible. If there are no openings in Part 1B, then the participant will be assigned to the next open part/cohort. Prioritization of participants eligible for both Part 1A and Part 1B may be modified to ensure the dose of Part 1B does not exceed the highest tolerated dose in Part 1A. If Part 1 is open upon the decision to initiate Part 2, treatment in the 2 parts will occur in parallel. Treatment assignments for participants eligible for Part 1A or Part 1B, and Part 2 will prioritize Part 2 through IRT whenever possible. If there are no openings in Part 2, then the participant will be assigned to the next open part/cohort.

In the BMS-986249 in Combination with Nivolumab Randomized Cohort Expansion in Melanoma (Part 2A) every participant that signs the informed consent form will be assigned a participant identification number in IRT. In order to be randomized, pre-treatment tumor tissue obtained in the metastatic setting or from an unresectable site of disease must be provided for biomarker analyses. A participant must have quantifiable PD-L1 expression (≥ 1% or < 1% tumor cell membrane staining) or be classified as PD-L1 indeterminate. Participants will be stratified by PD-L1 expression and M-stage. Participants meeting eligibility criteria were to be randomized in a 1:1:1:1:1 ratio to Arms A - E. As of Revised Protocol 07, further enrollment/randomization into Part 2A Arms A, B, and E is closed, and Arm F is added. Across study randomization for Part 2A participants meeting eligibility criteria will randomize in approximately a 1:1:1 ratio to open arms (eg, Part 2A Arms C, D, and F). If there is a change to randomization (eg, discontinuation of an

Arm or temporarily holding enrollment into an Arm while evaluation is ongoing), the adjusted randomization schedule will be documented by a note to file or administrative letter. Within 7 working days from randomization, the participant must receive the dose of study medication, unless otherwise agreed upon with the Medical Monitor (or designee). BMS will create a randomization schedule which will be uploaded into the IRT.

In the BMS-986249 in Combination with Nivolumab Additional Tumor Cohort Expansion (Part 2B) every participant that signs the informed consent form will be assigned a participant identification number in IRT. Participants will be assigned to a tumor-type specific cohort of HCC, CRPC, or TNBC, respectively.

For Part 1, participants will not be replaced if they are discontinued from the study secondary to an AE unless the AE can be determined to be unrelated to treatment.

For Part 2, participant replacement will not be allowed for participants who are discontinued after dosing.

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

7.3 Treatment Duration

Participants will be treated for up to 2 years in all study parts (see Section 5.4.4 for rationale).

7.4 Blinding

This is an open-label study and randomized in Part 2A. Designated staff of the Sponsor may receive access to treatment codes prior to database lock to facilitate early exploratory data analysis and the bioanalytical analysis of PK samples and immunogenicity. A bioanalytical scientist in the Sponsor's Bioanalytical Sciences department (or a designee in the external central bioanalytical laboratory) will have access to the randomized treatment assignments in order to minimize unnecessary bioanalytical analysis of samples. In addition, the Sponsor's Research and Development team will have access to the treatment codes prior to final data base lock for ongoing evaluation of preliminary available data (eg, safety, PK, and [redacted]).

7.5 Dosage Modification

Intra-participant dose escalation/reduction of BMS-986249, nivolumab, or ipilimumab is not permitted in this study in order to allow better evaluation of the safety and efficacy at individual dose levels and schedules.

7.5.1 Dose-limiting Toxicities

For the purpose of guiding dose escalation, DLTs will be defined based on the incidence, intensity, and duration of AEs that are possibly related to study treatment. The DLT period will be 5 weeks (35 days) in both BMS-986249 monotherapy and combination dose escalation (Parts 1A and 1B). Any toxicities that occur beyond the DLT period will be accounted for in making final dose level decisions. Participants who have received 2 doses of BMS-986249 and have completed or discontinued due to a DLT in the 5-week DLT period will be considered as DLT-evaluable participants for BMS-986249 monotherapy. Participants receiving either 2 dosing visits of

BMS-986249 and nivolumab, or participants who discontinued due to a DLT in the 5-week combination treatment DLT period, will be considered as DLT-evaluable participants for combination treatment. Participants who withdraw from the study during the DLT evaluation period or have received less than 2 dosing visits for reasons other than a DLT in both monotherapy and combination therapy will not be considered as DLT-evaluable participants and may be replaced with a new participant at the same dose level. Participants who are dose delayed during the DLT evaluation period for reasons other than a DLT in both monotherapy and combination therapy will be considered as DLT-evaluable participants if they received at least 2 doses of therapy.

For the purpose of participant management, any drug-related AE that meets DLT criteria, regardless of the cycle or cohort (including Part 2) in which it occurs, will lead to discontinuation of study treatment. The incidence of DLT(s) during the 5-week DLT evaluation period will be used in dose escalation decisions and to define the MTD. AEs occurring after the DLT period will be considered for the purposes of defining the recommended Phase 2 dose of BMS-986249 (RP2D) upon agreement between the Sponsor, Medical Monitor (or designee), and investigators.

AEs will be graded according to the NCI CTCAE v4.03.

Part 1B participants with NSCLC will only be evaluated in a cohort once the initial DLT evaluation for that cohort has been completed.

7.5.1.1 Gastrointestinal Dose-limiting Toxicity

The following study treatment-related event will be considered a GI DLT:

- Grade ≥ 3 diarrhea or colitis, regardless of duration

7.5.1.2 Hepatic Dose-limiting Toxicity

Any of the following study treatment-related events will be considered a hepatic DLT:

- Grade 4 elevations in serum transaminases (AST and ALT), alkaline phosphatase (ALP), or total bilirubin.
- Grade 3 elevations in serum AST, ALT, or ALP that last longer than 5 days, or is associated with clinical symptoms, or bilirubin > 2× ULN in the absence of cholestasis.
- Grade 2 elevations in AST or ALT with symptomatic liver inflammation (eg, right upper quadrant tenderness, jaundice).
- AST or ALT > 3× ULN and concurrent total bilirubin > 2× ULN without initial findings of cholestasis (elevated ALP, eg, findings consistent with Hy's law or FDA definition of potential drug-induced liver injury [p-DILI]). Note that this specific category of DLT uses ULN rather than NCI CTCAE grade for definition.

Any of the following study treatment-related events will be considered a hepatic DLT for participants with HCC:

- ALT or AST > 15× ULN, regardless of duration.

- ALT or AST > 10× ULN for greater than 2 weeks.
- Total bilirubin > 8× ULN for participants with elevated bilirubin at study entry or > 5× ULN for participants with normal bilirubin at study entry, regardless of duration.
- ALT > 10× ULN and concurrent total bilirubin > 2× ULN.

7.5.1.3 Hematologic Dose-limiting Toxicity

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

- Grade 4 neutropenia ≥ 7 days in duration
- Grade 4 thrombocytopenia
- Grade 3 thrombocytopenia with bleeding or any requirement for platelet transfusion
- Grade 3 hemolysis (ie, requiring transfusion or medical intervention such as steroids)
- Neutropenic fever of any duration
- Grade 4 anemia not explained by underlying disease

7.5.1.4 Dermatologic Dose-limiting Toxicity

Any of the following study treatment-related events will be considered a dermatologic DLT:

- Grade 4 rash
- Grade 3 rash if no improvement (ie, resolution to ≤ Grade 1) after a 1- to 2-week infusion delay

7.5.1.5 Other Dose-limiting Toxicities

Any of the following events will be considered a DLT:

- Grade ≥ 4 hypersensitivity reaction or Grade 3 that does not resolve to Grade 1 in < 6 hours
- Grade 2 pneumonitis that does not respond to dose delay and systemic steroids within 14 days.
- Any death not clearly due to the underlying disease or extraneous causes
- Grade 2 drug-related uveitis, episcleritis, iritis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks OR requires systemic treatment.
- Grade 3 drug-related uveitis, episcleritis, iritis, pneumonitis, bronchospasm, or neurologic toxicity

Checkpoint inhibitor molecules, have been uncommonly associated with ocular drug-related AEs. Inflammation of components within the eye (eg, episcleritis, uveitis) are uncommon events of nivolumab or ipilimumab monotherapy (< 1% of cases). These events are usually of low or intermediate grade, reversible, detected early in the course of therapy and manageable with topical or systemic steroids.

- Routine eye examinations should be performed in participants receiving immune checkpoint inhibitors. Upon clinical suspicion of an ocular event consider ophthalmic consult, dose delay, or dose discontinuation
- Permanently discontinue for clinically significant or severe immune-mediated adverse reactions. Initiate systemic corticosteroids for severe immune-mediated adverse reactions
- For Grade 2-4 ophthalmologic reactions that require systemic treatment or that do not improve to Grade 1 within 2 weeks while receiving topical therapy, permanently discontinue
- Permanently discontinue for immune-mediated ocular disease that is unresponsive to local immunosuppressive therapy
- Administer corticosteroid eye drops to participants who develop uveitis, iritis, or episcleritis

Other ≥ Grade 3 study treatment-related toxicity will be considered a DLT. However, the following Grade 3-4 events will **not** be considered DLTs:

- Grade 3-4 electrolyte abnormalities that are not complicated by associated clinical adverse experiences, last less than 72 hours, and either resolve spontaneously or respond to conventional medical intervention.
- Grade 3 nausea or vomiting that lasts less than 48 hours and either resolves spontaneously or responds to medical intervention.
- Grade 3-4 elevation of amylase or lipase not associated with clinical or radiographic evidence of pancreatitis
- Grade 3 fever not associated with hemodynamic compromise (eg, hypotension, clinical or laboratory evidence of impaired end-organ perfusion)
- Grade 3 endocrinopathy that is well controlled by hormone replacement
- Grade 3 tumor flare (defined as pain, irritation, or rash that localizes to sites of known or suspected tumor)
- Grade 3 fatigue lasting < 1 week
- Grade 3 infusion reaction that returns to Grade 1 in < 6 hours

7.5.2 Management Algorithms for Immuno-oncology Agents

I-O agents are associated with irAEs that can differ in severity and duration from AEs caused by other therapeutic classes. BMS-986249, ipilimumab, and nivolumab are considered I-O agents in this protocol. Early recognition and management of irAEs associated with I-O agents may mitigate severe toxicity. Management algorithms have been developed from extensive experience with ipilimumab and nivolumab to assist investigators in assessing and managing the following groups of irAEs:

- GI
- Renal
- Pulmonary

- Hepatic
- Endocrinopathies
- Skin
- Neurological (including encephalitis)
- Myocarditis

The clinical nature of AEs noted with BMS-986249 will determine the role of the algorithms for use in toxicities related to its use in this study. The standard algorithms recommended for the management of irAEs in this protocol are in Appendix 9.

GI AE management for BMS-986249 Grade 2 diarrhea/colitis irAEs may require earlier initiation of steroids.

7.5.3 Dose Delays Due To Toxicity

If an event is attributed to BMS-986249, ipilimumab, or nivolumab, alone or in combination, then all study treatments must be delayed until treatment can resume (See Section 7.5.3.1). Tumor assessments for all participants should continue per protocol even if dosing is delayed. Participants who experience the following must have all study treatment(s) withheld:

- SARS-CoV-2 infection either confirmed or suspected
- Potential DLTs, until DLT relatedness is defined
- Drug-related select AEs and laboratory abnormalities as follows:
  - Any Grade ≥ 2 non-skin AE, with the following exceptions:
    - Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay
  - Dose delay for AST, ALT, or total bilirubin abnormalities in HCC participants should be managed as follows:
    - If baseline AST, ALT, or bilirubin is within normal limits, delay dosing for Grade ≥ 2 toxicity
    - If baseline AST, ALT, or bilirubin is within the Grade 1 toxicity range, delay dosing for Grade ≥ 3 toxicity
    - If baseline AST, ALT, or bilirubin is within the Grade 2 toxicity range, delay dosing for a 2-fold drug-related increase in AST, ALT, or bilirubin, or for AST, ALT, or bilirubin values 8× ULN (whichever is lower).
  - Grade 3 skin AE
  - Grade 3 laboratory abnormality, with the following exceptions:
    - Grade 3 lymphopenia does not require a dose delay
    - ≥ Grade 3 amylase or lipase abnormality that is not associated with clinical manifestations or radiographic evidence of pancreatitis does not require dose delay
  - All troponin elevations require a dose delay

- AE, laboratory abnormality, or concurrent illness that, in the judgment of the investigator, warrants delaying study treatment administration

Participants who require a delay of study treatment should be re-evaluated weekly or more frequently if clinically indicated. For participants receiving a combination (eg, Part 1B and Part 2), if dosing is delayed, then both study treatments must be delayed together. If dosing with both study treatments is to be resumed after a delay, then both must be resumed on the same day. Criteria for participants who are required to permanently discontinue study treatments are listed in Section 8.2. In addition, all Grade 2 GI, renal, pulmonary, hepatic, and neurological AEs should be evaluated and managed per the toxicity management algorithms in Appendix 9. Participants not meeting guidelines for permanent discontinuation will be permitted to resume therapy based on the criteria specified below in Section 7.5.3.1. Participants eligible to resume study therapy will resume study therapy at the nominal treatment visit after their last received study medication dose.

7.5.3.1 Criteria to Resume Treatment

Participants experiencing AEs not meeting criteria for permanent discontinuation as outlined in Section 8.1 may resume treatment with study medication under the following criteria:

- Participants may resume treatment with study treatment when the drug-related AE(s) resolve to Grade ≤ 1 or baseline value, with the following exceptions:
  - Participants may resume treatment in the presence of Grade 2 fatigue.
  - Participants who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
  - Participants with Grade 2 uveitis, episcleritis, iritis, eye pain, or blurred vision not meeting DLT criteria (Section 8.1) must resolve to baseline prior to resuming study therapy.
- Participants who require dose delays for drug-related elevations in AST, ALT, or total bilirubin may resume treatment when laboratory values return to baseline CTCAE Grade or normal and management with corticosteroids (if needed) is complete, provided the criteria for permanent discontinuation are not met (Section 8.1).
  - For HCC participants 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.
- Participants with combined Grade 2 AST/ALT **and** total bilirubin values meeting DLT criteria (Section 7.5.1) should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed.
- Participants with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment. Adrenal insufficiency requires discussion with and approval from the Medical Monitor (or designee).
- Participants with SARS-CoV-2 infection (either confirmed or suspected) may resume treatment after all of the following:

- at least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared or positive test result (eg, RT-PCR or viral antigen), and
- resolution of acute symptoms (including at least 24 hours has passed since last fever without fever reducing medications), and
- evaluation by the Investigator with confirmation that there are no sequelae that would place the participant at a higher risk of receiving investigational treatment, and
- consultation by the Medical Monitor.

For suspected cases, treatment may also resume if SARS-CoV-2 infection is ruled-out and other criteria to resume treatment are met.

7.5.4 Exceptions to Permanent Discontinuation Criteria

Any drug-related AE occurring at any time that meets DLT criteria as outlined in Section 7.5.1 will require permanent discontinuation, **with the exception of the following**:

- Grade 3 nausea, vomiting, or abdominal pain that returns to Grade 1 or baseline within 48 hours either spontaneously or with medical intervention.
- Grade 3 pruritus or rash that returns to Grade 1 or baseline within 7 days with medical intervention.
- Isolated Grade 3-4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 3 days of their onset.
- Grade 4 neutropenia < 7 days in duration.
- Grade 4 lymphopenia or leukopenia.
- Grade 3-4 increase in amylase or lipase that is not associated with clinical or radiographic evidence of pancreatitis.
- Grade 3 infusion reactions that return to Grade 1 in < 6 hours.
- Grade 3 fever not associated with hemodynamic compromise (eg, hypotension, clinical, or laboratory evidence of impaired end-organ perfusion).
- Grade 3 tumor flare (defined as pain, irritation, or rash that localizes to sites of known or suspected tumor).
- Grade 3 fatigue lasting < 1 week
- Grade 3-4 drug-related endocrinopathy AEs, such as adrenal insufficiency, adrenocorticotropic hormone, hyper- or hypothyroidism, or glucose intolerance, which resolve or adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the Medical Monitor (or designee).
- Any event that leads to delay in dosing, lasting > 8 weeks from the previous dose, requires discontinuation, with the exception of the following:
  - Dosing delays for prolonged steroid tapers to manage drug-related AEs are allowed. Prior to re-initiating treatment in a participant with a dosing delay lasting > 8 weeks from the

previous dose, the Medical Monitor (or designee) must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue Q4W, or more frequently if clinically indicated, during such dosing delays.

  - Dosing delays lasting > 8 weeks from the previous dose that occur for non-drug-related reasons may not require discontinuation, if approved by the Medical Monitor (or designee). Prior to re-initiating treatment in a participant with a dosing delay lasting > 8 weeks, the Medical Monitor (or designee) must be consulted.
- Any AE, laboratory abnormality, or concurrent illness, which, in the judgment of the investigator, presents a substantial clinical risk to the participant with continued dosing.

Even if the criteria to resume treatment are met, the consideration to re-initiate study therapy under the following exception will be made on a case-by-case basis after considering the overall benefit-risk profile and in consultation between the investigator and the Sponsor. Any AE with clinical risk will be assessed on a case-by-case basis with the investigator and the Medical Monitor (or designee) to determine the risks and benefits of continuing on therapy following resolution versus discontinuing therapy permanently.

All participants who discontinue IP should comply with protocol-specified follow-up procedures as outlined in Sections 2 and 8.2. The only exception to this requirement is when a participant withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (eg, imprisonment, involuntarily incarceration for the treatment of either a psychiatric or physical illness).

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

7.5.5 Management of Drug-related Infusion Reactions

Because BMS-986249, ipilimumab, and nivolumab contain only human Ig protein sequences, they are unlikely to induce hypersensitivity reactions. However, based on the nonclinical toxicology evaluation of BMS-986249, infusion reactions due to T cell activation and cytokine release may occur in both monotherapy and combination with nivolumab. If such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgia, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3-4 infusion reactions should be reported within 24 hours to the Medical Monitor (or designee) and reported as an SAE. Infusion reactions should be graded according to NCI CTCAE v4.03 guidelines.

Treatment recommendations for infusion reactions 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), recommendations are as follows:

- Remain at bedside and monitor participant until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1,000 mg at least 30 minutes before study treatment administrations.

For Grade 2 symptoms (moderate reaction requiring therapy or infusion interruption but responding promptly to symptomatic treatment such as antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids, or prophylactic medications indicated for ≤ 24 hours), recommendations are as follows:

- Stop the study treatment infusion, begin an IV infusion of normal saline, and treat the participant with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1,000 mg; remain at bedside and monitor participant 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, then the rate may be increased to 100% of the original infusion rate. Monitor participant closely. If symptoms recur, then no further BMS-986249, ipilimumab, or nivolumab 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 1,000 mg should be administered at least 30 minutes before study treatment infusions. If necessary, corticosteroids (up to 25 mg of hydrocortisone or equivalent) may be used.

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

- Immediately discontinue infusion of study treatment. Begin an IV infusion of normal saline and treat the participant as follows: recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Participant should be monitored until the investigator is comfortable that the symptoms will not recur. Study treatment will be permanently discontinued except for a Grade 3 infusion reaction that returns to Grade 1 in less than 6 hours. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor participant 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).

7.6 Preparation/Handling/Storage/Accountability

The IP should be stored in a secure area according to local regulations. It is the responsibility of the investigator or designee where permitted, to ensure that IP is only dispensed to study participants. The IP must be dispensed only from official study sites by authorized personnel according to local regulations.

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

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

IP documentation (whether supplied by BMS or not) must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

For study treatments not provided by BMS and obtained commercially by the site, storage should in accordance with the product label.

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

Infusion-related supplies (eg, IV bags, in-line filters, 0.9% sodium chloride solution) will not be supplied by the Sponsor and should be purchased locally if permitted by local regulations.

Please refer to the current version of the IB and/or Pharmacy Manual/reference sheets for complete storage, handling, dispensing, and infusion information for BMS-986249, ipilimumab, and nivolumab.

Further guidance and information for final disposition of unused study treatment are provided in Appendix 2 and the Pharmacy Manual.

7.6.1 Retained Samples for Bioavailability/Bioequivalence

Not applicable.

7.7 Treatment Compliance

Not applicable.

7.8 Concomitant Therapy

7.8.1 Prohibited and/or Restricted Treatments

The following medications are prohibited during the study (unless utilized to treat a drug-related AE):

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 6.2)
- Loco-regional therapies for HCC

- Any concurrent approved or investigational anti-neoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy). For participants with CRPC, castrate status should be maintained, therefore, participants who have not had an orchiectomy can continue on LHRH/GnRH agonist therapy. For TNBC participants, Goserelin (or other applicable GnRH agonist therapy) may be administered per institutional guidelines for prevention of premature menopause in premenopausal women.
- Any non-palliative radiation therapy. Radiation therapy administered with palliative intent (ie, for pain, bleeding, spinal cord compression, brain metastasis, new or impending pathologic fracture, superior vena-cava syndrome, or obstruction) is permitted. See Section 7.8.2.
- Any complementary medications (eg herbal supplements or traditional Chinese medicines) intended to treat the disease under study. Such medications are permitted if they are used as supportive care.
- Any live/attenuated vaccine (eg, varicella, zoster, yellow fever, rotavirus, oral polio, measles, mumps, and rubella) during treatment and until 100 days post last dose.

7.8.2 Permitted Therapy

Participants are permitted the use of the following treatments:

- Topical, ocular, intra-articular, intra-nasal, and inhalational corticosteroids
- Adrenal replacement steroid doses > 10 mg daily prednisone equivalent in the absence of active autoimmune disease
- A brief (less than 3 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen)
- Participants may continue to receive hormonal replacement therapy if initiated prior to enrollment.
- Participants already receiving agents for the management of skeletal-related events are allowed to continue with anti-bone resorptive therapy (including, but not limited to, bisphosponate or receptor activator of nuclear factor kappa ligand inhibitor), as per institutional standard-of-care guidelines, if on stable dose for more than 28 days prior to start of study treatment.
- HCC participants on antiviral therapy for HBV or HCV should continue the treatment during the study. Changing of dosage and regimens of antiviral therapy will be at the discretion of the Investigator.
  - If a participant has a > 1 log IU/mL increase in HBV DNA, then virologic breakthrough should be considered and HBV DNA confirmed. Adherence to current antiviral therapy should be assessed, and resistance testing performed according to local practices. If a participant has documented virologic breakthrough due to antiviral resistance, then this should be managed based on standardized regional guidelines and study treatment should be temporarily held. The participant may resume study treatment once virologic control is re-established (HBV DNA < 500 IU/mL).
  - For HCC participants who continue to be HCV RNA positive after receiving BMS-986249 in combination with nivolumab, current guidelines for management of chronic HCV infection, including those from American Association for the Study of Liver Disease,

European Association for the Study of the Liver, or Asian Pacific Association for the Study of the Liver may be consulted. Initiation of direct-acting antivirals for HCV is allowed at the discretion of the Investigator after discussion with the Medical Monitor (or designee).

- 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.
  - 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-986249 is unknown.

7.8.3 Palliative Local Therapy

Palliative and supportive care for disease-related symptoms may be offered to all participants on the study. Limited radiation treatment or surgery to control isolated lesions may be permitted for participants following consultation with the Medical Monitor (or designee).

Participants should not receive study treatment during radiation because the potential for overlapping toxicities with radiotherapy and study treatment is not known. If palliative radiotherapy in short courses and for isolated fields is required to control symptoms not clearly related to disease progression, then study treatment administration should be withheld, if possible, for at least 1 week before radiation and for at least 1 week after its completion.

Participants should be closely monitored for any potential toxicity during and after receiving radiotherapy. Prior to resuming study treatment, radiotherapy-related AEs should resolve to Grade ≤1 or baseline, and participants must meet relevant eligibility criteria as determined by the Medical Monitor (or designee) in discussion with the investigator. The Medical Monitor (or designee) must be consulted prior to re-initiating study treatment in a participant with a dosing delay lasting > 8 weeks from the previous dose.

Details of palliative radiotherapy should be documented in the source records and CRF. Details in the source records should include dates of treatment, anatomic site, dose administered and fractionation schedule, and AEs.

Symptoms requiring palliative radiotherapy must be evaluated for objective evidence of disease progression (ie, imaging). If a participant is considered to have progressed at the time of palliative therapy, then they must meet the treatment beyond progression criteria (Section 8.1.1) prior to re-initiating study treatment. Participants receiving palliative radiation of target lesions will have the evaluation of ORR just prior to radiotherapy, but these participants will no longer be evaluable for the determination of response subsequent to the date palliative radiation occurs.

For participants who need to undergo surgery during the study, it is recommended to hold study treatment(s) for at least 2 weeks before (if elective) and 2 weeks after surgery, or until the participant recovers from the procedure, whichever is longer. Prior to resuming study treatment, surgery-related AEs should resolve to Grade 1 or baseline, and participants must meet relevant eligibility criteria as determined by the Medical Monitor (or designee) in discussion with the

investigator. The Medical Monitor (or designee) must be consulted prior to re-initiating study treatment in a participant with a dosing delay lasting > 8 weeks from the previous dose.

7.8.3.1 Imaging Restriction and Precautions

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

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

7.9 Treatment After the End of the Study

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

BMS reserves the right to terminate access to BMS-supplied study treatment if any of the following occur: a) the study is terminated due to safety concerns; b) the development of BMS-986249 is terminated for other reasons, including but not limited to lack of efficacy and/or not meeting the study objectives; or c) the participant can obtain medication from a government-sponsored or private health program. In all cases BMS will follow local regulations.

8 DISCONTINUATION CRITERIA

8.1 Discontinuation from Study Treatment

Participants MUST discontinue IP for any of the following reasons:

- Documented disease progression as defined by RECIST v1.1 (Appendix 5) or PCWG3 (Appendix 6) unless participants meet criteria for treatment beyond progression (Section 8.1.1).
- Clinical deterioration while receiving active study therapy that, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant.
- Any drug-related AE occurring at any time that meets DLT criteria as outlined in Section 7.5.1 will require permanent discontinuation. Exceptions to permanent discontinuation are listed in Section 7.5.4.
- Participant's request to stop study treatment. Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol-specified

follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information.

- Any clinical AE, laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant.
- Termination of the study by the Sponsor.
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness. (Note: Under specific circumstances and only in countries where local regulations permit, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply and BMS approval is required).
- Inability to comply with protocol.
- Discretion of the investigator.
- Pregnancy.
- Individual participants with confirmed CR will be given the option to discontinue study therapy on a case by case basis after specific consultation and agreement between the investigator and Medical Monitor (or designee) in settings where benefit/risk justifies discontinuation of study therapy.
- Any event that leads to delay in dosing lasting > 8 weeks from the previous dose requires discontinuation, with the following exceptions:
  - Dosing delays for prolonged steroid tapers to manage drug-related AEs are allowed.
  - Dosing delays lasting > 8 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the Medical Monitor (or designee).
- For Part 2A Arms A and D during the Combination Therapy Phase, decisions to discontinue study treatment therapy must include both nivolumab as well as BMS-986249 or ipilimumab. It is not permitted to continue nivolumab without BMS-986249 or ipilimumab. Part 2A Arm A and D participants who do not complete all scheduled cycles of BMS-986249 or ipilimumab and nivolumab combination therapy will not be eligible for the nivolumab monotherapy Maintenance Phase.
- For Part 1B, Part 2A Arms B, C, and F, and Part 2B, the assessment for discontinuation of nivolumab should be made separately from the assessment made for discontinuation of BMS-986249, if possible. Although there is overlap among the discontinuation criteria, if discontinuation criteria are met only for BMS-986249 but not for nivolumab, treatment with nivolumab may continue after discussion and approval by the Medical Monitor (or designee). Treatment with BMS-986249 may continue if nivolumab is discontinued only if the investigator is able to clearly determine the discontinuation event is only related to nivolumab treatment and the decision is discussed with and approved by the Medical Monitor (or designee).

BMS-986249, as a Probody of ipilimumab, is predicted to have a similar but attenuated irAE profile compared to ipilimumab. The activation of a pre-existing but attenuated immune response

to cancer by checkpoint blockade is associated with an AE profile that is inherent to immune activation. Hence, distinguishing between an ipilimumab and nivolumab AE can be difficult. Clinical trial experience and labeled indications have characterized the AE profiles of ipilimumab and nivolumab and suggest that some events are more frequently associated with a specific agent (eg, pneumonitis is more common with nivolumab than ipilimumab). Listed below are the most common irAE and AEs of ipilimumab and nivolumab. Refer to section 7.5.1 for information on DLTs.

The irAEs associated with ipilimumab include; colitis, hepatitis, nephritis, endocrinopathy, neurologic, eye, myocarditis, myositis, and skin AEs. The most common adverse reactions (≥ 5%) are fatigue, diarrhea, pruritus, rash, and colitis. Additional common adverse reactions at the 10 mg/kg dose (≥ 5%) include nausea, vomiting, headache, weight loss, pyrexia, decreased appetite, and insomnia.

The overall safety experience with nivolumab is based on experience with approximately 23,507 participants as either monotherapy or in combination with other therapeutics and include: pneumonitis, colitis, hepatitis, nephritis, endocrinopathy, neurologic, eye, myocarditis, myositis and skin. Most common adverse reactions (≥ 20%) in participants were: fatigue, rash, musculoskeletal pain, pruritus, diarrhea, nausea, asthenia, cough, dyspnea, constipation, decreased appetite, back pain, arthralgia, upper respiratory tract infection, and pyrexia.

Further safety information will be provided once available from Part 1A BMS-986249 monotherapy escalation that may to help distinguish AEs due to BMS-986249 from those due to nivolumab in Part 1B.

- If a participant in any of the BMS-986249 in combination with nivolumab arms meets criteria for discontinuation and the investigator is unable to determine whether the event is related to both or one study treatment, the participant should discontinue both nivolumab and BMS-986249 and be taken off the treatment phase of the study.

In the case of pregnancy, the investigator must immediately notify the Medical Monitor/designee of this event. In the event a normal healthy female participant becomes pregnant during a clinical trial, the study treatment must be discontinued immediately. In most cases, the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). Please call the Medical Monitor/designee within 24 hours of awareness of the pregnancy. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion between the investigator and the Medical Monitor/designee must occur.

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

If study treatment is discontinued prior to the participant's completion of the study, the reason for the discontinuation must be documented in the participant's medical records per local regulatory requirements in each region/country and entered on the appropriate CRF page.

8.1.1 Treatment Beyond Progression

As described in Section 5.4.5, accumulating evidence indicates that a minority of participants with tumors treated with immunotherapy may derive clinical benefit despite initial evidence of PD.[58]

Participants will be permitted to continue treatment beyond initial PD defined by RECIST v1.1 (see Appendix 5) or PCWG3 for prostate cancer (see Appendix 6), assessed by the investigator, as long as they meet the following criteria:

- Investigator-assessed clinical benefit and no rapid disease progression.
- Continue to meet all other study protocol eligibility criteria.
- Tolerance of study treatment.
- Stable performance status.
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases).
- Participant provides written informed consent, using an ICF describing any reasonably foreseeable risks or discomforts, or other alternative treatment options prior to receiving any additional nivolumab, ipilimumab, or BMS-986249 treatment.
- Radiographic assessment/scan(s) should continue in accordance with Section 2 for the duration of the treatment beyond progression and should be submitted to the central imaging vendor.

The assessment of clinical benefit should take into account whether the participant is clinically deteriorating and unlikely to receive further benefit from continued treatment. If the investigator feels that the participant continues to achieve clinical benefit by continuing treatment with the study treatments, the participant should remain in the study and continue to be monitored according to the Schedule of Activities (see Section 2). All decisions to continue treatment beyond initial progression must be discussed with the Medical Monitor (or designee), and an assessment of the benefit/risk of continuing with study therapy must be documented in the study records (see Appendix 2).

8.1.1.1 Discontinuation Due to Further Progression (Confirmed Progression)

Participants will continue to be monitored according to the on-treatment assessments in Section 2. Radiographic assessment, by CT (preferred) or MRI described in Section 9.1.1, is required when participants continue post-progression treatment and should be performed. A follow-up scan should be performed within 6 weeks (± 5 days) of original investigator-assessed PD to determine whether there has been a decrease in the tumor size, or continued progression of disease. Subsequent scans should be performed as outlined in Table 2-2, Table 2-3, Table 2-4 and detailed in Section 9.1.1. Participants should discontinue study therapy upon evidence of further progression, defined as an additional 10% or greater increase in tumor burden volume with a minimum 5 mm absolute increase from the time of initial progression (including all target lesions

and new measurable lesions). In situations where the 10% relative increase in total tumor burden is solely due to inclusion of new lesions which become measurable, these new lesions must demonstrate an absolute increase of at least 5 mm.

The tumor burden volume from time of initial progression should be used as the reference baseline for comparison with the post-progression assessment.

Any new lesion considered non-measurable at the time of initial progression may become measurable and, therefore, must be included in the tumor burden measurement according to the following:

- For solid tumors: new lesions are considered measurable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes, which must have a short axis of at least 15 mm).

For statistical analyses that include the investigator-assessed progression date, participants who continue treatment beyond initial investigator-assessed, RECIST v1.1 or PCWG3-defined progression will be considered to have investigator-assessed PD at the time of the initial progression event.

8.1.2 Post-treatment Study Follow-up

In this study, safety and efficacy are key endpoints of the study. Post study follow-up is of critical importance and is essential to preserving participant safety and the integrity of the study. Participants who discontinue study treatment should continue to be followed (in this study or a rollover study) for collection of outcome and/or survival follow-up data as required and in line with Section 5.1.5 until death or the conclusion of the study.

Participants who discontinue study treatment may continue to be followed.

8.2 Discontinuation from the Study

Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by the participant to provide this information.

- Participants should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible.
- The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study treatment only or also from study procedures and/or post-treatment study follow-up, and entered on the appropriate CRF page.
- In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

8.2.1 Individual Discontinuation Criteria

- A participant may withdraw completely from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. The participant will be permanently discontinued both from the study intervention and from the study at that time. This is expected to be uncommon. Stopping study intervention is not considered withdrawal from the study.
- At the time of discontinuing from the study, if possible, an early termination visit should be conducted, as shown in the Schedule of Activities. See the Schedule of Activities for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

8.3 Lost to Follow-up

- All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant.
- Lost to follow-up is defined by the inability to reach the participant after a minimum of **3** documented phone calls, faxes, or emails as well as lack of response by participant to one registered mail letter. All attempts should be documented in the participant's medical records.
- If it is determined that the participant has died, the site will use permissible local methods to obtain date and cause of death.
- If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the participant's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining participant's contact information or other public vital status data necessary to complete the follow-up portion of the study.
- The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information.
- If after all attempts, the participant remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the participant's medical records.

9 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and timing are summarized in the Schedule of Activities (see Section 2).

Protocol waivers or exemptions are not allowed.

All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.

Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before randomization. The investigator will maintain a screening log to

record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Schedule of Activities.

Additional measures, including non-study required laboratory tests, should be performed as clinically indicated or in compliance with local regulations. Laboratory toxicities (eg, suspected drug-induced liver enzyme evaluations) will be monitored during the follow-up phase via on-site/local laboratories until all study treatment-related toxicities resolve, return to baseline, or are deemed irreversible.

If a participant shows pulmonary-related signs (eg, hypoxia, fever, or cough) or symptoms (eg, dyspnea) consistent with possible pulmonary AEs, the participant should be immediately evaluated to rule out pulmonary toxicity, according to the suspected pulmonary toxicity management algorithm in Appendix 9.

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

9.1 Efficacy Assessments

Efficacy assessments for the anti-tumor activity of BMS-986249, alone and in combination with nivolumab, ipilimumab in combination with nivolumab, and nivolumab monotherapy will be based on tumor measurements, using RECIST v1.1 (all indications except prostate) or PCWG3 criteria (for prostate cancer).

Only data for the procedures and assessments specified in this protocol should be submitted to the Sponsor or Designee on a CRF. Additional procedures and assessments may be performed as part of standard of care. However, data for these assessments should remain in the participant's medical record and should not be provided to the Sponsor or Designee, unless specifically requested from BMS or Designee.

9.1.1 Imaging Assessment for the Study

Images will be submitted to an imaging core laboratory and, at the Sponsor's discretion, may be reviewed by BICR at a later date or at any time during the study. Sites should be trained prior to scanning the first study participant. Image acquisition guidelines and the submission process will be outlined in the CA030001 Imaging Manual to be provided by the core laboratory.

Screening, on-treatment, and follow-up images should be acquired as outlined in Section 2.
Tumor assessments at other time points may be performed if clinically indicated and should be submitted to the central imaging vendor.

Contrast-enhanced CT of the chest, abdomen, pelvis, and all other known/suspected sites of disease should be performed for tumor assessments.

For participants with HCC, a triphasic CT/MRI of the liver is required.

For participants with TNBC without measurable lesions outside of the breast, contrast-enhanced MRI of the breasts should be performed along with body imaging.

Participants with prostate cancer should have bone lesions assessed using technetium-99m radionuclide bone scans at each imaging assessment. Anterior and posterior whole body planar images should be acquired. Additional (including spot views and single-photon emission computerized tomography) images should also be submitted if acquired. Participants with other malignancies may have bone scans as clinically indicated.

Images should be acquired with slice thickness of 5 mm or less with no intervening gap (contiguous). Every attempt should be made to image each participant using an identical acquisition protocol on the same scanner for all imaging time points. Tumor measurements should be made by the same investigator or radiologist for each assessment whenever possible.

Should a participant have contraindication for a CT IV contrast, a non-contrast CT of the chest and a contrast-enhanced MRI of the abdomen, pelvis, and other known/suspected sites of disease should be obtained. If the primary tumor is not of lung origin, a contrast-enhanced MRI of the chest may be obtained instead of a non-contrast CT of the chest.

Should a participant have contraindication for both MRI and CT IV contrasts, a non-contrast CT of the chest and a non-contrast MRI of the abdomen, pelvis, and other known/suspected sites of disease should be obtained. If the primary tumor is not of lung origin, a non-contrast MRI of the chest, abdomen, pelvis, and other known/suspected sites of disease is also acceptable.

Should a participant have contraindication for MRI (eg, incompatible pacemaker) in addition to contraindication to CT IV contrast, a non-contrast CT of the chest, abdomen, pelvis, and other known/suspected sites of disease is acceptable.

Use of CT component of a positron emission tomography (PET)/CT scanner: Combined modality scanning such as with PET-CT is increasingly used in clinical care and is a modality/technology that is in rapid evolution; therefore, the recommendations outlined here may change rather quickly with time. At present, low-dose or attenuation correction CT portions of a combined PET-CT are of limited use in anatomically based efficacy assessments; therefore, it is suggested that they should not be substituted for dedicated diagnostic contrast-enhanced CT scans for anatomically based RECIST measurements. However, if a site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST v1.1 measurements. Note, however, that the PET portion of the CT introduces additional data that may bias an investigator if it is not routinely or serially performed.

Bone scan or PET scan is not adequate for assessment of RECIST v1.1 response in target lesions. In selected circumstances where such modalities are the sole modality used to assess certain non-target organs, those non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when CR is identified in target disease or when progression in bone is suspected.

Brain and/or bone scans may be collected per local standards, as clinically indicated.

Tumor assessments for all participants should continue per protocol even if dosing is delayed or discontinued. Changes in tumor measurements and tumor responses will be assessed by the investigator per study design using RECIST v1.1 or PCWG3 (for prostate cancer) criteria.

Assessments of PR and CR must be confirmed at least 4 weeks after initial response. A Best Response of SD can only be made after the participant is on-study for a minimum of 49 days from the date of treatment initiation (ie, first dose). Investigators will also report the number and size of new lesions that appear while on study. Investigators will also report the number and size of new lesions that appear while on study treatment. The time point of tumor assessments will be reported on the CRF based on the investigator's assessment.

9.2 Adverse Events

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

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

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

Contacts for SAE reporting specified in Appendix 3.

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

For all study participants, safety reporting of all AEs (non SAEs and SAEs) should take place from date of informed consent through 100 days post EOT. All SAEs, and all AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection, must be collected from the date of the participant's written consent through 100 days following EOT.

The IB describes the Reference Safety Information to determine expectedness of SAEs for expedited reporting. Following the participant's written consent to participate in the study, all SAEs, whether related or not related to study treatment, must be collected, including those thought to be associated with protocol-specified procedures.

- All AEs and SAEs must be collected that occur during the screening period and through 100 days post EOT, except in cases where a study participant has started a new anti-neoplastic therapy. Any SAE occurring after the start of a new anti-neoplastic therapy that is suspected to be related to study treatment by the investigator should be reported as an SAE.
- The investigator must report any SAE that occurs after these time periods and that is believed to be related to study treatment or protocol-specified procedure.
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the appropriate section of the CRF section.
- All SAEs will be recorded and reported to Sponsor or designee within 24 hours, as indicated in Appendix 3.

- The investigator will submit any updated SAE data to the Sponsor within 24 hours of this being available.

Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify the Sponsor.

The method of evaluating and assessing causality of AEs and SAEs and the procedures for completing and reporting/transmitting SAE reports are provided in Appendix 3.

9.2.2 Method of Detecting AEs and SAEs

AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a participant. In order to prevent reporting bias, participants should not be questioned regarding the specific occurrence of 1or more AEs.

Every AE must be assessed by the investigator with regard to whether it is considered immune-mediated. For events which are potentially immune-mediated, additional information will be collected on the participant's CRF.

9.2.3 Follow-up of AEs and SAEs

- Non-serious AEs should be followed to resolution or stabilization or reported as SAEs if they become serious (see Appendix 3).
- Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study treatment and for those present at the end of study treatment as appropriate.
- All identified non-serious AEs must be recorded and described on the non-serious AE page of the CRF (paper or electronic). Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and non-serious AEs of special interest (as defined in Section 9.2), including those associated with confirmed or suspected SARS-CoV-2 infection, will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, until the event is deemed irreversible, until the participant is lost to follow-up (as defined in Section 8.3), or for suspected cases, until SARS-CoV-2 infection is ruled out.

Further information on follow-up procedures is given in Appendix 3.

9.2.4 Regulatory Reporting Requirements for SAEs

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

the IB and will notify the Institutional Review Board/Independent Ethics Committee, if appropriate according to local requirements.

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

9.2.5 Pregnancy

If, following initiation of the study treatment, it is subsequently discovered that a participant is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half-lives after product administration, the investigator must immediately notify the Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Appendix 3.

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

Protocol-required procedures for study discontinuation and follow-up must be performed on the participant.

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

Any pregnancy that occurs in a female partner of a male study participant should be reported to the Sponsor or designee. In order for the Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an ICF for disclosure of this information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

In cases where a study treatment can be present in seminal fluid, at exposures sufficient to potentially cause fetal toxicity, and if any sexual activity (eg, vaginal, anal, oral) has occurred between a male participant and a pregnant WOCBP partner(s), the information should be reported to the Sponsor or designee, even if the male participant has undergone a successful vasectomy. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner(s) must sign an informed consent form for disclosure of this information. Information on the pregnancy will be collected on the Pregnancy Surveillance Form.

9.2.6 Laboratory Test Result Abnormalities

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

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

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

9.2.7 Immune-mediated Adverse Events

Immune-mediated AEs are AEs consistent with an immune-mediated mechanism or immune-mediated component for which non-inflammatory etiologies (eg, infection or tumor progression) have been ruled out. Immune-mediated AEs can include events with an alternate etiology that were exacerbated by the induction of autoimmunity. Information supporting the assessment will be collected on the participant's CRF.

9.2.8 Potential Drug-induced Liver Injury

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

A p-DILI is defined as follows:

1) Aminotransaminases (ATs; ALT or AST) elevation > 3× ULN

AND

2) Total bilirubin > 2× ULN, without initial findings of cholestasis (elevated serum ALP),

AND

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

For HCC participants, a p-DILI is defined as follows and takes into account anticipated baseline compromise of liver function:

1) Concurrent ALT ≥ 10× ULN

AND

2) Total bilirubin ≥ 2× ULN or baseline value (if elevated bilirubin at study entry)

AND

3) No other immediately apparent possible causes of ALT elevation and hyperbilirubinemia, including, but not limited to, tumor progression, acute viral hepatitis, cholestatis, pre-existing hepatic disease, or the administration of other drug(s), herbal medications, and substances known to be hepatotoxic.

The key responsibilities for investigators DILI assessment include (1) early detection, medical evaluation (including the exclusion of other potential causes) and rapid laboratory confirmation of liver-related abnormalities and (2) BMS notification of p-DILI cases via SAE forms. Following the gathering and assessment of relevant clinical information, BMS is responsible for (1) timely evaluation and triaging of p-DILI cases, (2) expedited reporting of p-DILI cases, and (3) expanded review of p-DILI cases including a detailed assessment of all available clinical information, investigations, and biochemical data.

Investigators are expected to monitor ongoing routine and ad hoc hepatic laboratory test results to rapidly determine whether a participant meets p-DILI criteria. They are expected to promptly notify BMS of all p-DILI cases. p-DILI cases may be identified by abnormal liver biochemistry values, whether or not they are accompanied by liver-related signs and/or symptoms. In both cases, expedited confirmation with repeat laboratory testing should occur within 3 business days using a hepatic laboratory panel (ALT, AST, total bilirubin, and ALP). Any participant with an abnormal hepatic laboratory panel that meets p-DILI criteria is a candidate for study treatment discontinuation. Any confirmed p-DILI events must be reported (along with a description of the clinical findings) to BMS as an SAE within 24 hours of confirmation.

An extensive clinical history, examination, and appropriate investigations should be obtained to exclude cholestatic and other apparent causes that may explain the observed abnormalities in liver function and/or hepatic signs and symptoms. Other apparent causes include, non-exhaustively and by way of example only, the following: infectious diseases (such as active hepatitis A, B, and C), congenital diseases (such as Gilbert's syndrome), neoplastic diseases, autoimmune diseases (such as primary biliary cirrhosis), and the use of concomitant hepatotoxic medications (such as antibiotics, the oral contraceptive pill, and herbal medicines). All investigations to exclude potential causes of liver function abnormalities or hepatic signs and/or symptoms should be guided by relevant factors such as the participant's age, gender, clinical history, and signs and symptoms.

9.2.9 Other Safety Considerations

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

9.3 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important.

For this study, any dose of BMS-986249, ipilimumab, or nivolumab greater than the assigned dose and considered excessive and medically important by the investigator will be considered an overdose.

All occurrences of overdose must be reported as SAEs (see Section 9.2).

In the event of an overdose the investigator should:

1) Contact the Medical Monitor (or designee) immediately.

2) Closely monitor the participant for AEs/SAEs and laboratory abnormalities until BMS-986249, ipilimumab, or nivolumab can no longer be detected systemically (at least 125 days).
3) Obtain a blood sample for PK analysis after the last dose of study treatment if requested by the Medical Monitor (or designee) (determined on a case-by-case basis).
4) Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions or modifications secondary to an overdose will be made by the investigator in consultation with the Medical Monitor (or designee) based on the clinical evaluation of the participant.

9.4 Safety

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

Safety assessments will be based on reported AE and the measurement results of vital signs, ECGs, PEs, and clinical laboratory tests. AEs will be coded using the most current version of Medical Dictionary for Regulatory Activities and the incidence of observed AEs will be tabulated and reviewed for potential significance and clinical importance. For all study participants, safety reporting of all AEs (non SAEs and SAEs) should take place from date of informed consent through 100 days post EOT. Local laboratory will perform the clinical laboratory tests and will provide reference ranges for these tests. Both AEs and laboratory tests will be graded using the NCI CTCAE v4.03. Testing for COVID-19 to inform decisions about clinical care during the study should follow local standard practice.

9.4.1 Physical Examinations

Refer to the Schedule of Activities for timing of assessments in Table 2-1, Table 2-2, Table 2-3, Table 2-4, and Table 2-5.

9.4.2 Vital Signs

Refer to the Schedule of Activities for timing of assessments in Table 2-1, Table 2-2, Table 2-3, Table 2-4, and Table 2-5.

9.4.3 Electrocardiograms

Refer to the Schedule of Activities for timing of assessments in Table 2-1, Table 2-2, Table 2-3, and Table 2-4.

The effect of BMS-986249 on the corrected QT interval will be evaluated by a central reader using all of the ECG data collected. For BMS-986249 Monotherapy Dose Escalation (Part 1A) ECGs will be taken in triplicate at select time points (see Table 2-2) along with time-matched PK (eg, 1 ECG test equals 3 consecutive individual 12-lead ECGs performed 5 minutes apart). All other ECGs completed in screening, on-treatment in Parts 1B, 2A, and 2B, and in follow-up will be a single 12-lead ECG at select time points (see Section 2).

For the purposes of monitoring participant safety, outside the central reader time points the investigators will review the 12-lead ECGs using their site's standard ECG machines throughout the study.

The QTcF will be applied to each ECG reading.

9.4.4 Clinical Safety Laboratory Assessments

- Investigators must document their review of each laboratory safety report.
- A local laboratory, unless otherwise specified, will perform the analyses and will provide reference ranges for these tests. Results of clinical laboratory tests performed on Day -1 must be available prior to dosing.
- The laboratory tests that will be performed for study participants are shown in Table 9.4.4-1.
- Results of all laboratory tests required by this protocol must be provided to the Sponsor, recorded either 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.

Table 9.4.4-1: Clinical Laboratory Assessments

Hematology	
Hemoglobin and hematocrit	
Total leukocyte count, including differential	
Platelet count	
Prothrombin time, activated partial thromboplastin time, and international normalized ratio (at screening only)[a]	
Serum Chemistry	
Aspartate aminotransferase	Total protein
Alanine aminotransferase	Albumin
Total bilirubin	Sodium
Direct bilirubin (reflex)[b]	Potassium
Alkaline phosphatase	Chloride
Lactate dehydrogenase	Calcium
Creatinine	Phosphorus
Creatine kinase/ Creatine phosphokinase	Magnesium
C-reactive protein	Creatinine clearance (Cockcroft-Gault method, at screening only)
Blood urea nitrogen	Troponin
Uric acid	Serum Alpha-fetoprotein[e]
Glucose	Prostate-specific antigen (PSA)[f]
Lipase	Testosterone[f]
Amylase	

Table 9.4.4-1: Clinical Laboratory Assessments

Gamma glutamyl transferase (reflex only)[c]
Thyroid stimulating hormone
Free T3 and T4 (screening and reflex only)[d]
Urinalysis
Protein
Glucose
Blood
Leukocyte esterase
Specific gravity
pH
Microscopic examination of the sediment if blood, protein, or leukocytes esterase are positive on the dipstick
Serology
Serum for hepatitis C Ab, hepatitis B surface antigen, HIV-1 and HIV-2 Ab (at screening, and as mandated by local requirement)
Additional testing for viral hepatitis required and must be completed at the central laboratory for HCC participants only: Epstein-Barr virus Ab, hepatitis B surface Ab, hepatitis B core Ab, hepatitis B DNA viral load (PCR), HCV RNA viral load (PCR), hepatitis D Ab (if chronic HBV infection). See Section 2.
Other Analyses
Pregnancy test (WOCBP only: screening, predose, and discharge).
Follicle stimulating hormone (screening only and women only)

Abbreviations: Ab = antibody; aPTT = activated partial thromboplastin time; CRPC = castration-resistant prostate cancer; DNA = deoxyribonucleic acid; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HIV = human immunodeficiency virus; INR = international normalized ratio; PCR = polymerase chain reaction; PSA = prostate-specific antigen; PT = prothrombin time; RNA = ribonucleic acid; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential.

[a] PT, aPTT, and INR required for participants with HCC and CRPC as outlined in Section 2.

[b] Reflex testing to be performed only if total bilirubin is abnormal.

[c] Reflex testing to be performed only if liver function test is abnormal.

[d] Reflex testing to be performed only if TSH is abnormal.

[e] Required for participants with HCC only.

[f] Required for participants with CRPC only.

9.4.5 Imaging Safety Assessment

Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the study investigator per standard medical/clinical judgment.

9.5 Pharmacokinetics and Immunogenicity Assessments

The PK of BMS-986249 will be derived from plasma concentration-time data. The PK parameters that will be assessed following serial PK collection are shown in Table 9.5-1. Sparse ipilimumab and nivolumab serum samples will be collected and may be used in an integrated PPK or exposure response analysis along with data from other ipilimumab and nivolumab studies, which would be the subject of a separate report. Separate PK and ADA samples will be collected for BMS-986249, ipilimumab, and nivolumab at the end of a sequential dosing or co-administration. Separate samples will be collected for PK and ADA assessments using validated methods.

ADA samples for BMS-986249 and serum samples for ipilimumab and nivolumab ADA will be collected from all participants at specified time points (see Table 9.5-2 through Table 9.5-9). Blood samples may be analyzed by an exploratory method that measures different forms of the Probody mAb for technology exploration purposes; exploratory results may be reported. Blood 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 AEs), and vice versa.

Table 9.5-1: BMS-986249 Pharmacokinetic Parameters

Parameters	Definition
Cmax	Maximum observed concentration
Tmax	Time of maximum observed concentration
AUC(0-T)	Area under the concentration-time curve from time zero to time of last quantifiable concentration; may be calculated if concentrations are not quantifiable up to TAU across a treatment group
AUC(TAU)	Area under the concentration-time curve in 1 dosing interval
Ctau	Observed concentration at the end of a dosing interval
Ctrough	Trough observed concentrations (this includes predose concentrations [C0] and Ctau)
Parameters That May be Assessed Following the Dose Administration in Cycle 4	
CLT	Total body clearance
Css-avg	Average concentration over a dosing interval (AUC[TAU]/tau) at steady state
AI	Ratio of an exposure measure at steady state to that after the first dose (exposure measure includes AUC[TAU] and Cmax)
T-HALF	Terminal half-life

Individual participant PK parameter values will be derived by noncompartmental methods using a validated PK analysis program. Actual times will be used for all formal analyses.

Table 9.5-2 through Table 9.5-9 list the sampling schedule to be followed for the assessment of PK in Parts 1A, 1B, 2A, and 2B. Further details of blood collection and processing will be provided to the site in the Laboratory Manual.

All predose samples should be taken within approximately 30 minutes prior to the start of the infusion. Since the end of infusion-PK (EOI-PK) sample is drawn with the intent of accurately estimating the Cmax of the study treatment, draw the EOI-PK when all the study treatment has been infused. If the site infuses study treatment without a flush, then collect the EOI-PK sample within approximately 5 minutes after EOI. If a flush is administered to clear the IV lines of the study treatment and to ensure delivery of the entire study treatment dose, then draw the EOI-PK sample within approximately 5 minutes after end of the flush. Do not draw EOI samples from the same IV access that the study treatment was administered. Refer to Table 7.1.1-1 for infusion duration.

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. If it is known that a dose is going to be delayed, then the predose sample should be collected just prior to the delayed dose. A PK and ADA sample may be taken in the event of a Grade 3+ infusion reaction or hypersensitivity reaction. Further details of sample collection, processing, and shipment will be provided in the Laboratory Manual.

Addendum per Protocol Amendment 09: Removed all PK and ADA samples after Cycle 3 Day 1 (C3D1), with the exception of occurrence of Grade 3+ infusion reactions to decrease participant and site burden as available sample collections are sufficient for proposed analysis of the secondary objective of PK characterization and the exploratory objective of ADA analysis.

Table 9.5-2: PK and ADA Sampling Schedule for BMS-986249 Q4W Monotherapy in Dose Escalation (Part 1A)

Study Day of Sample Collection (1 cycle = 4 weeks)	Event	Time (Relative To Start of BMS-986249 Infusion) Hour: Min	BMS-986249 PK Plasma Sample	BMS-986249 ADA Serum Samples
C1D1	Predose[a]	00:00	X	X
	EOI	See note[b]	X	
		04:00	X	
C1D2		24:00	X	
C1D4 (± 1 days)		72:00	X	
C1D8 (± 2 days)		168:00	X	
C1D15 (± 2 days)		336:00	X	
C1D22 (± 2 days)		504:00	X	
C2D1	Predose[a]	00:00	X	X
	EOI	See note[b]	X	
C2D8 (± 3 days)		168:00	X	
C3D1	Predose[a]	00:00	X	X
	EOI	See note[b]	X	
Grade 3+ Infusion Reaction			X	X

Abbreviations: ADA = anti-drug antibody; C = cycle; D = day; EOI = end of infusion; PK = pharmacokinetics; Q4W = every 4 weeks.

[a] Predose: All predose samples should be taken within approximately 30 minutes prior to the start of the infusion, unless previously discussed with Medical Monitor (or designee).

[b] Refer to Section 9.5 and Table 7.1.1-1 for additional information and infusion duration. If the EOI is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.

Table 9.5-3: PK and ADA Sampling Schedule for BMS-986249 Q4W in Combination with Nivolumab Q4W in Dose Escalation (Part 1B)

Study Day of Sample Collection (1 cycle = 4 weeks)	Event	Time (Relative To Start of BMS-986249 in Combination with nivolumab Co-administration Infusion) Hour: Min	BMS-986249 PK Plasma Sample	nivolumab PK Serum Sample	BMS-986249 ADA Serum Samples	nivolumab ADA Serum Samples
C1D1	Predose[a]	00:00	X	X	X	X
	EOI	See note[b]	X	X		
		04:00	X			
C1D2		24:00	X			
C1D8 (± 2 days)		168:00	X			
C1D15 (± 2 days)		336:00	X			
C1D22 (± 2 days)		504:00	X			
C2D1	Predose[a]	00:00	X	X	X	X
	EOI	See note[b]	X	X		
C2D8 (± 3 days)		168:00	X			
C3D1	Predose[a]	00:00	X	X	X	X
	EOI	See note[b]	X	X		
Grade 3+ Infusion Reaction			X	X	X	X

Abbreviations: ADA = anti-drug antibody; C = cycle; D = day; EOI = end of infusion; PK = pharmacokinetics; Q4W = every 4 weeks.

[a] Predose: All predose samples should be taken within approximately 30 minutes prior to the start of the infusion, unless previously discussed with Medical Monitor (or designee).

[b] Refer to Section 9.5 and Table 7.1.1-1 for additional information and infusion duration. Separate EOI samples (1 each for BMS-986249 and nivolumab) should be collected following co-administration of BMS-986249 and nivolumab and recorded as having the same collection time. If the EOI is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.

Table 9.5-4: PK and ADA Sampling Schedule for Part 2A Arm A

Study Day of Sample Collection (1 cycle = 3 weeks for Cycles 1-4 Combination Therapy Phase, then 1 cycle = 4 weeks starting Cycle 5 nivolumab monotherapy Maintenance Phase)	Event	Time (Relative To Start of nivolumab Infusion) Hour:Min	BMS-986249 PK Plasma Sample	nivolumab PK Serum Sample	BMS-986249 ADA Plasma Samples	nivolumab ADA Serum Samples
C1D1	Predose[a]	0:00	X	X	X	X
	EOI	See note[b]	X	X		
		4:00	X			
C1D2		24:00	X			
C1D5[c] (± 3 days)	See note	96:00	X			
C1D8 (± 2 days)		168:00	X			
C1D15 (± 2 days)[c]		336:00	X			
C2D1	Predose[a]	0:00	X	X	X	X
	EOI	See note[b]	X	X		
C2D8 (± 3 days)[c]		168:00	X			
C3D1	Predose[a]	0:00	X	X	X	X
	EOI	See note[b]	X	X		
Grade 3+ Infusion Reaction			X	X	X	X

Abbreviations: ADA = anti-drug antibody; C = cycle; D = day; EOI = end of infusion; PK = pharmacokinetics.

[a] Predose: All predose samples should be taken within approximately 30 minutes prior to the start of the infusion, unless previously discussed with Medical Monitor (or designee).

[b] Refer to Section 9.5 and Table 7.1.1-1 for additional information and infusion duration. Separate EOI samples (1 each for BMS-986249 and nivolumab) should be collected following co-administration of BMS-986249 and nivolumab and recorded as having the same collection time. If the EOI is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.

[c] To align with the scheduled [redacted], the time window can be the same as [redacted] (± 3 days). C1D5 and C2D8 PK samples should only be collected if participant is scheduled for a corresponding [redacted]. If [redacted] is assigned, C1D5 and C2D8 PK samples should not be collected. C1D15 PK sample should be collected at the time of [redacted]. If [redacted] is assigned at C1D15, PK sample should still be collected. See Table 2-3.

Table 9.5-5: PK and ADA Sampling Schedule for Part 2A Arm B and Arm C

Study Day of Sample Collection (1 cycle = 4 weeks)	Event	Time (Relative To Start of nivolumab Infusion) Hour:Min	BMS-986249 PK Plasma Sample	nivolumab PK Serum Sample	BMS-986249 ADA Plasma Samples	nivolumab ADA Serum Samples
C1D1	Predose[a]	0:00	X	X	X	X
	EOI[b]	See note	X	X		
C1D2		24:00	X			
C1D5[c] (± 3 days)	See note	96:00	X			
C1D8 (± 2 days)		168:00	X			
C1D15 (± 2 days)[c]		336:00	X			
C1D22 (± 2 days)		504:00	X			
C2D1	Predose[a]	0:00	X	X		X
	EOI[b]	See note		X		
C2D8[c] (± 3 days)	See note	168:00	X			
C3D1	Predose[a]	0:00	X	X	X	X
	EOI[b]	See note	X	X		
Grade 3+ Infusion Reaction			X	X	X	X

Abbreviations: ADA = anti-drug antibody; C = cycle; D = day; EOI = end of infusion; PK = pharmacokinetics.

[a] Predose: All predose samples should be taken within approximately 30 minutes prior to the start of the infusion, unless previously discussed with Medical Monitor (or designee).

[b] Refer to Section 9.5 and Table 7.1.1-1 for additional information and infusion duration. For co-administration visits, separate EOI samples (1 each for BMS-986249 and nivolumab) should be collected following co-administration of BMS-986249 and nivolumab and recorded as having the same collection time. If the EOI is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.

[c] To align with the scheduled [redacted], the time window can be the same as [redacted] (± 3 days). C1D5 and C2D8 PK samples should only be collected if participant is scheduled for a corresponding [redacted]. If [redacted] is assigned, C1D5 and C2D8 PK samples should not be collected. C1D15 PK samples should be collected at the [redacted]. If [redacted] is assigned at C1D15, PK sample should still be collected. See Table 2-4.

Table 9.5-6: PK and ADA Sampling Schedule for Part 2A Arm D

Study Day of Sample Collection (1 cycle = 3 weeks for Cycles 1-4 Combination Therapy Phase; then 1 cycle = 4 weeks starting Cycle 5 nivolumab monotherapy Maintenance Phase)	Event	Time (Relative To Start of nivolumab Infusion) Hour:Min	nivolumab PK Serum Sample	ipilimumab PK Serum Sample	nivolumab ADA Serum Sample	ipilimumab ADA Serum Sample
C1D1	Predose[a]	0:00	X	X	X	X
	EOI[b]	See note	X	X		
C1D5[c]	See note	96:00		X		
C1D15[c]	See note	336:00		X		
C2D1	Predose[a]	0:00	X	X	X	X
	EOI[b]	See note	X	X		
C2D8[c]	See note	168:00		X		
C3D1	Predose[a]	0:00	X	X	X	X
	EOI[b]	See note	X	X		
Grade 3+ Infusion Reaction			X	X	X	X

Abbreviations: ADA = anti-drug antibody; C = cycle; D = day; EOI = end of infusion; PK = pharmacokinetics.

[a] Predose: All predose samples should be taken within approximately 30 minutes prior to the start of the infusion, unless previously discussed with Medical Monitor (or designee).

[b] Refer to Section 9.5 and Table 7.1.1-1 for additional information and infusion duration. Separate EOI samples (1 each for ipilimumab and nivolumab) should be collected immediately after stopping the infusion of ipilimumab (preferably within 2 minutes) and recorded as having same collection time. If the EOI is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.

[c] To align with the scheduled [redacted], the time window can be the same as [redacted] (± 3 days). C1D5, C1D15, and C2D8 PK samples should only be collected if participant is scheduled for corresponding [redacted]. See Table 2-3.

Table 9.5-7: PK and ADA Sampling Schedule for Part 2A Arm E

Study Day of Sample Collection (1 cycle = 4 weeks)	Event	Time (Relative To Start of nivolumab Infusion) Hour:Min	nivolumab PK Serum Sample	nivolumab ADA Serum Sample
C1D1	Predose[a]	0:00	X	X
	EOI	See note[b]	X	
C2D1	Predose[a]	0:00	X	X
	EOI	See note[b]	X	
C3D1	Predose[a]	0:00	X	X
	EOI	See note[b]	X	
Grade 3+ Infusion Reaction			X	X

Abbreviations: ADA = anti-drug antibody; C = cycle; D = day; EOI = end of infusion; PK = pharmacokinetics.

[a] Predose: All predose samples should be taken within approximately 30 minutes prior to the start of the infusion, unless previously discussed with Medical Monitor (or designee).

[b] Refer to Section 9.5 and Table 7.1.1-1 for additional information and infusion duration. If the EOI is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.

Table 9.5-8: PK and ADA Sampling Schedule for Part 2A Arm F

Study Day of Sample Collection (1 cycle = 4 weeks)	Event	Time (Relative to Start of BMS-986249 in Combination with Nivolumab Co-administration Infusion) Hour: Min	BMS-986249 PK Plasma Sample	Nivolumab PK Serum Sample	BMS-986249 ADA Plasma Samples	Nivolumab ADA Serum Samples
C1D1	Predose[a]	00:00	X	X	X	X
	EOI	See note[b]	X	X		
C1D2		24:00	X			
C1D5[c] (± 3 days)	See note	96:00	X			
C1D8 (± 2 days)		168:00	X			
C1D15[c] (± 2 days)		336:00	X			

Table 9.5-8: PK and ADA Sampling Schedule for Part 2A Arm F

Study Day of Sample Collection (1 cycle = 4 weeks)	Event	Time (Relative to Start of BMS-986249 in Combination with Nivolumab Co-administration Infusion) Hour: Min	BMS-986249 PK Plasma Sample	Nivolumab PK Serum Sample	BMS-986249 ADA Plasma Samples	Nivolumab ADA Serum Samples
C1D22 (± 2 days)		504:00	X			
C2D1	Predose[a]	00:00	X	X	X	X
	EOI	See note[b]	X	X		
C2D8 [c] (± 3 days)	See note	168:00	X			
C3D1	Predose[a]	00:00	X	X	X	X
	EOI	See note[b]	X	X		
Grade 3+ Infusion Reaction			X	X	X	X

Abbreviations: ADA = anti-drug antibody; C = cycle; D = day; EOI = end of infusion; Min = minutes; PK = pharmacokinetics.

[a] Predose: All predose samples should be taken within approximately 30 minutes prior to the start of the infusion, unless previously discussed with Medical Monitor (or designee).

[b] Refer to Section 9.5 and Table 7.1.1-1 for additional information and infusion duration. Separate EOI samples (1 each for BMS-986249 and nivolumab) should be collected following co-administration of BMS-986249 and nivolumab and recorded as having the same collection time. If the EOI is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.

[c] To align with the scheduled [redacted], the time window can be the same as [redacted] (± 3 days). C1D5 and C2D8 PK samples should only be collected if participant is scheduled for corresponding [redacted]; if [redacted] is assigned, C1D5 and C2D8 PK samples should not be collected. C1D15 PK samples should be collected at the [redacted]. If [redacted] is assigned at C1D15, PK sample should still be collected. See Section 2.

Table 9.5-9: PK and ADA Sampling Schedule for Part 2B

Study Day of Sample Collection (1 cycle = 4 weeks)	Event	Time (Relative to Start of Nivolumab Infusion) Hour:Min	BMS-986249 PK Plasma Sample	Nivolumab PK Serum Sample	BMS-986249 ADA Plasma Samples	Nivolumab ADA Serum Samples
C1D1	Predose[a]	00:00	X	X	X	X
	EOI	See note[b]	X	X		
C1D2		24:00	X			
C1D8 (± 2 Day)		168:00	X			
C1D15 (± 3 Day)	See note[c]	336:00	X			
C1D22 (± 2 Day)		504:00	X			
C2D1	Predose[a]	00:00	X	X		X
	EOI	See note[b]		X		
C2D8 (± 2 Day)		168:00	X			
C3D1	Predose[a]	00:00	X	X	X	X
	EOI	See note[b]	X	X		
Grade 3+ Infusion Reaction			X	X	X	X

Abbreviations: ADA = anti-drug antibody; C = cycle; D = day; EOI = end of infusion; Min = minutes; PK = pharmacokinetic.

[a] Predose: All predose samples should be taken within approximately 30 minutes prior to the start of the infusion, unless previously discussed with Medical Monitor (or designee).

[b] Refer to Section 9.5 and Table 7.1.1-1 for additional information and infusion duration. For co-administration visits, separate EOI samples (1 each for BMS-986249 and nivolumab) should be collected following co-administration of BMS-986249 and nivolumab and recorded as having the same collection time. If the EOI is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.

[c] C1D15 PK sample should be collected at the [redacted]. See Table 2-4.

[redacted]

9.7 Pharmacogenomics

Not applicable.

9.7.1 ADME Sampling

Not applicable.

9.8 Biomarkers

[redacted]. Additional biomarkers related to mechanism of action, such as, but not limited to safety biomarkers, and associations with response to BMS-986249 alone and in combination with nivolumab, ipilimumab in combination with nivolumab, and nivolumab monotherapy will be explored.

[redacted] If biomarker samples are drawn but study treatment(s) is not administered, samples will be retained. A detailed description of each biomarker sample analysis and assessment is described below, and a schedule of biomarker sample collections is provided in Table 9.8.3-1. Further details of blood, serum, and tumor tissue collection and processing will be provided to the site in the Laboratory Manual.

Addendum per Protocol Amendment 09: Biomarker sample collection after [redacted] has been reduced to decrease participant and site burden as available sample collections are sufficient for proposed analysis of the exploratory endpoint.

9.8.1 Peripheral Blood Biomarkers

A variety of factors that may impact the immunomodulatory properties and efficacy of BMS-986249, ipilimumab, and nivolumab will be investigated in peripheral blood specimens taken from all participants prior to or during treatment at the time points indicated in Table 9.8.3-1. Results from these investigations will be evaluated for associations with dose, response, survival, and/or safety (AE) data. Several analyses will be completed and are described briefly below.

9.8.1.1 Soluble Biomarkers

Serum samples as well as blood samples used for PK analysis may also be used to evaluate circulating levels of immune factors, such as [redacted], over the course of the treatment. [redacted]

9.8.1.2 Immunophenotyping

The proportion of specific lymphocyte subsets and expression levels of T cell co-stimulatory markers in PBMC preparations will be quantified by flow cytometry. [redacted]

9.8.1.3 T cell Repertoire Analysis

The diversity of the peripheral T cell compartment and changes over the course of treatment with immunotherapeutic agents may be related to the mechanism of action of BMS-986249. [redacted]

9.8.1.4 Germline DNA Variants

Whole blood will be collected from all participants prior to treatment to generate genomic DNA for single nucleotide polymorphism (SNP) analyses and to serve as a reference for tumor genomic testing, including tumor mutational load assessment. [redacted]

9.8.2 Tumor Samples

Tumor biopsy specimens will be obtained from all participants to characterize immune cell populations and expression of selected tumor markers including, dMMR and MSI-H. See Section 2 and Table 9.8.3-1 for the tumor collection schedule time points. Pre-treatment biopsy tissue required for all participants. Refer to Table 2-1 and Laboratory Manual for details.

- For Part 1: The on-treatment biopsy will be collected on [redacted], and tumor specimens may be collected within 3 days of the specified time point and must be obtained prior to administration of study treatments. Bone lesion biopsies are unacceptable for submission.
- For Part 2A: Pre-treatment tumor tissue specimens will be submitted for central PD-L1 IHC assessment prior to randomization (refer to Laboratory Manual for details). These biopsy samples should be excisional, incisional, punch or core needle. Fine needle aspirates or other cytology specimens are insufficient for downstream biomarker analyses. PD-L1 stained tissue sections will be assessed by a pathologist and scored as PD-L1 positive if membrane staining is observed in ≥ 1% tumor cells among a minimum of a hundred (100) evaluable tumor cells.

Samples with < 1% tumor cell membrane staining in a minimum of a hundred (100) evaluable tumor cells will be scored as PD-L1 negative and samples where membrane staining is obscured by high cytoplasmic staining or melanin content, but contain the minimum number of evaluable tumor cells will be deemed PD-L1 indeterminate.

- For Part 2A: The on-treatment biopsy will be first collected on [redacted] for approximately the first 75 participants treated (about 25 participants per active Arm), and then collected per Investigator preference on [redacted] or [redacted] for approximately the next 105 participants treated (about 35 participants per active Arm). On-treatment tumor specimens may be collected within 3 days of the specified time point and must be obtained prior to administration of study treatment. Bone lesion biopsies are unacceptable for submission.
- For Part 2A: [redacted]. The varying number of participants for each of the different timed on-treatment tumor biopsy collections is to enable a sufficient number of samples for analysis while accounting for on-treatment attrition and factors related to biopsy heterogeneity.
- For Part 2B, the on-treatment biopsy will be collected on [redacted]. Tumor specimens may be collected within 3 days of the specified time point and must be obtained prior to administration of study treatment. Bone lesion biopsies are unacceptable for submission.
- A tumor biopsy is mandatory upon confirmation of PD (within 7 days) **except for**:
  - Participants who have an on-treatment biopsy and progress within 4 cycles.
  - Participants who will be imminently (within 4 weeks) enrolling in a subsequent clinical research study that requires a screening biopsy, then the new trial enrollment criteria supersede the required post-progression tumor biopsy.
  - Participants who consent to be treated beyond progression will only require the PD biopsy at the subsequent confirmation of progression.
- Both the screening and on-treatment tumor biopsies should be preferentially collected from the same site, if feasible. At the time of progression, the biopsy should be performed using a progressive lesion or a new lesion, if feasible.
- Tumor biopsy samples should be excisional, incisional, or core needle as fine needle aspirates and other cytology specimens are insufficient for downstream biomarker analyses. Bone lesion biopsies are unacceptable for submission.
- On-treatment and PD biopsies are mandated at acceptable clinical risk (as determined by the investigator). Notify the Medical Monitor (or designee) if on-treatment biopsy may pose unacceptable clinical risk or if tumor at the time of on-treatment biopsy is not accessible for sampling. Institutional guidelines for the safe performance of biopsies should be followed.
- All tumor tissue collection (fresh biopsy or archival) will follow the same guidance methodology for sample collections provided in the Laboratory Manual.

[redacted] In addition, tissue biopsies will assist in characterizing the PK of ipilimumab and the various Probody species. [redacted]

[redacted]

If available, [redacted] and IHC expression between fresh formalin-fixed, paraffin-embedded and archival tumor specimens may also be made.

9.8.2.1 Characterization of Tumor Immune Microenvironment

IHC 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 after exposure to therapy. [redacted]

9.8.3 Biomarker Sampling Schedule

Table 9.8.3-1: Biomarker Sampling Schedule for All Study Parts

Study Day of Sample Collection	Time (Relative to infusion time) Hour:Min	Tumor Biopsy[a]	Serum	Whole Blood (Germline and TCR)	Whole Blood (PAXgene)	Blood (Immuno-phenotyping)	Plasma	Anti-SARS-CoV-2 Serology
[redacted]								

Abbreviations: [redacted]; PD = progressive disease; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TCR = T cell receptor.

[a] For additional information regarding tumor sample collection, refer to Section 2, Section 9.8.2, and Laboratory Manual for details.

[redacted]

9.8.4 Additional Research Collection

This protocol will include both sample collection and residual sample storage for additional research (AR).

For All Sites:

Additional research is required for all study participants, except where prohibited by IRBs/ethics committees, prohibited by local laws or regulations, or academic/institutional requirements.

- If the IRB/ethics committees and site agree to the mandatory additional research retention and/or collection, then the study participant must agree to the mandatory additional research as a requirement for inclusion in the study.
- If optional participation is permitted and approved, then the study participants may opt out of the additional research retention and/or collection.

Additional research is intended to expand the R&D capability at Bristol-Myers Squibb, and will support as yet undefined research aims that will advance our understanding of disease and options for treatment. This may also include genetic/genomic exploration aimed at exploring disease pathways, progression, and response to treatment.

Sample Collection and Storage

All requests for access to samples or data for AR will be vetted through a committee of the study Sponsor's senior leaders in Research and Development to ensure the research supports appropriate and well-defined scientific research activities.

Samples kept for future research will be securely stored at the [redacted], or a BMS-approved third-party storage management facility.

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 BMS 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 BMS researcher to connect a sample to a specific individual.

Further details of sample retention and processing will be provided to the site in the Laboratory Manual. See Table 9.8.4-1 for time points for retention of each sample type.

Table 9.8.4-1: Residual Sample Retention for Additional Research Schedule

Sample Type	Time points for which residual samples will be retained
PK/ADA	All
Tumor Biopsy	All
Blood biomarker samples	All

Abbreviations: ADA = anti-drug antibody; PK = pharmacokinetic.

9.9 Patient-reported Outcomes

Quality of life (QoL) in oncology clinical studies is becoming increasingly important to understand the impact of benefit/risk from the patient perspective. Participants enrolled in the BMS-986249 in Combination with Nivolumab Randomized Cohort Expansion in Melanoma (Part 2A) and Participants enrolled in BMS-986249 in Combination with Nivolumab Additional Tumor Cohort Expansion (Part 2B) will be asked to complete the EORTC QLQ-C30, EQ-5D-3L, FACIT GP5 item, and a selection of items from the PRO-CTCAE prior to first dose, at designated on-treatment clinic visits, and at safety follow-up visits 1, 2 and 3. Only the EQ-5D-3L will be completed, via telephone, during Survival Follow-up Period.

The questionnaires will be provided in the participant's preferred language if available. The EQ-5D-3L may be administered by telephone during survival follow-up. There exists a standardized guide that can be used to facilitate telephone administration of the EQ-5D-3L.

Section 2 provides information regarding the timing of PRO assessments. The questionnaires should be administered at the start of any visit before the participant sees the physician and before any study-related procedures are performed. If exceptional circumstances preclude the continued administration of measures using planned modalities, then alternate administration methods may be required.

9.9.1 EORTC QLQ-C30

Health-related QoL will be assessed using the EORTC QLQ-C30[59]. The EORTC QLQ-C30 is a 30-item instrument that has gained wide acceptance in oncology clinical studies and is composed of multi-item and single-item scales. The global health status/QoL scale is composed of 2 items. In addition to the global health status/QoL scale, the EORTC QLQ-C30 includes 5 functional scales (physical, role, emotional, social, and cognitive), 3 symptom scales (fatigue, nausea and vomiting, and pain), and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). The overall health status/QoL responses are 7-point Likert scales ranging from 1 (Very Poor) to 7 (Excellent), while the responses for all functional and symptom items are 4-point categorical scales ranging from 1 (Not at all) to 4 (Very much). Scale items are scored using recommended EORTC procedures.[60] Raw scores are transformed to a linear scale ranging from 0 to 100, with a higher score representing a higher global health status/QoL. A score difference of 10 is used as an estimate of the minimal important difference (MID) for the subscales

of the EORTC QLQ-C30.[61] The reliability and validity of the questionnaire is highly consistent across different language-cultural groups.

9.9.2 EQ-5D-3L

General health status will be measured using the EQ-5D-3L.[62] The EQ-5D-3L is a standardized instrument used to measure self-reports of health status and functioning. The instruments descriptive system consists of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels, reflecting "no health problems", "moderate health problems" and "extreme health problems". A dimension for which there are no problems is said to be at level 1, while a dimension for which there are extreme problems is said to be at level 3. Thus the vectors 11111 and 33333 represent the best health state and the worst health state, respectively. Altogether, the EQ-5D-3L describes 243 different health states. Empirically derived weights can be applied to an individual's response to the EQ-5D-3L descriptive system to generate an index measuring the value to society for that specific health state. Such preference weighting systems have been developed for many geographical areas. In addition, the EQ-5D-3L includes a visual analogue scale (VAS) that allows respondents to rate their own current health on a 100-point scale, ranging from "best imaginable" to "worst imaginable" health. The utility data generated from the EQ-5D-3L is recommended for, and commonly used in, cost effectiveness analyses. A score difference of 0.08 for the EQ-5D utility score and of 7 for the EQ VAS will be used as MID estimates for the EQ-5D-3L.[63]

9.9.3 FACIT GP5

A single item drawn from the FACIT measurement system, item GP5, will be administered to assess the overall extent of perceived bother due to symptomatic adverse events (symAEs). Evidence exists for the validity of this item and its usefulness as an overall summary measure of burden due to symptomatic treatment toxicities.[64]

9.9.4 PRO-CTCAE

Given evidence that clinicians underreport symptomatic AEs, selected items from the PRO-CTCAE will be used to enhance the assessment of symAEs in the study. Items will be chosen based on the known clinical profile of ipilimumab in combination with nivolumab, clinical judgement, experience of the study team members, and what is known for Part 2A and Part 2B treatments.

9.10 Health Economics OR Medical Resource Utilization and Health Economics

Health economics/medical resource utilization and health economics parameters will not be evaluated in this study.

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

10.1.1 Dose Escalation

Dose escalation in Part 1A (BMS-986249 monotherapy) and Part 1B (BMS-986249 combination therapy with nivolumab) will be guided by BLRM employing the EWOC principle [redacted]. The BLRM method is fully adaptive; makes use of all the information available at the time of each dose assignment, not just data from the current dose level; and directly addresses the ethical need to control the probability of overdosing. Furthermore, the BLRM uses the knowledge gained from participants treated with ipilimumab (for Part 1A) or ipilimumab in combination with nivolumab (for Part 1B). [redacted] The use of the EWOC principle limits the risk of exposing participants in the next cohort to an intolerable dose by ensuring that the posterior probability of the DLT rate exceeding [redacted] at any dose is capped at [redacted].

Approximately 4 participants (3 + 1) will be treated at the starting dose levels of BMS-986249 alone or BMS-986249 in combination with nivolumab. While the BLRM will use DLT information from the DLT period only, clinical assessment will take into consideration the entirety of available preliminary data, including PK/[redacted] from all treated participants in assigning a dose level for the next cohort of 3 participants. AEs meeting DLT criteria outside of the 5-week DLT period may also be incorporated into the BLRM and dose de-escalation may be considered as appropriate based on the BLRM recommendation. At least 6 DLT-evaluable participants will be treated at the BLRM-recommended MTD (BLRM-MTD). A maximum of 12 DLT-evaluable participants will be treated at each dose level. Once the BLRM-MTD is identified, then additional participants may be treated at the BLRM-MTD or any dose level below the BLRM-MTD for further evaluation of safety, PK, or [redacted] parameters as required. The maximum number of participants to be treated will be up to 45 for Part 1A (BMS-986249 monotherapy) and up to 60 for Part 1B (BMS-986249 combination therapy with nivolumab).

The BLRM-MTD is the dose that satisfies the following 3 conditions:

- The empirical posterior probability that the "DLT rate of 16% to [redacted]" is greater than a pre-specified value (ie, 50%).
- This probability needs to be the largest among the dose levels that satisfy the EWOC condition [redacted]
- A minimum number of participants (ie, 6) was treated at this dose level.

The final MTD/RP2D will be based on the recommendations from the BLRM and overall clinical assessment of all available safety, PK, [redacted], and efficacy data. Lower doses may be tested if none of the planned doses are found to be tolerable. Such decisions will be made after discussion and agreement between the investigators and the Medical Monitor (or designee).

10.1.2 Part 2A Cohort Expansion

10.1.2.1 Original Sample Size Calculation

The BMS-986249 in Combination with Nivolumab Randomized Cohort Expansion in Melanoma (Part 2A) sample size determination is based on primary efficacy and primary safety objectives.

The sample size estimation takes into consideration:

The potential for detecting a higher ORR in BMS-986249 in combination with nivolumab (Arms A, B, and C) relative to nivolumab monotherapy (Arm E).

The potential for detecting improved tolerability based on incidence of Grade 3-5 TRAEs within 24 weeks in BMS-986249 in combination with nivolumab (Arms A, B, and C) relative to ipilimumab in combination with nivolumab (Arm D).

Approximately 270 evaluable participants will be randomized in a 1:1:1:1:1 ratio to Arms A - E respectively, with at least 54 evaluable participants in each arm. Randomization will be stratified by PD-L1 status and AJCC M-staging. Assuming a [redacted] ORR in nivolumab monotherapy (Arm E), the two-sided 60% CIs for the difference in ORR comparing each BMS-986249 in combination with nivolumab arm (Arms A, B, and C) versus nivolumab monotherapy for a range of ORRs in BMS-986249 in combination with nivolumab arm (Arms A, B, and C) close to the ORR observed in ipilimumab in combination with nivolumab based on Study CA209067 are presented in [redacted]. At 60% confidence level, the lower bound of the two-sided CI will exceed a minimum [redacted] difference in ORR if an ORR of [redacted] or higher is observed in BMS-986249 in combination with nivolumab arm (Arm A, B, and C).

[redacted]

In addition, assuming a [redacted] incidence rate of drug-related Grade 3-5 AEs within 24 weeks in ipilimumab in combination with nivolumab (Arm D), with 54 evaluable participants in each of BMS-986249 in combination with nivolumab arms (Arm A, B, and C) and ipilimumab in combination with nivolumab arm (Arm D), 60% two-sided CI of treatment difference in incidence rate for each BMS-986249 in combination with nivolumab arm (Arm A, B, and C) versus ipilimumab in combination with nivolumab arm (Arm D) is [redacted] for a [redacted] drop in

incidence rate of drug-related Grade 3-5 AEs within 24 weeks in BMS-986249 in combination with nivolumab arms (Arm A, B, and C). Besides the primary safety endpoint of drug-related Grade 3-5 AEs by within weeks, the safety profile will also be evaluated based on the entirety of available clinical safety data.

The final analysis will take place when all randomized participants have completed at least 36 weeks follow-up or discontinue earlier. Due to exploratory nature of the proof of concept (PoC) design, no multiplicity adjustment will be made for testing multiple endpoints or multiple treatment arms.

10.1.2.2 Changes to Sample Size Assumptions for Revised Protocol 07

The original sample size calculation was based on a 60% two-sided CI of ORR for the difference between treatments and required 54 participants per arm. As participants in Arm E will not be randomized as originally planned, the efficacy evaluation and the statistical comparison will use a reference value of [redacted] based on nivolumab monotherapy historical data in melanoma (see Section 5.4.7.2).

One of the main objectives of this study is to evaluate the preliminary safety and tolerability of BMS-986249 in combination with nivolumab (Part 2A Arm C and Arm F).

Based on final analysis of CA209511, the ipilimimab 3 mg/kg in combination with nivolumab 1 mg/kg, the incidence rate of drug-related Grade 3-5 AEs within 24 weeks is estimated to be [redacted]. A [redacted] relative improvement in the incidence of Grade 3-5 TRAEs is considered to be clinically relevant.

Using a two group $\chi 2$ test with a 0.10 one-sided significance alpha level, assuming a 1:1 randomization ratio of experimental BMS-986249 in combination with nivolumab containing regimen to control ipilimumab in combination with nivolumab, a sample size of 60 participants per arm will have approximately 70% power to detect a ratio in favor of the alternative hypothesis of [redacted] compared to the null hypothesis proportion of [redacted].

The null hypothesis is the ratio of proportions above or equal to 1, the alternative hypothesis is the ratio of proportion is below to 1.

$$H0: P1 / P2 \geq 1. \; H1: P1 / P2 = R1 < 1$$

[redacted]

The final analysis will take place when all randomized participants have completed at least 36 weeks follow-up or discontinue earlier. Due to exploratory nature of the PoC design, no multiplicity adjustment will be made for testing multiple endpoints or multiple treatment arms.

10.1.3 Part 2B Cohort Expansion

In Part 2B, approximately 40 participants will be treated in tumor-specific cohorts of HCC, CRPC, and TNBC, respectively.

This sample size will allow for a meaningful safety analyses assuming the incidence rate of drug-related Grade 3-5 AEs within 24 weeks for historical ipilimumab 3 mg/kg in combination with nivolumab 1 mg/kg [redacted] and is similar across the tumor types (see Section 5.5.6). A target of [redacted] Grade 3-4 TRAE is considered to be clinically relevant in these patient populations.

Using a one group $\chi 2$ test with a 0.10 one-sided significance alpha level, a sample size of 40 participants per arm will have approximately 95% power to detect the difference between the Null hypothesis proportion of [redacted] and the alternative proportion of [redacted].

This sample size will provide reasonable power across the range of safety benchmark assuming an alpha level of 10% one sided [redacted].

This sample size will also provide reasonable power across the range of efficacy benchmarks cited in the Part 2B tumor types assuming an alpha level of 20% one-sided .

For the HCC protocol-defined population, the lowest ORR response value is predicted to be and the target ORR response is assumed to be .

For the CRPC and TNBC protocol-defined populations, the lowest ORR response value is predicted to be and the target ORR response is assumed to be .

10.2 Populations for Analyses

For purposes of analysis, the populations are defined in Table 10.2-1.

Table 10.2-1: Populations for Analyses

Population	Description
Enrolled	All participants who sign informed consent
Randomized	All participants who are randomized to treatment arm (Part 2A)
Treated	All participants who take at least 1 dose of study treatment
Pharmacokinetic	All treated participants who have evaluable concentration-time data
Immunogenicity	All treated participants who have baseline and at least 1 post-baseline pre-infusion immunogenicity assessment for the analyte evaluated

Table 10.2-1: Populations for Analyses

Population	Description
Biomarker	All treated participants with available biomarker data.
Patient-reported outcome	All treated participants with patient-reported outcome data at baseline and at least 1 post-baseline assessment.

10.3 Statistical Analyses

The Statistical Analysis Plan will be developed, finalized, and signed before database lock. Below is a summary of planned statistical analyses of the primary and secondary endpoints. The final analysis is planned when all participants have successfully completed at least two post-baseline scans or discontinued early. Based on the post baseline scan assessment this is due approximately 6 months after the last participant first visit.

10.3.1 Analyses

The Part 2A efficacy analyses will be performed on the randomized population, with supplemental analyses on the treated population, while the efficacy analysis of Part 2B will be performed on the treated population (Table 10.3.1-1). The efficacy and safety analysis for Part 2B will be evaluated by tumor-specific cohort. Analysis of the treated participants from Part 1 will be presented separately. The following censoring rules will be applied for the definition of PFS and DoR:

- 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 evaluable on study tumor assessments and did not die will be censored on their date of randomization (for Part 2A) or first dosing (Part 1 and Part 2B).
- Subjects who receive subsequent anti-cancer therapy prior to documented progression or death will be censored at the date of the last evaluable tumor assessment conducted on or prior to the date of initiation of the subsequent anti-cancer therapy.

Additional details of the calculation of time-to-event endpoints such as DOR and PFS will be described in the Statistical Analysis Plan.

The efficacy and safety data from participants randomized in Part 2A Arms A, B, and E before Revised Protocol 07 will be analyzed using descriptive measures only.

Table 10.3.1-1: Efficacy - Statistical Analyses[a]

Endpoint	Statistical Analysis Methods
Best observed response (BOR) BOR for a participant will be assessed per RECIST v1.1 or PCWG3 by investigator, unless otherwise specified	Summary and listing of BOR

Table 10.3.1-1: Efficacy - Statistical Analyses[a]

Endpoint	Statistical Analysis Methods
ORR ORR is defined as the proportion of participants whose BOR is either CR or PR per RECIST v1.1 in the population of interest or PCWG3 for participants with prostate cancer.	Point estimate and CI by arm/cohort in Parts 2A and 2B Part 2A: Chi square test and sensitivity analysis using Cochran-Mantel-Haenszel test with the stratification factors as strata
DOR DOR for a participant with a BOR of CR or PR is defined as the time between the date of first response and the date of the first objectively documented tumor progression per RECIST v1.1 or PCWG3 or death, whichever occurs first.	Median and CI by K-M method for participants who responded, by arm/cohort
PFS PFS for a participant is defined as the time from the first dosing date (Part 1, Part 2B) or randomization date (Part 2A) to the date of first objectively documented disease progression per RECIST v1.1 or PCWG3 or death due to any cause, whichever occurs first.	Median and CI by K-M method and PFS rates
PSA Response Rate (For Part 2B CRPC Participants Only) Decrease in the level of PSA of at least 50% from baseline maintained for at least 3 weeks	Point estimate and CI
TTR TTR is defined as the time from the first dosing date (Part 1, Part 2B) or randomization date (Part 2A) to the date of the first confirmed response (CR or PR) per RECIST v1.1 or PCWG3.	Summary statistics for TTR
OS OS is defined as the time from enrollment (Part1, Part 2B) or randomization (Part 2A) to the date of death from any cause	Median and CI by K-M method (including OS rates, for example at 1 year and 2 years)

Abbreviations: BOR = best overall response; CI = confidence interval; CR = complete response; DOR = duration of response; K-M = Kaplan Meier ; ORR = Objective Response Rate; OS = overall survival; PCWG3 = Prostate Cancer Working Group 3; PFS = progression-free survival; PR = partial response; PSA = prostate-specific antigen; RECIST = Response Evaluation Criteria in Solid Tumors; TTR = time to response.

[a] Efficacy analyses will be executed with a 60% two-sided CI.

10.3.2 Safety Analyses

All safety analyses will be performed on the treated population. See Table 10.3.2-1 for a description of the safety analyses.

Table 10.3.2-1: Safety - Statistical Analyses

Endpoint	Statistical Analysis Methods
Incidence of DLTs (Part 1 only), AEs, SAEs, AEs leading to discontinuation, and death AEs will be graded according to CTCAE v4.03	DLT rate by dose level, frequency distribution of treated participants with AE using the worst CTC grade. Participants will be counted only (1) once at the PT level, (2) once at the system organ class level, and (3) once in the "total participant" row at their worst CTC grade, regardless of system organ class or PT.
Incidence of treatment-related Grade 3-5 AEs within 24 weeks	Incidence rate (Part 2A, Part 2B) along with the ratio and difference in incidence rates (Part 2A) will be presented by point estimates and CIs[a] (Parts 2A and 2B)
Laboratory abnormalities Laboratory values will be graded according to CTCAE v4.03.	Laboratory shift table using the worst CTC grade on treatment per participant

Abbreviations: AE = adverse event; CTC = common terminology criteria; CTCAE = Common Terminology Criteria for Adverse Events; DLT = dose-limiting toxicity; PT = preferred term; SAE = serious adverse event.

[a] Safety analyses will be executed with an 80% two-sided CI for primary endpoint of related Grade 3-4 AE rates.

10.3.3 Pharmacokinetic Analysis for BMS-986249

PK analyses are described in Table 10.3.3-1.

Table 10.3.3-1: Pharmacokinetic - Statistical Analyses

Endpoint	Statistical Analysis Methods
Cmax, AUC(0-T), AUC(TAU), Ctau, CLT, Css-avg, AI_Cmax, AI_AUC, and T-HALF	Summary statistics: geometric means and coefficients of variation
Cmax, AUC(0-T), and AUC(TAU)	Scatter plots versus dose for each cycle measured; dose proportionality based on a power model and a CI around the power coefficient
Tmax	Summary statistics: medians and ranges
Ctrough	Summary statistics to assess attainment of steady state: geometric means and coefficients of variation, by treatment and by day; plots versus time by dose

Abbreviations: AI_AUC = ratio of an exposure measure at steady state to that after the first dose (exposure measure includes AUC[TAU]); AI_Cmax = ratio of an exposure measure at steady state to that after the first dose (exposure measure includes Cmax); AUC(0-T) = area under the blood concentration-time curve from time zero to time of last quantifiable concentration (may be calculated if concentrations are not quantifiable up to TAU across a treatment group); AUC(TAU) = area under the concentration-time curve in 1 dosing interval; CLT = total body clearance; Cmax = maximum observed concentration; Css-avg = average blood concentration over a dosing interval (AUC[TAU]/tau) at steady state; Ctau = observed blood concentration at the end of a dosing interval; Ctrough = trough observed blood

concentrations (this includes predose concentrations [C0] and Ctau); T-HALF = terminal blood half-life; Tmax = median time of maximum observed concentration.

PK concentration-time data for ipilimumab and/or nivolumab may be pooled with data from other studies for integrated PPK and exposure analyses, which will be presented in a separate report.

10.3.4 Immunogenicity

Immunogenicity analyses are described in Table 10.3.4-1.

Table 10.3.4-1: Immunogenicity - Statistical Analyses

Endpoint	Statistical Analysis Methods
Incidence of ADA Baseline ADA-positive participant is defined as a participant who has an ADA-detected sample at baseline[a,b] ADA-positive participant is a participant with at least 1 ADA-positive sample relative to baseline after initiation of the treatment	Frequency distribution of baseline ADA-positive participants and ADA-positive participants after initiation of the treatment for each analyte

Abbreviation: ADA = anti-drug antibody.

[a] Baseline sample is the last sample before initiation of the treatment.

[b] Details of the immunogenicity data analysis, including ADA titers, will be provided in the Statistical Analysis Plan.

10.3.5 Biomarker Analyses

Biomarker statistical analyses are described in Table 10.3.5-1.

Table 10.3.5-1: Biomarker - Statistical Analyses

Endpoint	Statistical Analysis Methods
[redacted]	

10.3.6 ECG Analyses

All ECG data analyses, including summaries of each ECG parameter, frequency distribution of participants' 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, for participants with time matched ECG and PK data collection (Part 1A). The details of ECG data analysis will be provided in the Statistical Analysis Plan.

10.3.7 Patient-Reported Outcome Analyses

PRO analyses are described in Table 10.3.7-1.

Table 10.3.7-1: PRO - Statistical Analyses

Secondary Endpoint	Statistical Analysis Methods
To evaluate TTD in Global Health Status/QoL of the EORTC QLQ-C30 (Part 2A only)	TTD in Global Health Status/QoL and Physical Functioning will be defined as the time from randomization until a clinically meaningful decline (ie, reduction ≥10 points) from baseline in EORTC QLQ-C30 global health/quality of life subscale score and Physical Functioning Scale score. Estimates for both Global Health Status/QoL and Physical Functioning will be provided with associated 95% CIs.
To evaluate TTD in Physical Functioning Scale of the EORTC QLQ-C30 (Part 2A only)	The analysis will use all available data from randomized participants, including data collected during post-treatment follow up. Median deterioration times, hazard ratios, and 95% CIs will be calculated

Abbreviations: CI = confidence interval; EORTC = European Organisation for Research and Treatment of Cancer; PRO = patient-reported outcome; QLQ-C30 = Quality of Life Questionnaire – Core 30; QoL = quality of life; TTD = time to deterioration.

Analyses of PRO will be performed on participants who have an assessment at baseline and at least 1 post-baseline assessment.

Further exploratory analyses for Part 2A and Part 2B not specified here will be described in the Statistical Analysis Plan, which will be finalized before database lock and may be presented separately from the main clinical study report.

10.3.8 Interim Analyses

Interim analyses may be performed for administrative purposes or publication. Preliminary reviews of the data in Part 1 and Part 2 will occur prior to the final data base lock in order to assess the initial safety, PK, and [redacted] signal. The earliest exploratory analysis may also be performed for a Part 2A arm and/or Part 2B tumor cohort after approximately 15 to 20 participants are randomized based upon the available preliminary information including safety, PK, [redacted], and tumor response data after the first tumor scan. No formal inferences requiring any adjustment to statistical significance level will be performed.

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12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
Ab	antibody
ADA	anti-drug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
ADT	androgen deprivation therapy
AE	adverse event
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
AIDS	acquired immune deficiency syndrome
AJCC	American Joint Committee on Cancer
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AR	additional research
ART	antiretroviral therapy
AST	aspartate aminotransferase
AT	aminotransaminases
AUC	area under the concentration-time curve (exposure)
AUC(0-T)	area under the concentration-time curve from time zero to the time of the last quantifiable concentration
AUC(TAU)	area under the concentration-time curve in one dosing interval
BC	breast cancer
BICR	blinded independent central review
BLRM	Bayesian Logistic Regression Model
BMS	Bristol Myers Squibb
BOR	best overall response
BRAF	B-Raf proto-oncogene
C	cycle

Term	Definition
CD4	cluster of differentiation 4
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CLT	total body clearance
Cmax	maximum observed concentration
Cmaxss	maximum observed steady state concentration
Cminss	trough steady state concentrations
CNS	central nervous system
COVID-19	coronavirus disease of 2019
CR	complete response
CRC	colorectal cancer
CrCl	creatinine clearance
CRC	colorectal cancer
CRF	Case Report Form
CRPC	castration resistant prostate cancer
Css-avg	average concentration over a dosing interval at steady state
CT	computed tomography
CTA	clinical trial agreement
Ctau	concentration in a dosing interval (eg, concentration at 24 hours, concentration at 12 hours, etc.)
CTC	common terminology criteria
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T lymphocyte-associated protein 4
Ctrough	trough observed concentration
CXDY	cycle X day Y
D	day
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
dMMR	mismatch repair deficient

Term	Definition
DNA	deoxyribonucleic acid
DOR	duration of response
EC50	half-maximal effective concentration
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EFGR	epidermal growth factor receptor
EHR	electronic health record
ELISA	enzyme-linked immunosorbent assay
EMR	electronic medical record
EOI	end of infusion
EOI-PK	end-of-infusion pharmacokinetic sample
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30
EOT	end of treatment
EQ-5D-3L	European Quality of Life – 5 Dimension – 3 Level Questionnaire
ER	estrogen receptor
EWOC	escalation with overdose control
FACIT GP5	Functional Assessment of Chronic Illness Therapy General Physical item 5
FACS	fluorescence-activated cell sorting
FDA	Food and Drug Administration
FIH	first in human
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
GLP	Good Laboratory Practices
GnRH	gonadotropin-releasing hormone
GPVE	Global Pharmacovigilance and Epidemiology
HBV	hepatitis B virus
HCC	hepatocellular carcinoma

Term	Definition
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HER2	human epidermal growth factor receptor 2
HIV	human immunodeficiency virus
HNSTD	highest non-severely toxic dose
HR	hazard ratio
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICOS	inducible T cell costimulator
IFN	interferon
Ig	immunoglobulin
IHC	immunohistochemistry
IL	interleukin
IMP	investigational medicinal products
INR	international normalized ratio
I-O	immuno-oncology
IP	investigational product
irAE	immune-related adverse event
IRB	Institutional Review Board
iRECIST	modified RECIST v 1.1 for immune-based therapeutics
IRR	infusion-related reactions
IRT	Interactive Response Technology
IU	international unit
IV	intravenous
KI	knock-in
K-M	Kaplan Meier
KRAS	V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
LHRH	luteinizing hormone-releasing hormone
mAb	monoclonal antibody

Term	Definition
mCRPC	metastatic castration-resistant prostate cancer
ME	masking efficiency
[redacted]	[redacted]
MID	minimal important difference
MMP	matrix metalloproteinase
mRCC	metastatic renal cell carcinoma
MRI	magnetic resonance imaging
MSI-H	microsatellite instability-high
MST	Medical Surveillance Team
MTD	maximum tolerated dose
mWHO	modified World Health Organization
N	number of subjects or observations
NCI	National Cancer Institute
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
p-DILI	potential drug-induced liver injury
Pb	Probody
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PCWG3	Prostate Cancer Working Group 3
PD	progressive disease
PD-1	programmed cell death 1
PD-L1	programmed death ligand-1
PD-L2	programmed death ligand-2
PE	physical examination
PET	positron emission tomography
PFS	progression-free survival
PID	participant identification number
PoC	proof of concept

Term	Definition
PK	pharmacokinetics
PPK	population pharmacokinetic
PR	partial response
PRO	Patient-Reported Outcomes
PRO-CTCAE	Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events
PSA	prostate-specific antigen
PT	prothrombin time
Q12W	every 12 weeks
Q2W	every 2 weeks
Q3W	every 3 weeks
Q4W	every 4 weeks
Q6W	every 6 weeks
Q8W	every 8 weeks
QoL	quality of life
QTc	QT interval corrected
QTcF	QT interval corrected for heart rate using Fridericia's formula
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
REMS	risk evaluation and mitigation strategy
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose of BMS-986249
RT-PCR	reverse transcriptase polymerase chain reaction
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCCHN	squamous cell carcinoma of the head and neck
SCLC	small cell lung cancer
SD	stable disease
SEB	staphylococcal enterotoxin B
SI	stimulation index

Term	Definition
SNP	single nucleotide polymorphism
SUSAR	suspected, unexpected serious adverse reaction
symAEs	symptomatic adverse events
T3	triiodothyronine
T4	thyroxine
TCR	T-cell receptor
T-HALF	terminal half-life
Tmax	time of maximum observed concentration
TNBC	triple-negative breast cancer
TNF-α	tumor necrosis factor alpha
TRAE	treatment-related adverse event
Tregs	regulatory T cells
TSH	thyroid stimulating hormone
TTD	time to deterioration
TTR	time to response
ULN	upper limit of normal
uPA/UPA	urokinase-type plasminogen activator
US	United States
VAS	visual analogue scale
VEGF	vascular endothelial growth factor
Vss	volume of distribution at steady state
Vz	volume of distribution of terminal phase
WOCBP	women of childbearing potential

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

The terms "participant" and "subject" refer to a person who has consented to participate in the clinical research study. Typically, the term "participant" is used in the protocol and the term "subject" is used in the Case Report Form (CRF).

REGULATORY AND ETHICAL CONSIDERATIONS

This study will be conducted in accordance with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws, regulations, and requirements.

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

All potential serious breaches must be reported to the Sponsor or designee immediately. A potential serious breach is defined as a Quality Issue (eg, protocol deviation) that is likely to affect, to a significant degree, one or more of the following: (1) the rights, physical safety or mental integrity of one or more participants; (2) the scientific value of the clinical trial (eg, reliability and robustness of generated data). Items (1) or (2) can be associated with either GCP regulation(s) or trial protocol(s).

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).

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, Investigator's Brochure, product labeling information, ICF, participant recruitment materials (eg, advertisements), and any other written information to be provided to participants.

The investigator, Sponsor, or designee should provide the IRB/IEC with reports, updates, and other information (eg, expedited safety reports, amendments, administrative letters) annually, or more frequently, in accordance with regulatory requirements or institution procedures.

The investigator is responsible for providing oversight of the conduct of the study at the site and adherence to requirements of the following where applicable:

- ICH guidelines,
- United States Code of Federal Regulations, Title 21, Part 50 (21CFR50)
- European Union Directive 2001/20/EC; or
- European Regulation 536/2014 for clinical studies (if applicable),
- European Medical Device Regulation 2017/745 for clinical device research (if applicable),
- the IRB/IEC
- and all other applicable local regulations.

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion of an amendment from the IRB/IEC (and if applicable, also by local health authority) except where necessary to eliminate an immediate hazard(s) to study subjects/participants.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining relevant approval/favorable opinion(s) the deviation or change will be submitted, as soon as possible to:

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

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

If an amendment substantially alters the study design or increases the potential risk to the participant: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects/participants currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects/participants prior to enrollment.

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

FINANCIAL DISCLOSURE

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

INFORMED CONSENT PROCESS

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

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

Investigators must:

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

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

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

The confidentiality of records that could identify subjects/participants must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects'/participants' signed ICF, and, in the US, the subjects'/participants' signed HIPAA Authorization.

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

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

BMS COMMITMENT TO DIVERSITY IN CLINICAL TRIALS

The mission of BMS is to transform patients' lives through science by discovering, developing, and delivering innovative medicines that help them prevail over serious diseases.

BMS is committed to doing its part to ensure that patients have a fair and just opportunity to achieve optimal health outcomes.

BMS is working to improve the recruitment of a diverse participant population with the goal that the clinical trial becomes more reflective of the real-world population and the people impacted by the diseases studied.

DATA PROTECTION, DATA PRIVACY, AND DATA SECURITY

BMS collects and processes personal data of study participants, patients, health care providers, and researchers for biopharmaceutical research and development to advance innovative, high-quality medicines that address the medical needs of patients. BMS ensures the privacy, protection, and confidentiality of such personal data to comply with applicable laws. To achieve these goals, BMS has internal policies that indicate measures and controls for processing personal data. BMS adheres to these standards to ensure that collection and processing of personal data are limited and proportionate to the purpose for which BMS collects such personal data. This purpose is clearly and unambiguously notified to the individual at the time of collection of personal data. In the true spirit of science, BMS is dedicated to sharing clinical trial information and data with participants, medical/research communities, the media, policy makers, and the general public. This is done in a manner that safeguards participant privacy and informed consent while respecting the integrity of national regulatory systems. Clinical trial data, health-related research, and pharmacovigilance activities on key-coded health data transferred by BMS across national borders is done in compliance with the relevant data protection laws in the country and GCP requirements.

BMS protects Personal Information with adequate and appropriate security controls as indicated under the data protection laws. To align with the recommended security standards, BMS has adopted internal security standards and policies to protect personal data at every stage of its processing.

To supplement these standards, BMS enters into Clinical Trial Agreements (CTAgs) with confidentiality obligations to ensure proper handling and protection of personal data by third parties accessing and handling personal data.

BMS takes unauthorized access and disclosure of Personal Information very seriously. BMS has adopted the security standards that include National Institute of Standards and Technology Cybersecurity Framework for studies in the US. BMS aligns with these standards to continuously assess and improve its ability to protect, detect, and respond to cyber attacks and other unauthorized attempts to access personal data. These standards also aid in mitigating possible

adverse effects. Furthermore, BMS Information Technology has defined 6 principles to protect our digital resources and information:

1) Responsibilities of IT Personnel
2) Securing the BMS Digital Infrastructure
3) Identity and Access Management
4) External Partner Connections
5) Cyber Threat Detection and Response
6) Internal Cyber Incident Investigation

SOURCE DOCUMENTS

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data reported on the CRF or entered in the electronic CRF (eCRF) that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained.

- The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

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

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

STUDY TREATMENT RECORDS

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

If	Then
Supplied by BMS (or its vendors):	Records or logs must comply with applicable regulations and guidelines and should include: • amount received and placed in storage area • amount currently in storage area • label identification number or batch number • amount dispensed to and returned by each participant, including unique participant identifiers • amount transferred to another area/site for dispensing or storage • nonstudy disposition (eg, lost, wasted) • amount destroyed at study site, if applicable • amount returned to BMS • retain samples for bioavailability/bioequivalence/biocomparability, if applicable • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.
Sourced by site, and not supplied by BMS or its vendors (examples include IP sourced from the site's stock or commercial supply or a specialty pharmacy)	The investigator or designee accepts responsibility for documenting traceability and study treatment integrity in accordance with requirements applicable under law and the SOPs/standards of the sourcing pharmacy.

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

CASE REPORT FORMS

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

For sites using the Sponsor or designee electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will

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

The confidentiality of records that could identify subjects/participants must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a sub-investigator and who is delegated this task on the Delegation of Authority Form. Sub-investigators in Japan may not be delegated the CRF approval task. For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet Sponsor or designee training requirements and must only access the BMS electronic data capture tool using the unique user account provided by Sponsor or designee. User accounts are not to be shared or reassigned to other individuals.

MONITORING

Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

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

In addition, the study may be evaluated by Sponsor or designee internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to Sponsor or designee.

RECORDS RETENTION

The investigator (or head of the study site in Japan) must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or

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

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

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

RETURN OF STUDY TREATMENT

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

If	Then
Study treatments supplied by BMS (including its vendors	Any unused study treatments supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless study treatments containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics). Partially used study interventions and/or empty containers may be destroyed after proper reconciliation and documentation. But unused IMP must be reconciled by site monitor/Clinical Research Associate prior to destruction. If study treatments will be returned, the return will be arranged by the responsible Study Monitor.
Study treatments sourced by site, not supplied by BMS (or its vendors) (examples include study treatments sourced from the site's stock or commercial supply or a specialty pharmacy)	It is the investigator's or designee's responsibility to dispose of all containers according to the institutional guidelines and procedures.

It is the investigator's or designee's responsibility to arrange for disposal, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The following minimal standards must be met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, 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.

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

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

STUDY AND SITE START AND CLOSURE

The Sponsor/designee reserves the right to close the study site or to terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include, but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local Health Authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

DISSEMINATION OF CLINICAL STUDY DATA

In order to benefit potential study participants, patients, healthcare providers and researchers, and to help BMS honor its commitments to study participants, BMS will make information about clinical research studies and a summary of their results available to the public as per regulatory and BMS requirements. BMS will post study information on local, national or regional databases in compliance with national and international standards for disclosure. BMS may also voluntarily disclose information to applicable databases.

CLINICAL STUDY REPORT

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

For this protocol, the following criteria will be used to select the signatory investigator:

- Participant recruitment (eg, among the top quartile of enrollers)
- Regional representation (eg, among top quartile of enrollers from a specified region or country)
- Other criteria (as determined by the study team)

SCIENTIFIC PUBLICATIONS

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

Scientific Publications (such as abstracts, congress podium presentations and posters, and manuscripts) of the study results will be a collaborative effort between the study Sponsor and the external authors. No public presentation or publication of any interim results may be made by any principal investigator, sub-investigator or any other member of the study staff without the prior written consent of the Sponsor.

Authorship of publications at BMS is aligned with the criteria of the International Committee of Medical Journal Editors (ICMJE, www.icmje.org). Authorship selection is based upon significant contributions to the study (ie, ICMJE criterion #1). Authors must meet all 4 ICMJE criteria for authorship:

1) Substantial intellectual contribution to the conception or design of the work; or the acquisition of data (ie, evaluable subjects with quality data), analysis, or interpretation of data for the work (eg, problem solving, advice, evaluation, insights and conclusion); AND
2) Drafting the work or revising it critically for important intellectual content; AND
3) Final approval of the version to be published; AND

4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Those who make the most significant contributions, as defined above, will be considered by BMS for authorship of the primary publication. Sub-investigators will generally not be considered for authorship in the primary publication. Geographic representation will also be considered.

Authors will be listed by order of significant contributions (highest to lowest), with the exception of the last author. Authors in first and last position have provided the most significant contributions to the work.

For secondary analyses and related publications, author list and author order may vary from primary to reflect additional contributions.

APPENDIX 3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW UP AND REPORTING

ADVERSE EVENTS

Adverse Event Definition:

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study treatment and that does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study treatment, whether or not considered related to the study treatment.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or results from other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Note that abnormal lab tests or other safety assessments should only be reported as AEs if the final diagnosis is not available. Once the final diagnosis is known, the reported term should be updated to be the diagnosis.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose, as a verbatim term (as reported by the investigator), should not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae and should specify "intentional overdose" as the verbatim term

Events NOT Meeting the AE Definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

DEFINITION OF SAE

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

SERIOUS ADVERSE EVENTS

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
Requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below) NOTE: The following hospitalizations are not considered SAEs in BMS clinical studies: • a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event) • elective surgery, planned prior to signing consent • admissions as per protocol for a planned medical/surgical procedure • routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy) • medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases • admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason) • admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)
Results in persistent or significant disability/incapacity
Is a congenital anomaly/birth defect

Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 9.2.8 for the definition of potential DILI.)

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

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

EVALUATING AES AND SAES

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

Follow-up of AEs and SAEs
If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports must include the same investigator term(s) initially reported.) If an ongoing SAE changes in its intensity or relationship to study treatment or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report. All SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

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

SAE Email Address: worldwide.safety@BMS.com

SAE Facsimile Number: *Will be provided by local site monitor*.

SAE Telephone Contact (required for SAE and pregnancy reporting): *Will be provided by local site monitor*.

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

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

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

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

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.

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. For combination therapy with BMS-986249 plus nivolumab, relevant systemic exposure is defined as 125 days after the end of study treatment, plus 30 days, for a total of 155 days post treatment completion. For monotherapy with BMS-986249, relevant systemic exposure is defined as 75 days after the end of study treatment, plus 30 days, for a total of 105 days post treatment completion. For ipilimumab in combination with nivolumab therapy, the end of relevant systemic exposure is defined as 5 months after the end of study treatment. For monotherapy with nivolumab, the end of relevant systemic exposure is defined as 5 months after the end of study treatment.

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

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation and/or implantation (These methods of contraception cannot be used by WOCBP participants in studies where hormonal contraception is prohibited)[b] – Oral (birth control pills) – Intravaginal (vaginal birth control suppositories, rings, creams, gels) – Transdermal
• Progestogen-only hormonal contraception associated with inhibition of ovulation[b] – Oral – Injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation and/or implantation (This method of contraception cannot be used by WOCBP participants in studies where hormonal contraception is prohibited)[b] • Intrauterine device (IUD)[c] • Intrauterine hormone-releasing system (IUS) (This method of contraception cannot be used by WOCBP participants in studies where hormonal contraception is prohibited)[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 treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

- It is not necessary to use any other method of contraception when complete abstinence is elected.
- WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2.
- Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants choose to forego complete abstinence

NOTES:

[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

[b] Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the investigational medicinal product (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
- Lactation amenorrhea method (LAM)

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

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

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Male participants are required to use a condom for study duration and until the end of relevant systemic exposure, defined as 165 days after the end of BMS-986249 monotherapy treatment, 215 days after the end of BMS-986249 + nivolumab combination therapy treatment, 7 months after the end of ipilimumab + nivolumab combination therapy treatment, and 7 months after the end of nivolumab monotherapy treatment in the male participant.
- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as during the study treatment and until 165 days after the end of BMS-986249 monotherapy treatment, 215 days after the end of BMS-986249 + nivolumab combination therapy treatment , 7 months after the end of ipilimumab + nivolumab combination therapy treatment, and 7 months after the end of nivolumab monotherapy treatment in the male participant.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 165 days after the end of BMS-986249 monotherapy treatment, 215 days after the end of BMS-986249 + nivolumab combination therapy treatment, 7 months after the end of ipilimumab + nivolumab combination therapy treatment, and 7 months after the end of nivolumab monotherapy treatment.
- Refrain from donating sperm for the duration of the study treatment and for 165 days after the end of BMS-986249 monotherapy treatment, 215 days after the end of BMS-986249 + nivolumab combination therapy treatment, 7 months after the end of ipilimumab + nivolumab combination therapy treatment, and 7 months after the end of nivolumab monotherapy treatment.

COLLECTION OF PREGNANCY INFORMATION

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

APPENDIX 5 RECIST 1.1 CRITERIA

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 1 measurable tumor lesion. When computed tomographic (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.

1.1 Measurable Lesions

Measurable lesions must be accurately measured in at least 1 dimension (longest diameter in the plane of the measurement to be recorded) with a minimum size of:

- 10 mm by computed tomography (CT)/magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as nonmeasurable)
- 20 mm by chest X-ray
- *Malignant lymph nodes*: To be considered pathologically enlarged *and* measurable, a lymph node must be ≥ 15 mm in the ***short*** axis when assessed by CT scan (CT scan slice thickness is 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 nonmeasurable include the following: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of the skin or lung, and abdominal masses/abdominal organomegaly identified by physical examination that are not measurable by reproducible imaging techniques

1.3 Special Considerations Regarding Lesion Measurability

1.3.1 Bone Lesions

- Bone scan, positron emission tomography (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 nonmeasurable.

1.3.2 Cystic Lesions

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor nonmeasurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above in Section 1.1. 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. Unless the lesions being followed cannot be imaged, and are assessable only by clinical examination, imaging-based evaluation should always be done.

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 Examination

Lesions identified by clinical examination 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 examination 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.

2 BASELINE DOCUMENTATION OF 'TARGET' AND 'NON-TARGET' LESIONS

2.1 Target Lesions

When more than 1 measurable lesion is present at baseline, all lesions up to **a maximum of 5 lesions total (and a maximum of 2 lesions per organ) that are 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), should be representative of all involved organs, and should lend themselves to ***reproducible repeated measurements***.

A ***sum of the diameters*** for all target lesions will be calculated and reported as the ***baseline sum diameters***. For non-nodal lesions, the longest axis should be included in 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 baseline sum diameters. 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 that may be visible by imaging even if not involved by tumor. Pathological nodes that 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 diameters. Nodes that have a short axis < 10 mm are considered nonpathological 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 (eg, '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 also have reduction in the short axis to < 10 mm.

Partial Response (PR): At least a **30% decrease in the sum of the diameters of target lesions**, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a **20% increase in the sum of the 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 1 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.

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 that may be visible by imaging even if not involved by tumor. Pathological nodes that 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 nonnodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation. If the radiologist is able to provide an actual measurement, even if it is below 5 mm it should be recorded.

However, when such a lesion becomes difficult to assign an exact measurement 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 or lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned =. 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 timepoints specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions. All lymph nodes must also be nonpathological in size (< 10 mm short axis).

Non-CR/Non-PD: Persistence of 1 or more non-target lesion(s) above the normal limits.

Progressive Disease (PD): *Unequivocal progression* of existing non-target lesions. (*Note:* The appearance of 1 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.

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 the 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 1 or more non-target lesions is usually not sufficient to qualify 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 1 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 as the lesions are nonmeasurable, 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 target disease: that is, an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large' or 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. If markers are initially above the upper normal limit, however, they must normalize in order for a subject to be considered as having attained a CR.

3.3 New Lesions

The appearance of new malignant lesions denotes PD. The finding of a new lesion should be unequivocal: that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (eg, some 'new' bone lesions may be simply healing or a flare of pre-existing lesions). This distinction 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 PD. An example of this is the subject who has visceral disease at baseline and while on study has a CT or MRI brain scan that 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 PD should be declared using the date of the initial scan.*

3.3.1 FDG-PET Evaluation

While [^{18}F] fluorodeoxyglucose (FDG)-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of the qualitative assessment of FDG-PET scanning to complement CT scanning in assessment of PD (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up, is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up:
  - If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
  - If the positive FDG-PET at follow-up is not confirmed as a new site of disease by CT, additional follow-up CT scans are needed to determine if there is truly PD occurring at that site (if so, the date of PD will be the date of the initial positive FDG-PET scan).
  - If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

4 RESPONSE CRITERIA

4.1 Timepoint Response

A response assessment should occur at each timepoint specified in the protocol.

For subjects who have **measurable disease** at baseline Table 4.1-1 provides a summary of the overall response status calculation at each timepoint.

Table 4.1-1: Timepoint Response: Subjects with Target (+/– Non-Target) Disease

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

Abbreviation: NE =not evaluable

Missing Assessments and Not Evaluable Designation

When no imaging/measurement is done at all at a particular timepoint, the subject is **not evaluable** at that timepoint. If only a subset of lesion measurements are made at an assessment, the subject is also considered NE at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not have changed the assigned timepoint response.

4.1.1 Confirmation Scans

- **Verification of Response:** *Confirmation of PR and CR is required at least 4 weeks following initial assessment to ensure responses identified are not the result of measurement error.*

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 date of objectively documented PD based on RECIST v1.1, taking into account any requirement for confirmation or the date of subsequent anti-cancer therapy, whichever occurs first in the study. 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.

The best overall response is defined as the best response across all timepoints with subsequent confirmation. CR or PR may be claimed only if the criteria for each are met at a subsequent timepoint as specified in the protocol (generally 4 weeks later).

In this circumstance, the best overall response can be interpreted as specified in Table 4.2-1. When SD is believed to be best response, it must meet the protocol specified minimum time from baseline. Measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6 to 8 weeks) that is defined in the study protocol.

Table 4.2-1: Best Overall Response When Confirmation of CR and PR Is 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
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

.

[a] If a CR is truly met at the first timepoint, then any disease seen at a subsequent timepoint, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since the disease must have reappeared after CR). The best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may

be claimed when subsequent scans suggest small lesions were likely still present and in fact the subject had PR, not CR at the first timepoint. 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 PD is objectively documented (taking as reference for PD the smallest measurements recorded on study).

The duration of overall CR 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

SD 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).

CR (Complete Remission)

The designation of CR requires all of the following:

1. Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms, if present before therapy.
   a) Typically FDG-avid lymphoma: in patients without a pre-treatment PET scan or if the pre-treatment PET scan was positive, a post-treatment residual mass of any size is permitted as long as it is PET negative.
   b) Variably FDG-avid lymphomas/FDG avidity unknown: in patients without a pre-treatment PET scan, or if a pre-treatment PET scan was negative, all lymph nodes and nodal masses must have regressed on CT scan to normal size (≤ 1.5 cm in their greatest transverse diameter for nodes > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their long axis and > 1.0 cm in their short axis before treatment must have decreased to ≤ 1.0 cm in their short axis after treatment.
2. The spleen and/or liver, if considered enlarged before therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies, and nodules related to lymphoma should disappear. However, determination of splenic involvement is not always reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma.
3. If the bone marrow was involved by lymphoma before treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (with a goal of > 20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry, but demonstrates a small population of clonal lymphocytes by flow

cytometry, will be considered a CR until data become available demonstrating a clear difference in patient outcome.

PR (Partial Remission)

The designation of PR requires all of the following:

1. At least a 50% decrease in the sum of the product of the diameters (SPD) of up to 6 of the largest dominant nodes or nodal masses. These nodes or nodal masses should be selected according to all of the following: they should be clearly measurable in at least 2 perpendicular dimensions; if possible, they should be from disparate regions of the body; and they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
2. No increase should be observed in the size of other nodes, liver, or spleen.
3. Splenic and hepatic nodules must regress by ≥ 50% in their SPD or, for single nodules, in the greatest transverse diameter.
4. With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable, and no measurable disease should be present.
5. Bone marrow assessment is irrelevant for determination of a PR, if the sample was positive before treatment. However, if positive, the cell type should be specified (eg, large-cell lymphoma or small neoplastic B cells). Patients who achieve a CR by the above criteria but have persistent morphologic bone marrow involvement will be considered partial responders. When the bone marrow was involved before therapy and a clinical CR was achieved but with no bone marrow assessment after treatment, patients should be considered partial responders.
6. No new sites of disease should be observed.
7. FDG:
   a) Typically FDG-avid lymphoma: for patients without a pre-treatment PET scan or if the pre-treatment PET scan was positive, the post-treatment PET scan should be positive in at least 1 previously involved site.
   b) Variably FDG-avid lymphomas/FDG avidity unknown: for patients without a pre-treatment PET scan, or if a pre-treatment PET scan was negative, CT criteria should be used. In patients with follicular lymphoma or mantle-cell lymphoma, a PET scan is only indicated with 1 or at most 2 residual masses that have regressed by > 50% on CT; those with more than 2 residual lesions are unlikely to be PET negative and should be considered partial responders.

SD (Stable Disease)

1. The designation of SD requires all of the following: A patient is considered to have SD when he or she fails to attain the criteria needed for a CR or PR but does not fulfill those for PD (see Relapsed Disease [after CR]/PD [after PR, SD]).
2. Typically FDG-avid lymphomas: the PET should be positive at prior sites of disease with no new areas of involvement on the post-treatment CT or PET scan.

3. Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pre-treatment PET scan or if the pre-treatment PET was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.

PD: Relapsed Disease (after CR)/PD (after PR, SD)

Lymph nodes should be considered abnormal if the long axis is > 1.5 cm, regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if its short axis is > 1.0. Lymph nodes ≤ 1.0 × ≤ 1.0 cm will not be considered abnormal for relapse or progressive disease.

1. Appearance of any new lesion > 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or PD after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET scan without histologic confirmation.
2. At least a 50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (eg, splenic or hepatic nodules). To be considered PD, a lymph node with a diameter of the short axis of < 1.0 cm must increase by ≥ 50% and to a size of 1.5 × 1.5 cm or > 1.5 cm in the long axis.
3. At least a 50% increase in the longest diameter of any single previously identified node > 1 cm in its short axis.
4. Lesions should be PET positive if observed in a typical FDG-avid lymphoma or the lesion was PET positive before therapy, unless the lesion is too small to be detected with current PET systems (< 1.5 cm in its long axis by CT).

Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these assessments, the spleen is considered nodal disease. Disease that is only assessable by physical examination (eg, pleural effusions, bone lesions) will be recorded as present or absent only, unless, while an abnormality is still noted by imaging studies or physical examination, it is found to be histologically negative.

In clinical trials where PET is unavailable to the vast majority of participants, or where PET is not deemed necessary or appropriate for use (eg, a trial in patients with mucosa-associated lymphoid tissue lymphoma), response should be assessed as above, but only using CT scans. However, residual masses should not be assigned CRu status but should be considered a PR.

Reference: Cheson BD, Pfisner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol 2007;25:579-86.

APPENDIX 6 PCWG3 GUIDELINES (WITH MODIFIED RECIST CRITERIA FOR SOFT TISSUE LESION ASSESSMENT)

1 EVALUATION OF LESIONS

Bone lesions should be evaluated with Technecium-99m based radionuclide bone scan as per PCWG3.

At baseline, soft tissue lesions/lymph nodes will be categorized as measurable or non-measurable as follows.

1.1 Measurable

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

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

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

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

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

1.2 Non-Measurable

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

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

1.3 Special considerations regarding bone lesions

Bone lesions will be assessed with Technecium-99m based radionuclide bone scans as per PCWG3.

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

When more than one measurable lesion is present at baseline all lesions up to a maximum of 20 lesions total (and a maximum of 5 lesions per organ system) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

Note: A maximum of 5 lesions can be selected per organ system. For example, a maximum of 5 lung lesions can be selected. A maximum of 5 lymph nodes can be selected at baseline, as the lymphatic system is considered one organ.

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

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

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Pelvic lymph nodes and extrapelvic lymph nodes (retroperitoneal, mediastinal, thoracic and other) may be reported separately, per PCWG3. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g., 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

2 RESPONSE CRITERIA

2.1 Evaluation of Target Lesions

- **Complete Response (CR):** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- **Partial Response (PR):** At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive Disease (PD):** At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
- **Not Evaluable (NE):** If one or more target lesions cannot be measured or adequately assessed as either fully resolved or too small to measure (due to missing or poor quality images), and the sum of diameters of the remaining measured target lesions (if any) has not increased sufficiently to meet Progressive Disease as defined above.

2.1.1 Special Notes on the Assessment of Target Lesions

2.1.1.1 Lymph nodes

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

2.1.1.2 Target lesions that become 'too small to measure'

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

2.1.1.3 Lesions that split or coalesce on treatment

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

vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

2.2 Evaluation of Non-Target Lesions

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

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

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

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

2.2.1.1 When the patient also has measurable disease

In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy (see examples in Appendix 2 and further details below). A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. Pleural effusions, pericardial effusions and ascites will not be followed as target or non-target lesions and will not contribute to response or progression. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

2.2.1.2 When the patient has only non-measurable disease

This circumstance arises in some trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: 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 lymphangitic disease from localized to widespread, or may be described as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have

objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore the increase must be substantial.

2.2.2 New Lesions

New bone lesions

New bone lesions should be evaluated as per PCWG3 criteria. Bone lesions will be assessed by radionuclide bone scan only. Radiographic progression on bone scan is defined by the following criteria:

- At least 2 new lesions on the first posttreatment bone scan, on the next scan (performed at least 6 weeks later) AND with at least two additional lesions as compared to the first post-treatment bone scan. Date of progression is then the date of first post-treatment scan.
- For scans after the first post-treatment scan, at least 2 new lesions relative to the first post-treatment scan AND confirmed on a subsequent scan (performed at least 6 weeks later). Date of progression is the date of the scan that first documents at least 2 new lesions relative to the first post-treatment scan.

New soft tissue lesions

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

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

If a new lesion is equivocal, for example because of its small size, continued follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

2.3 Response Assessment

2.3.1 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until disease progression per PCWG3 criteria, or the last response recorded, taking into account any requirement for confirmation and censoring rules regarding subsequent therapy. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement.

2.3.2 Time Point Response

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

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

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

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

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

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

2.3.3 Best Overall Response

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

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

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

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

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

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

2.3.4 Confirmation Scans

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

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

Reference:

Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3. Scher et al. J Clin Oncol 2016, 34(12):1402-1418

APPENDIX 7 EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

ECOG PERFORMANCE STATUS[a]	
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 a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

[a] Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, and Carbone PP. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5: 649-655.

APPENDIX 8 NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION

Heart failure is usually classified according to the severity of the patient's symptoms. The table below describes the most commonly used classification system, the New York Heart Association (NYHA) functional classification. It places patients in 1 of 4 categories based on how much they are limited during physical activity.

Class	Patient Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, or dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Class	Objective Assessment
A	No objective evidence of cardiovascular disease. No symptoms and no limitation in ordinary physical activity.
B	Objective evidence of minimal cardiovascular disease. Mild symptoms and slight limitation during ordinary activity. Comfortable at rest.
C	Objective evidence of moderately severe cardiovascular disease. Marked limitation in activity due to symptoms, even during less-than-ordinary activity. Comfortable only at rest.
D	Objective evidence of severe cardiovascular disease. Severe limitations. Experiences symptoms even while at rest.

APPENDIX 9 MANAGEMENT ALGORITHMS

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology agents and regimens.

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

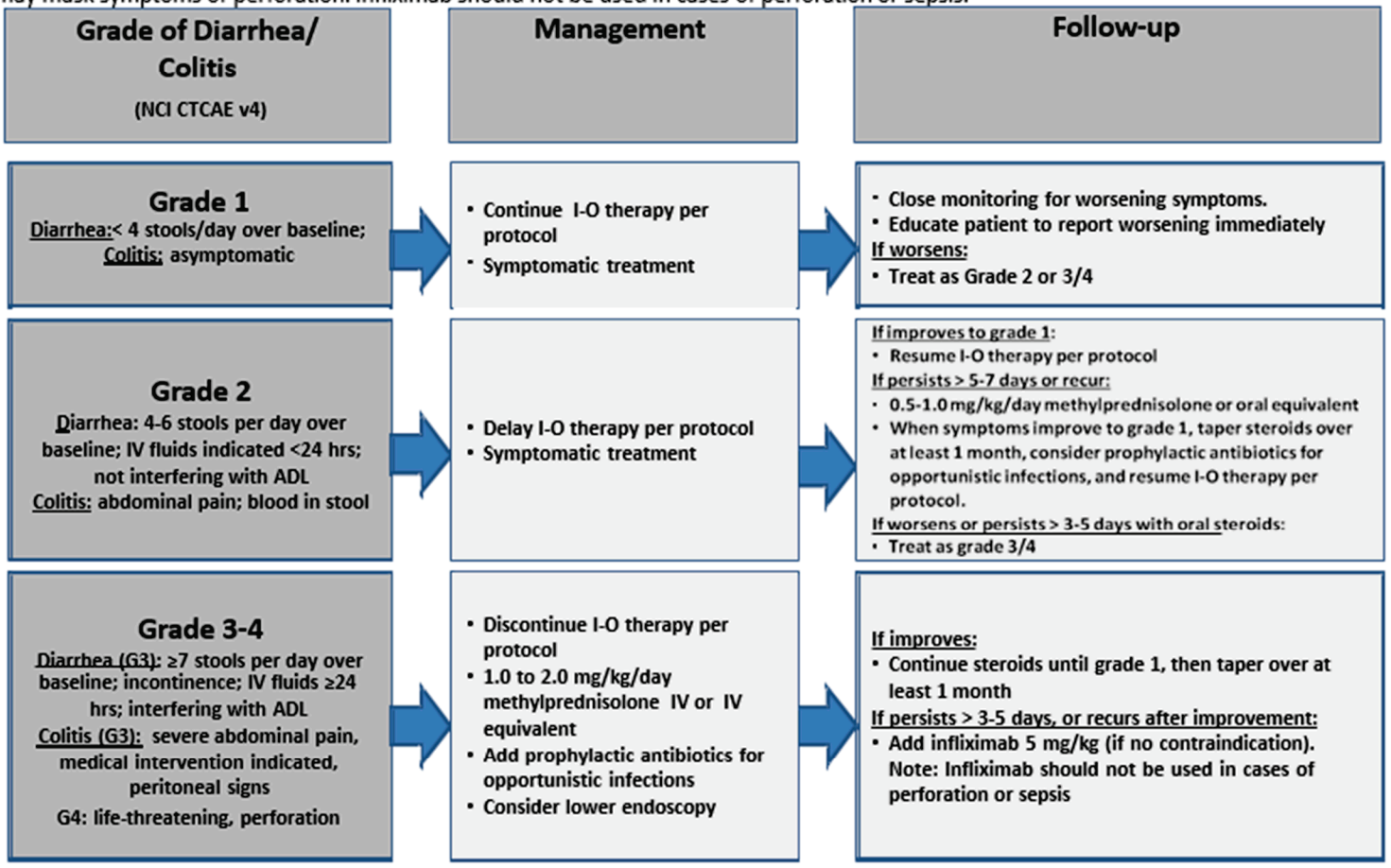
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

GI Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

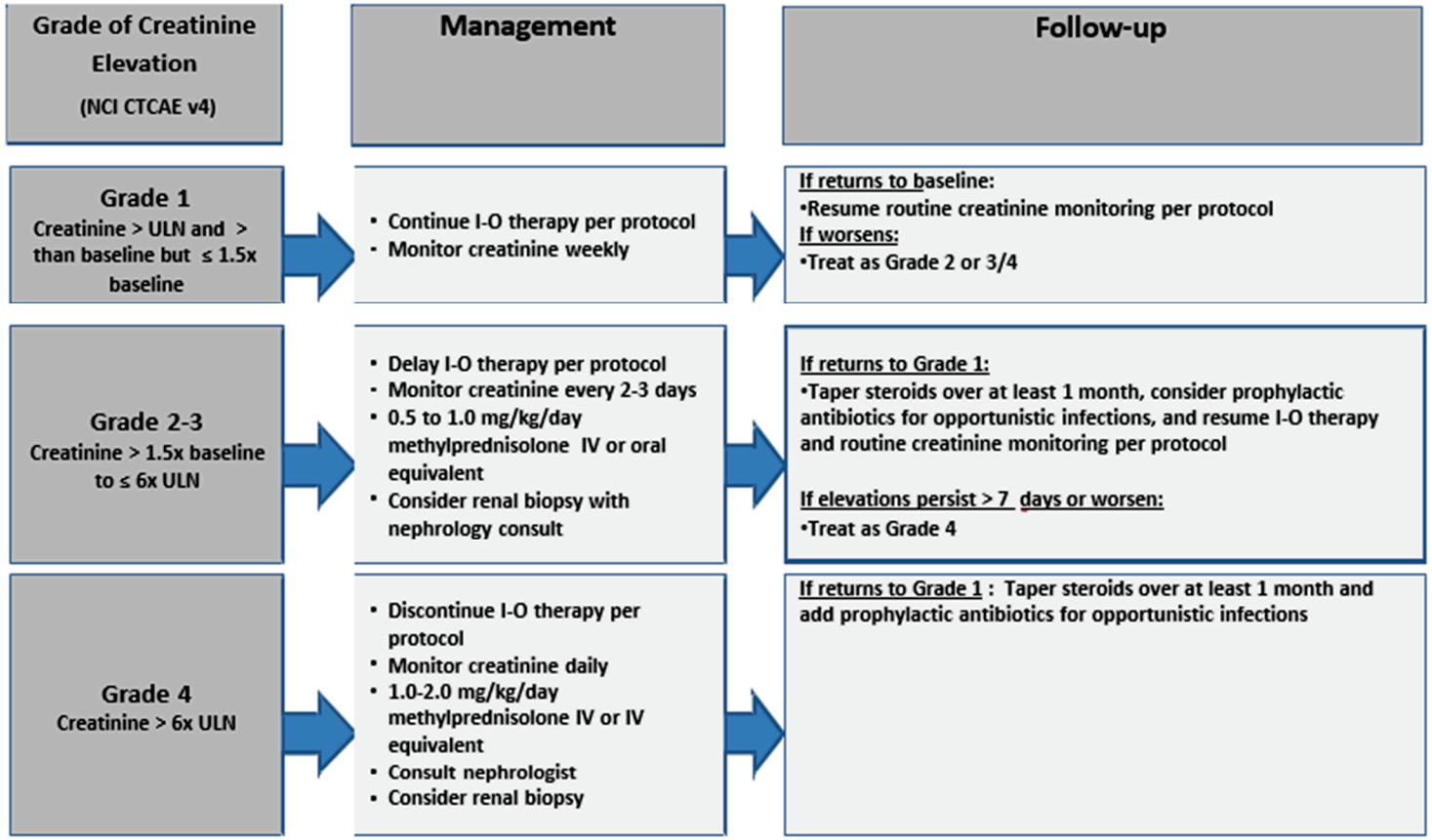


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

25-Jun-2019

Renal Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

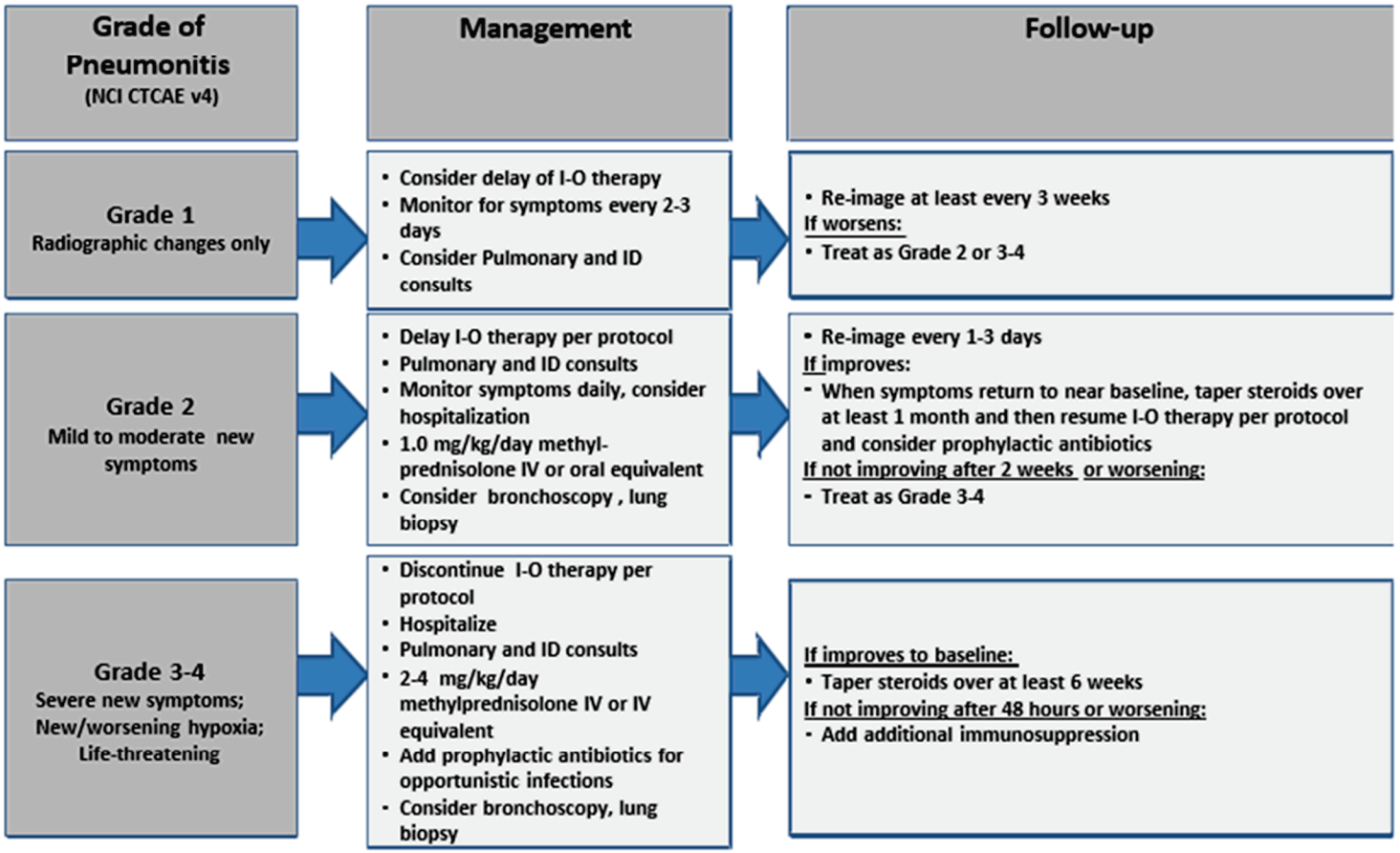


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

25-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.

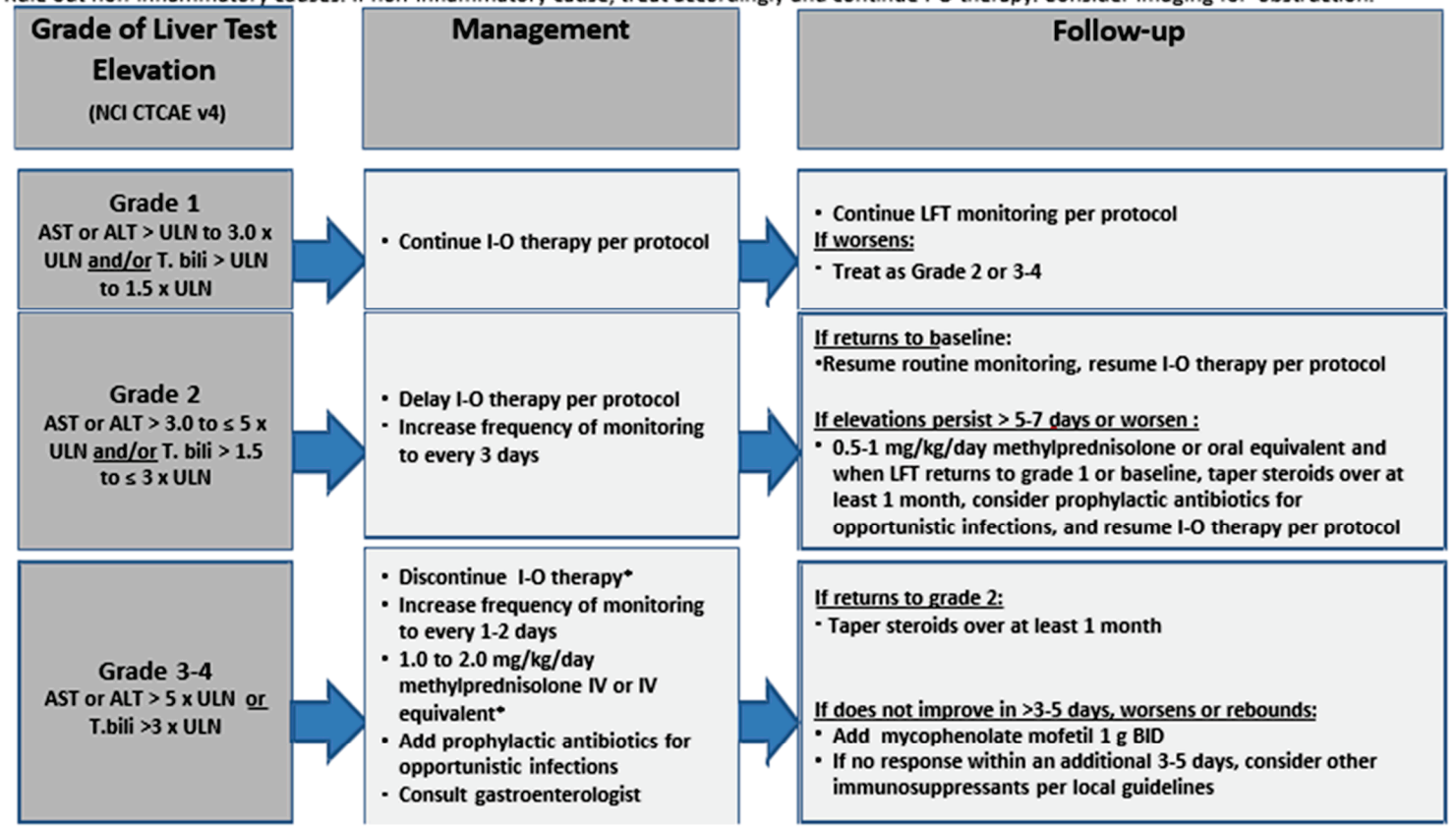


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids

25-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.

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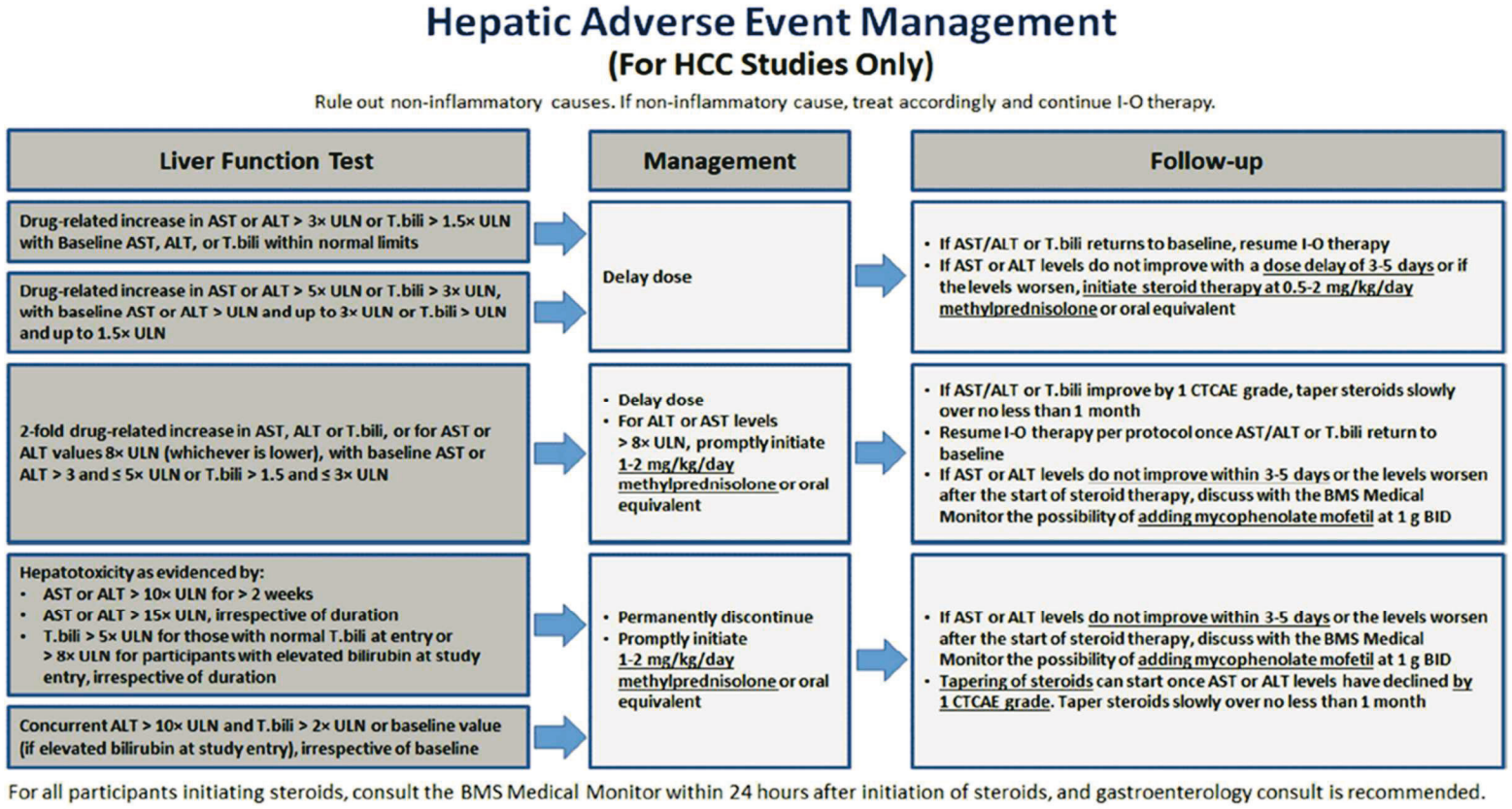
HEPATIC ADVERSE EVENT MANAGEMENT ALGORITHM (Modified for Part 2B Cohort 1: HCC Participants)

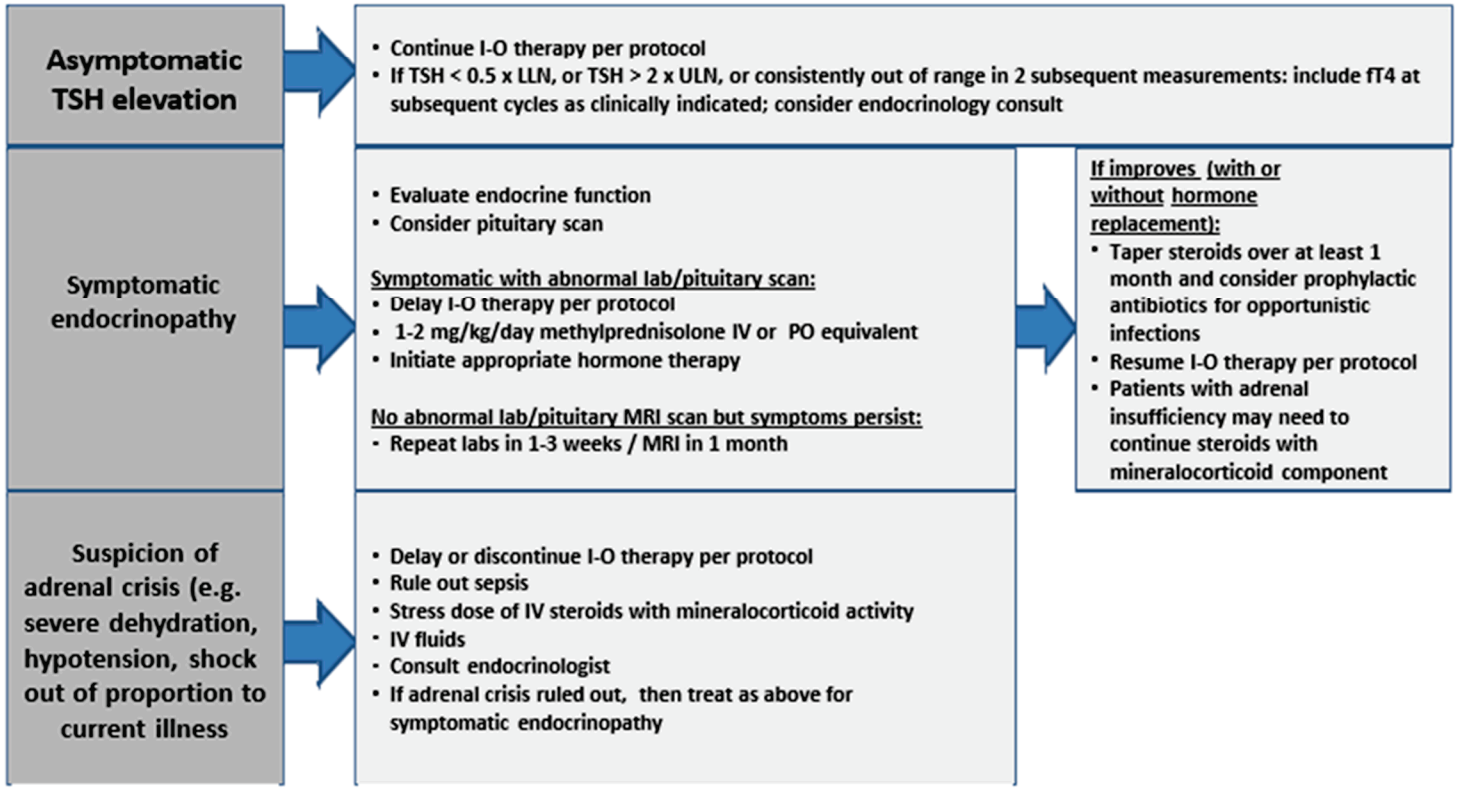
BMS has developed a standardized approach for the management of hepatic events based on cumulative data across the CTLA-4 and PD-1 programs in participants with normal hepatic function. Across most studies and CA030001 patient populations, the eligibility criteria for inclusion are based on a maximum AST or ALT < 3× ULN; therefore, only participants with normal to grade 1 LFTs have been enrolled.

Participants with HCC generally have underlying cirrhosis with decreased hepatic function. They may also have a concomitant chronic viral infection. For CA030001 Part 2B Cohort 1: HCC Participants, the upper limits for inclusion were adjusted to account for baseline liver dysfunction. Participants with AST or ALT elevations within the CTCAE Grade 2 range are eligible for inclusion. Criteria for dose delay, resumption, & discontinuation are in Section 7.4.3, Section 7.4.3.1, and Section 8.1, respectively.



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.

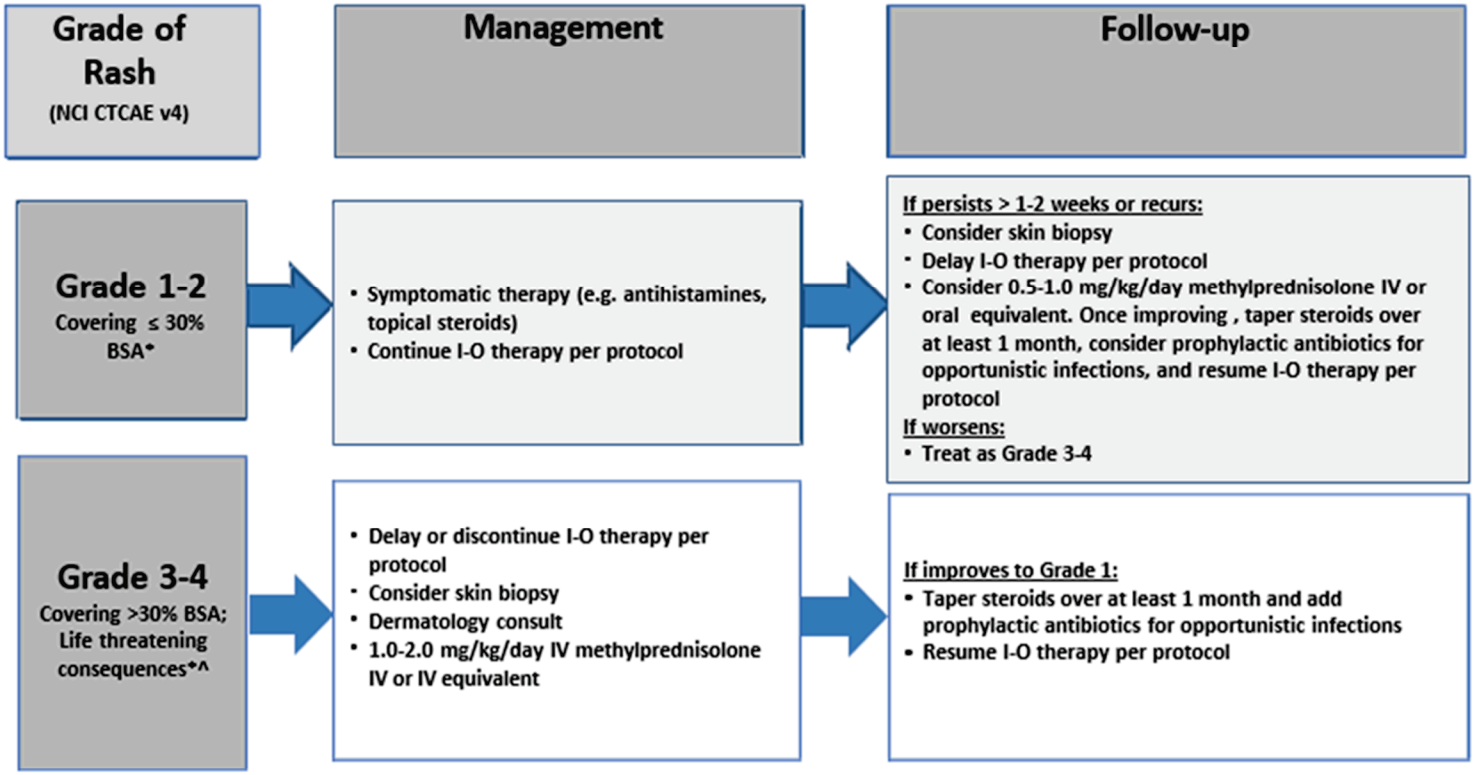


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

25-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.

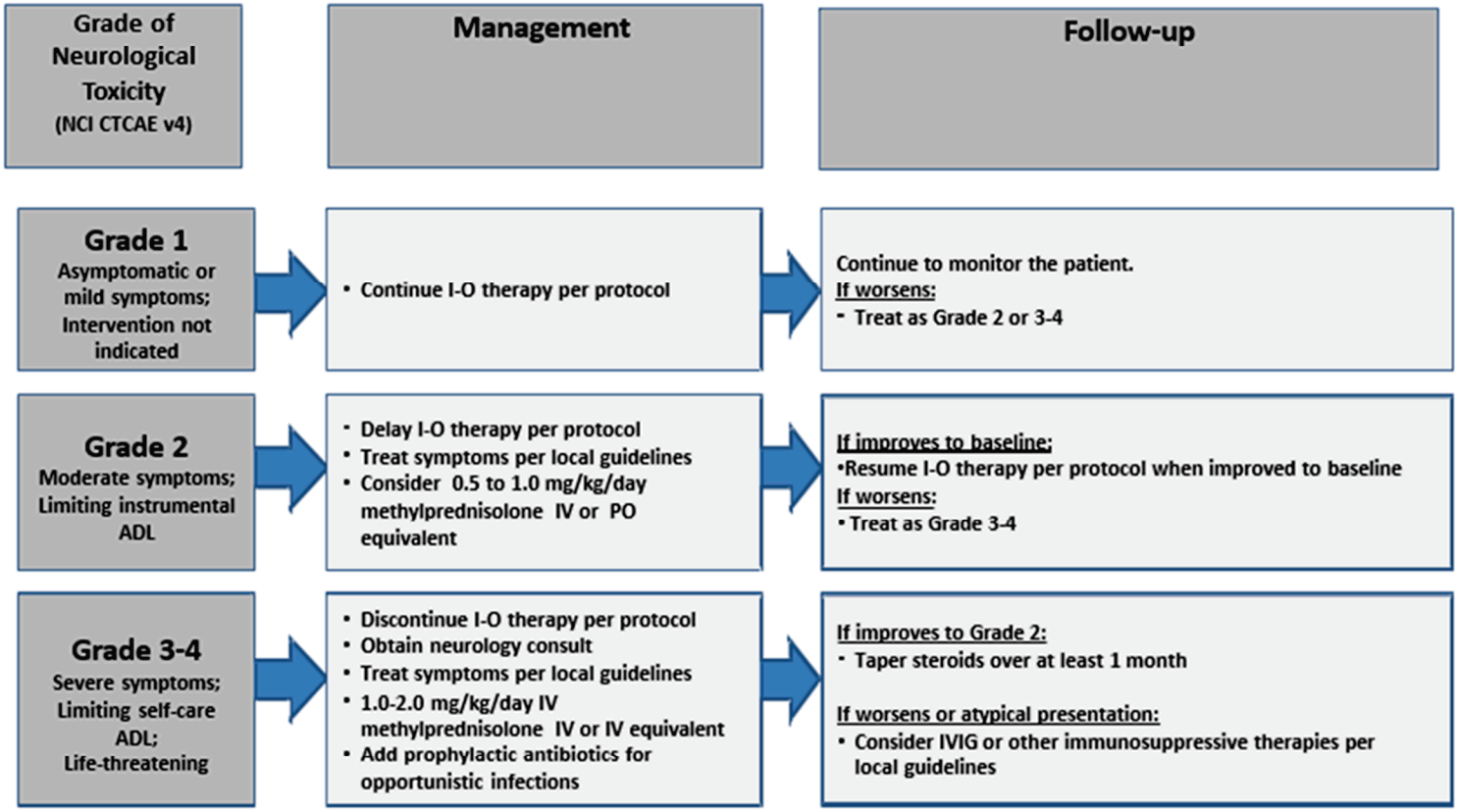
*Refer to NCI CTCAE v4 for term-specific grading criteria.

^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.

25-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.

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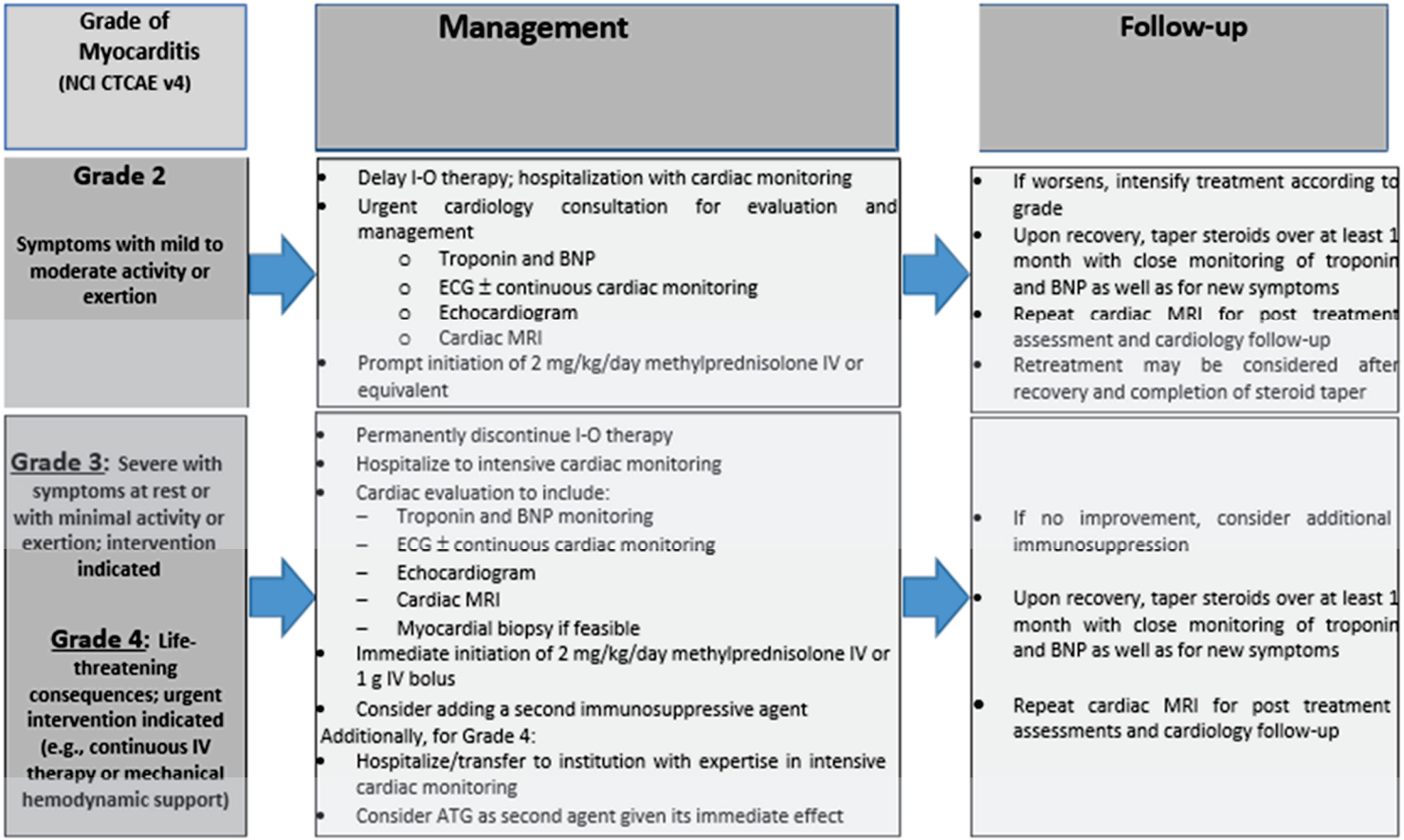
Myocarditis Adverse Event Management Algorithm



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

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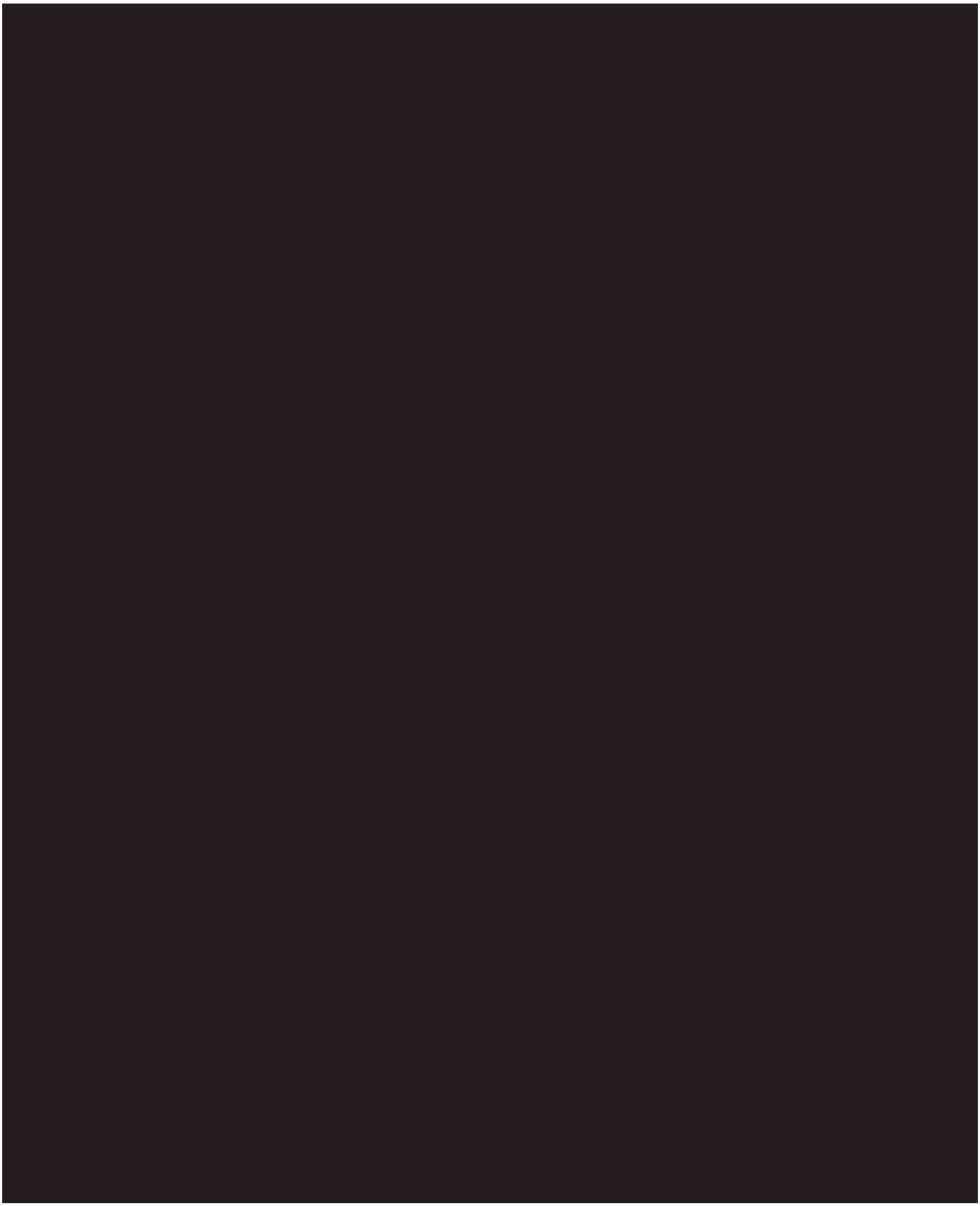

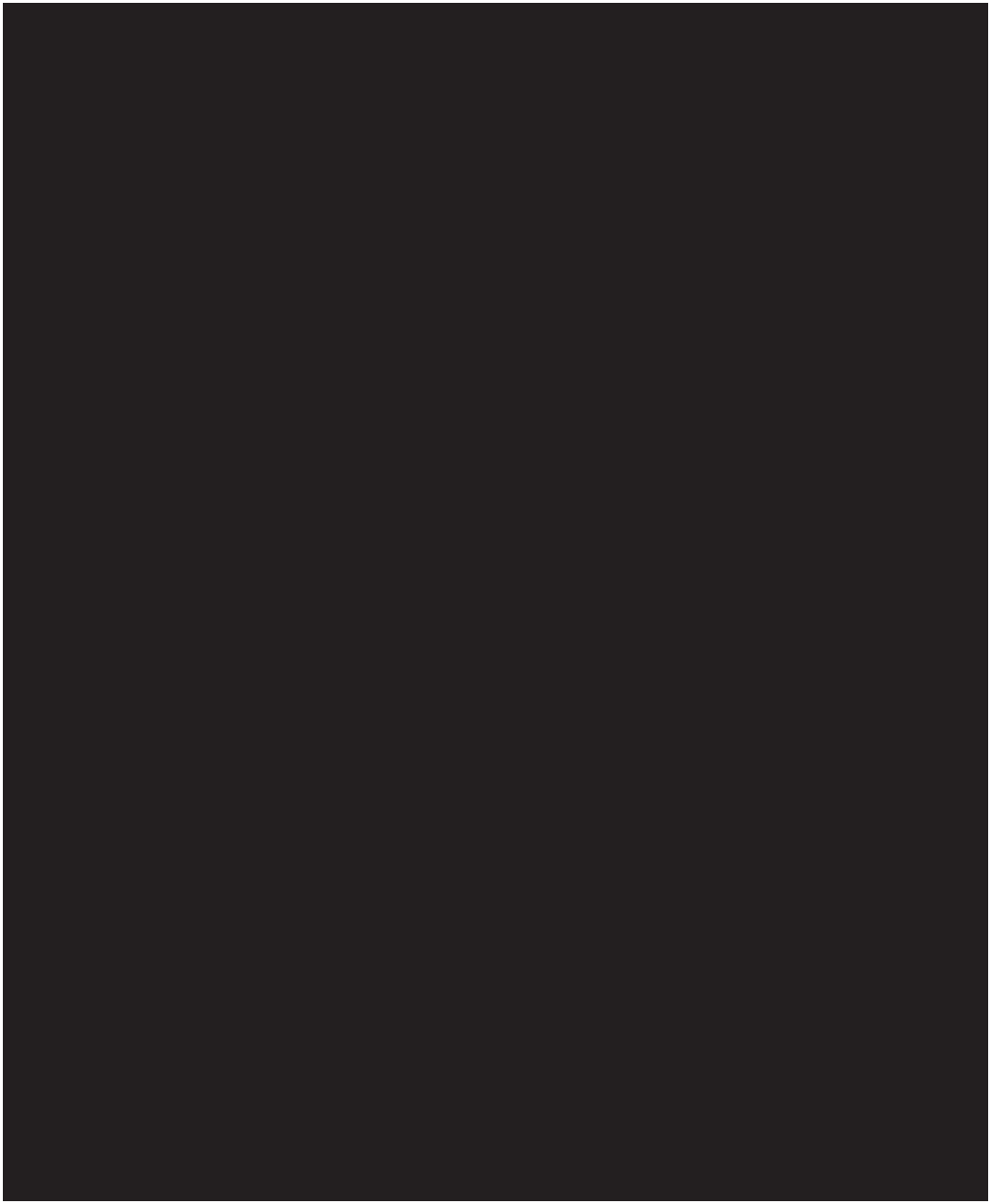

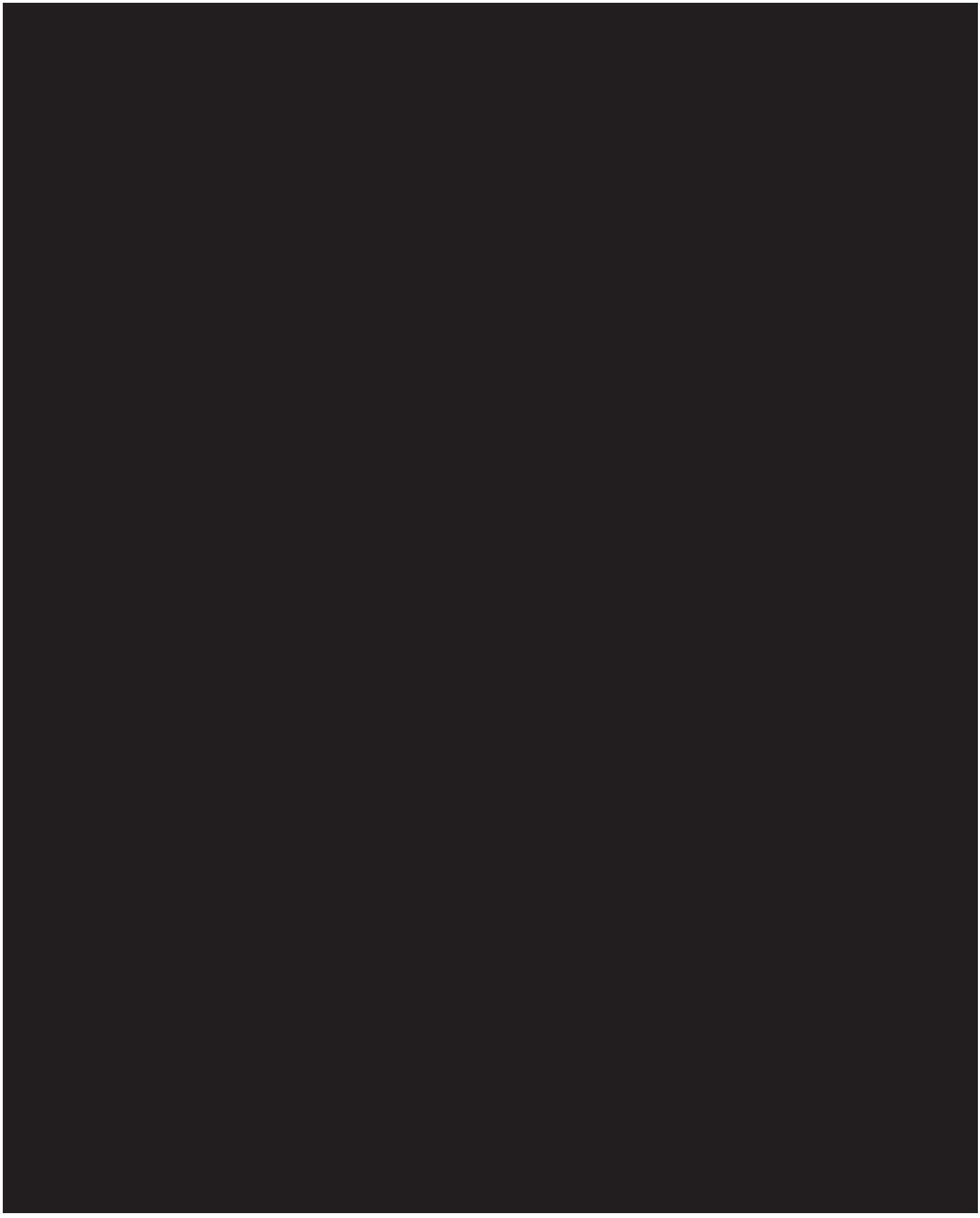

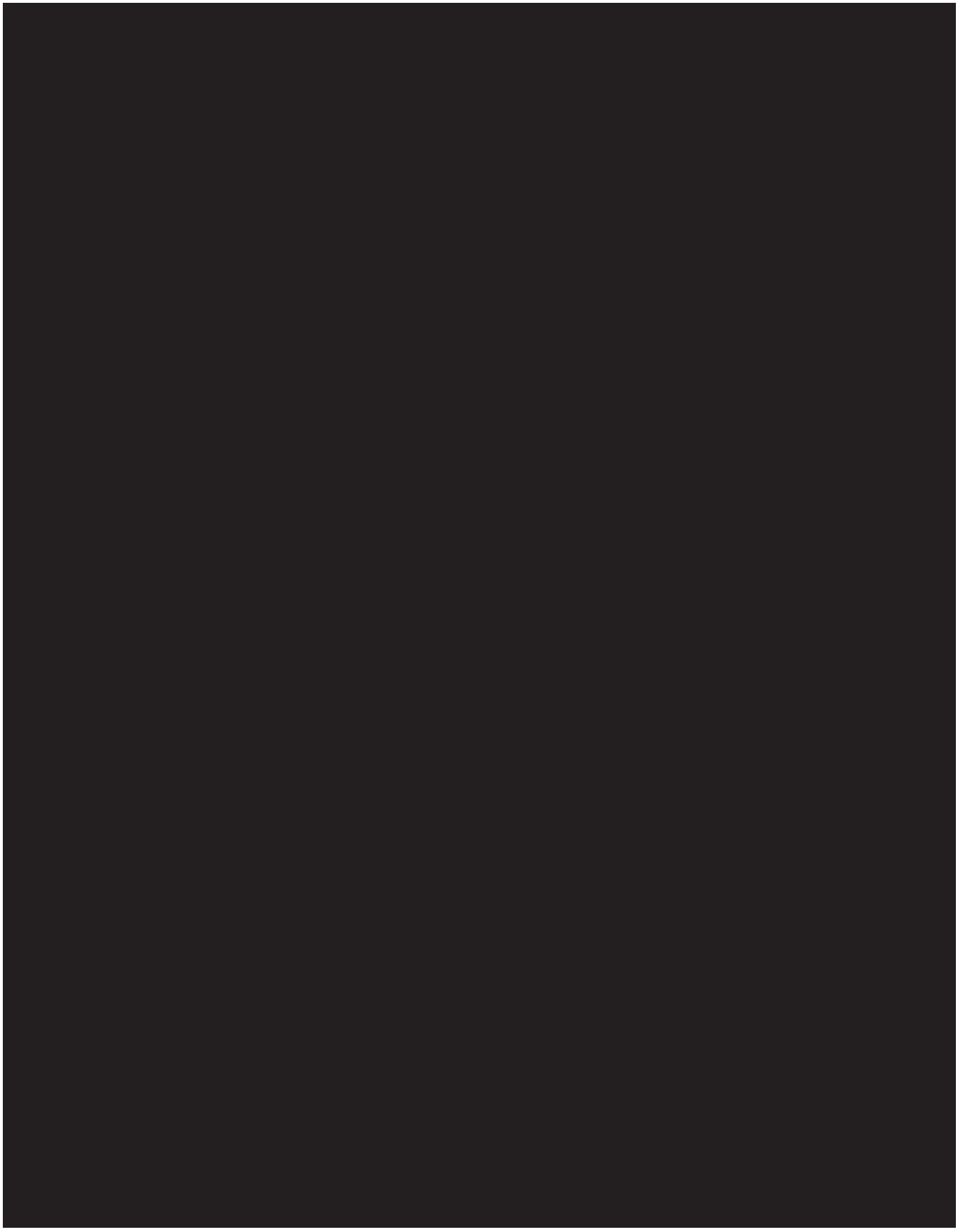

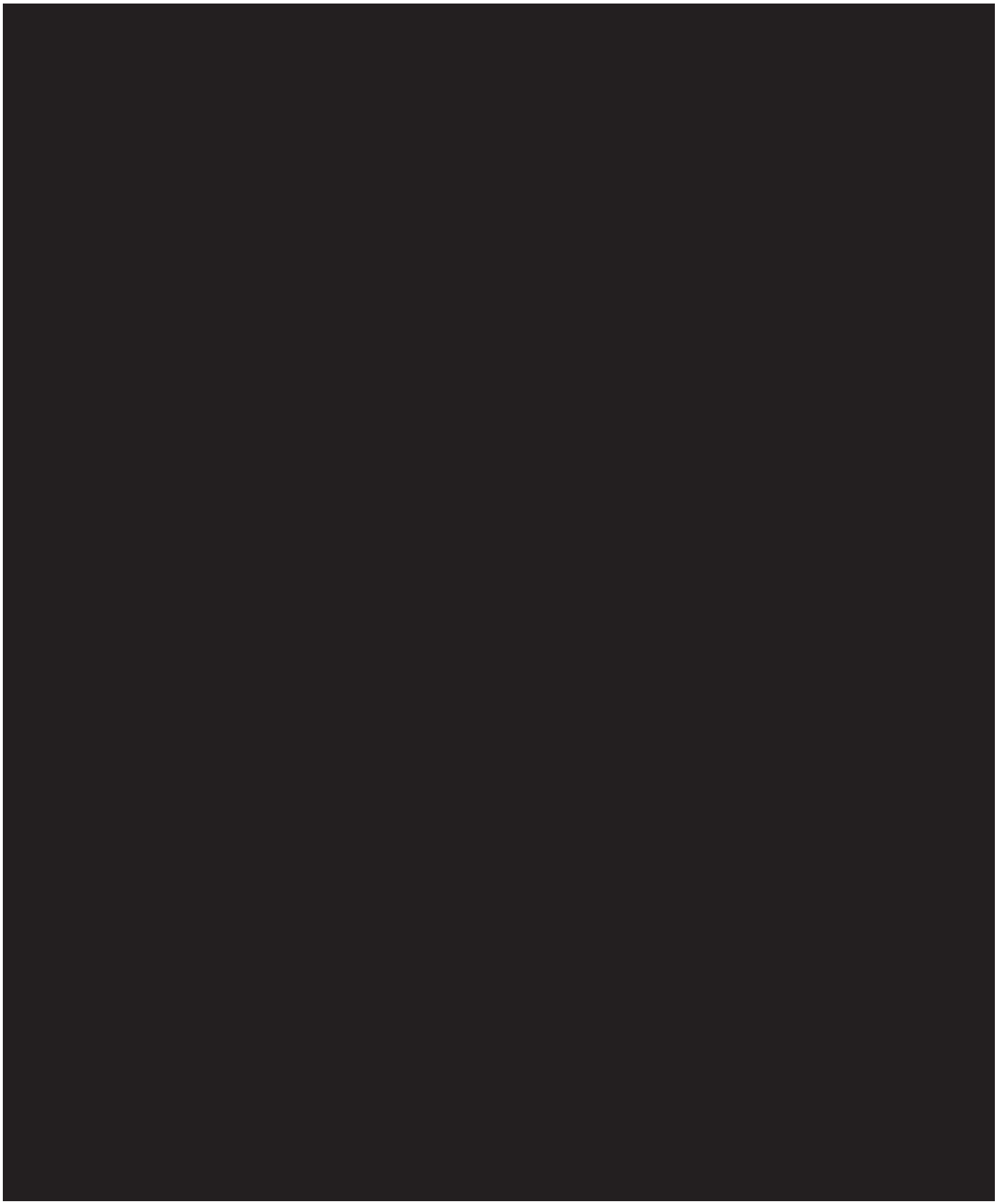

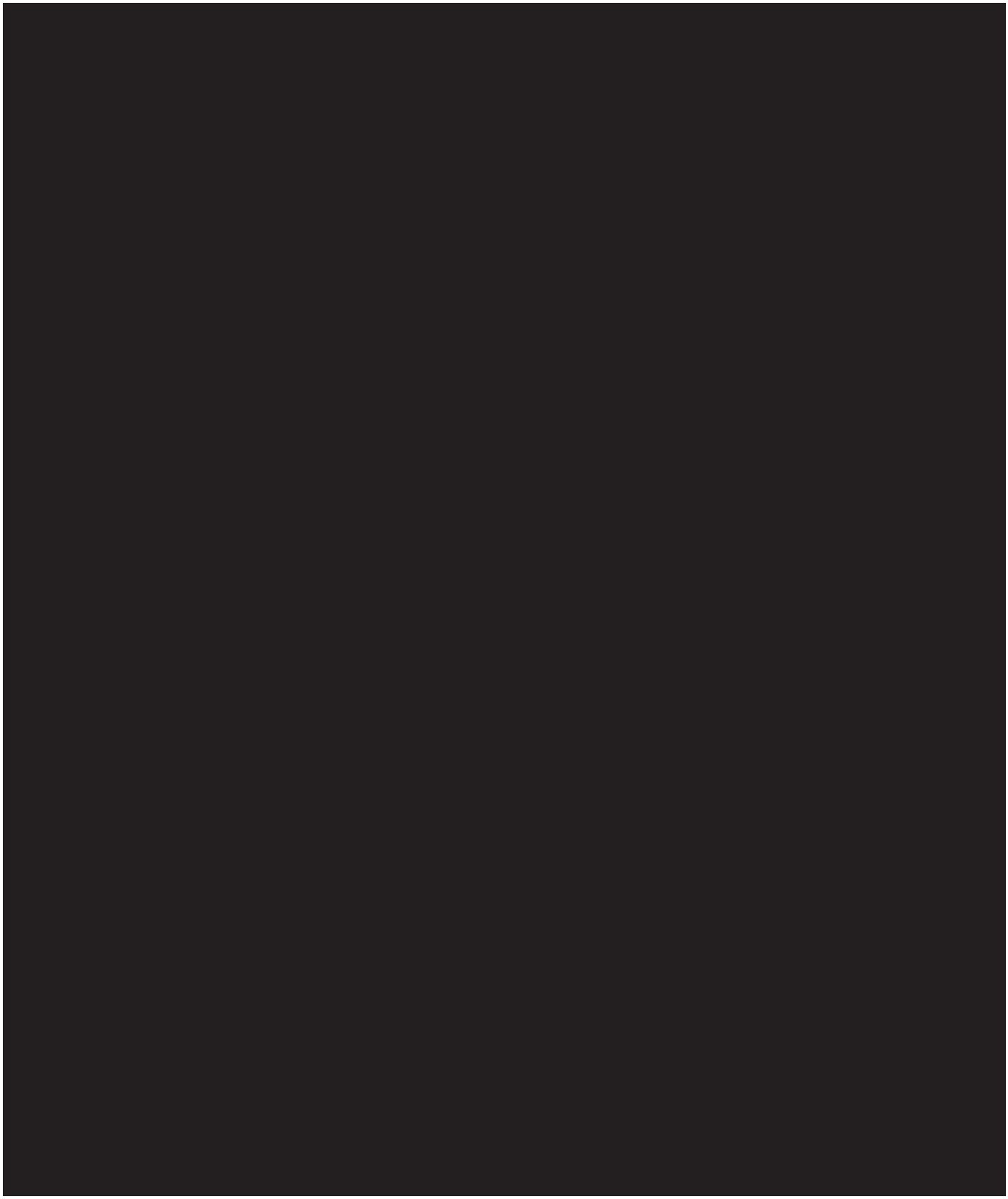

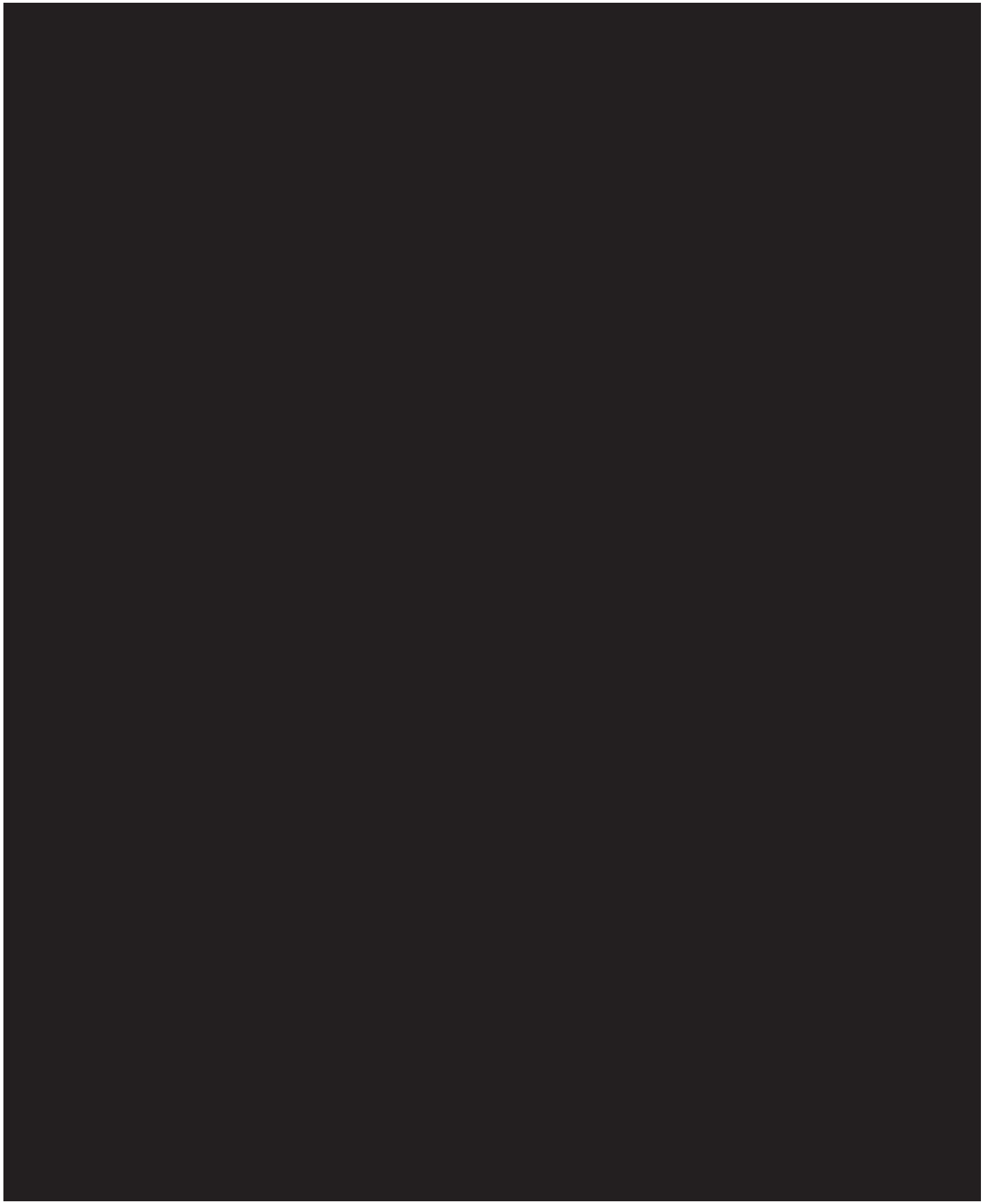

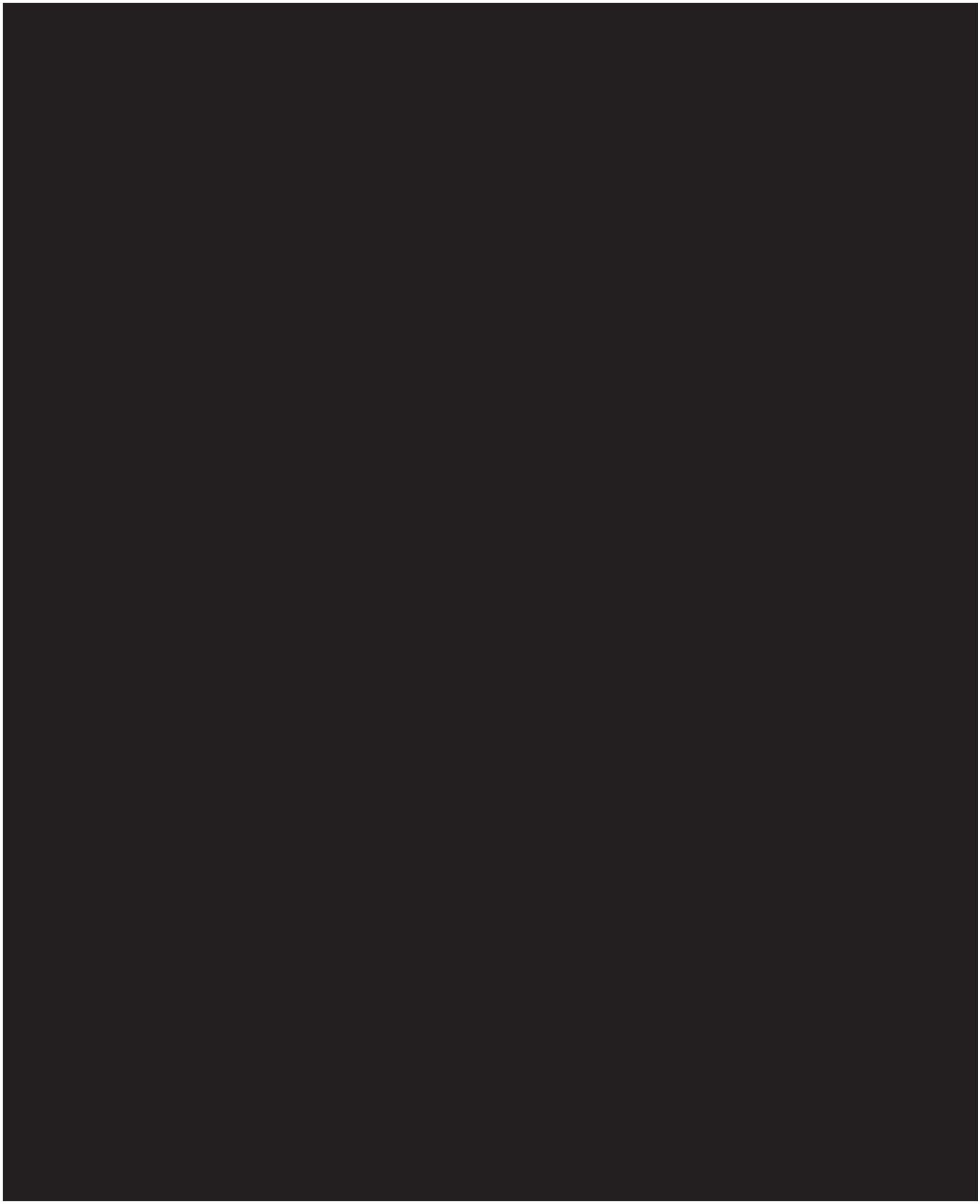

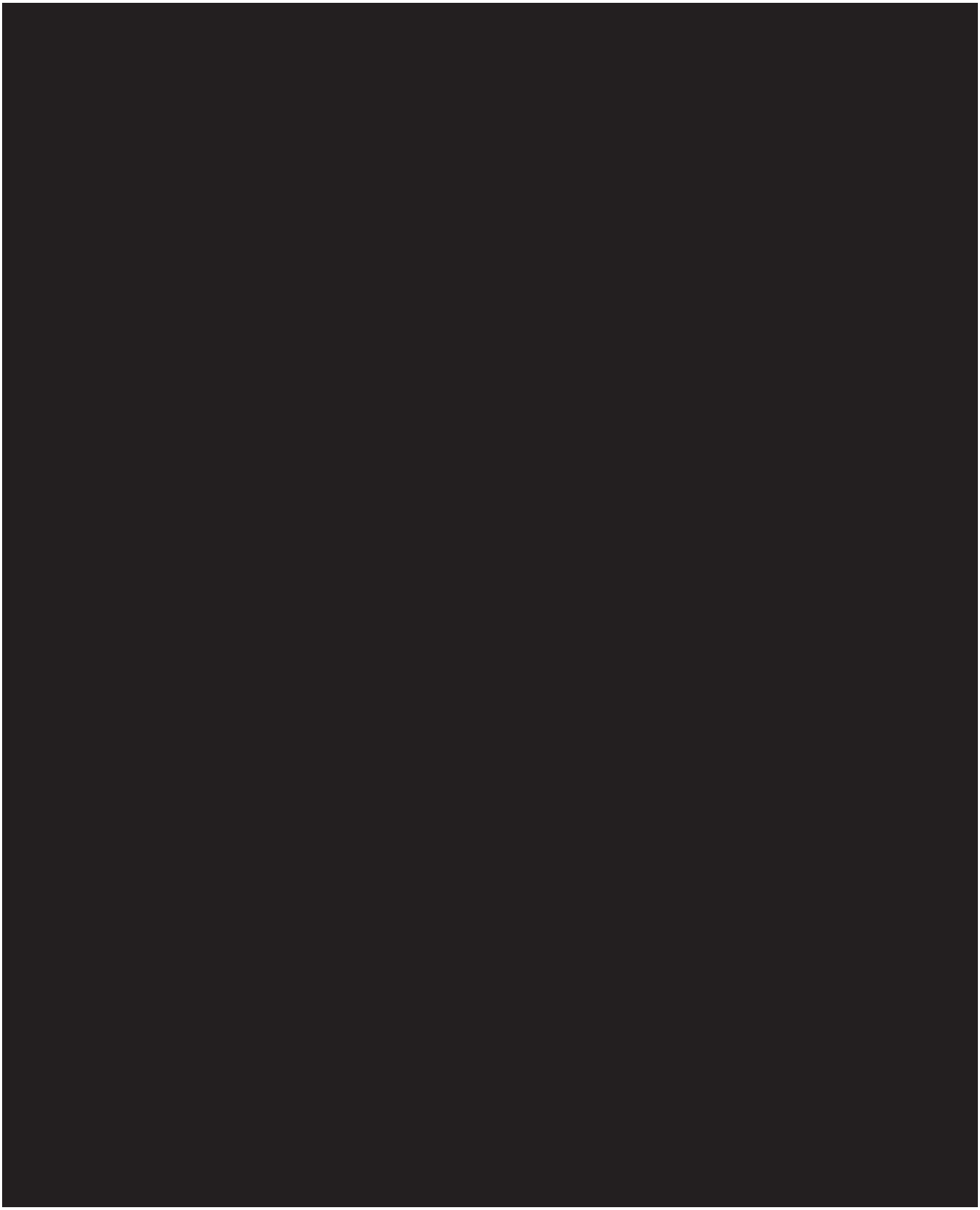

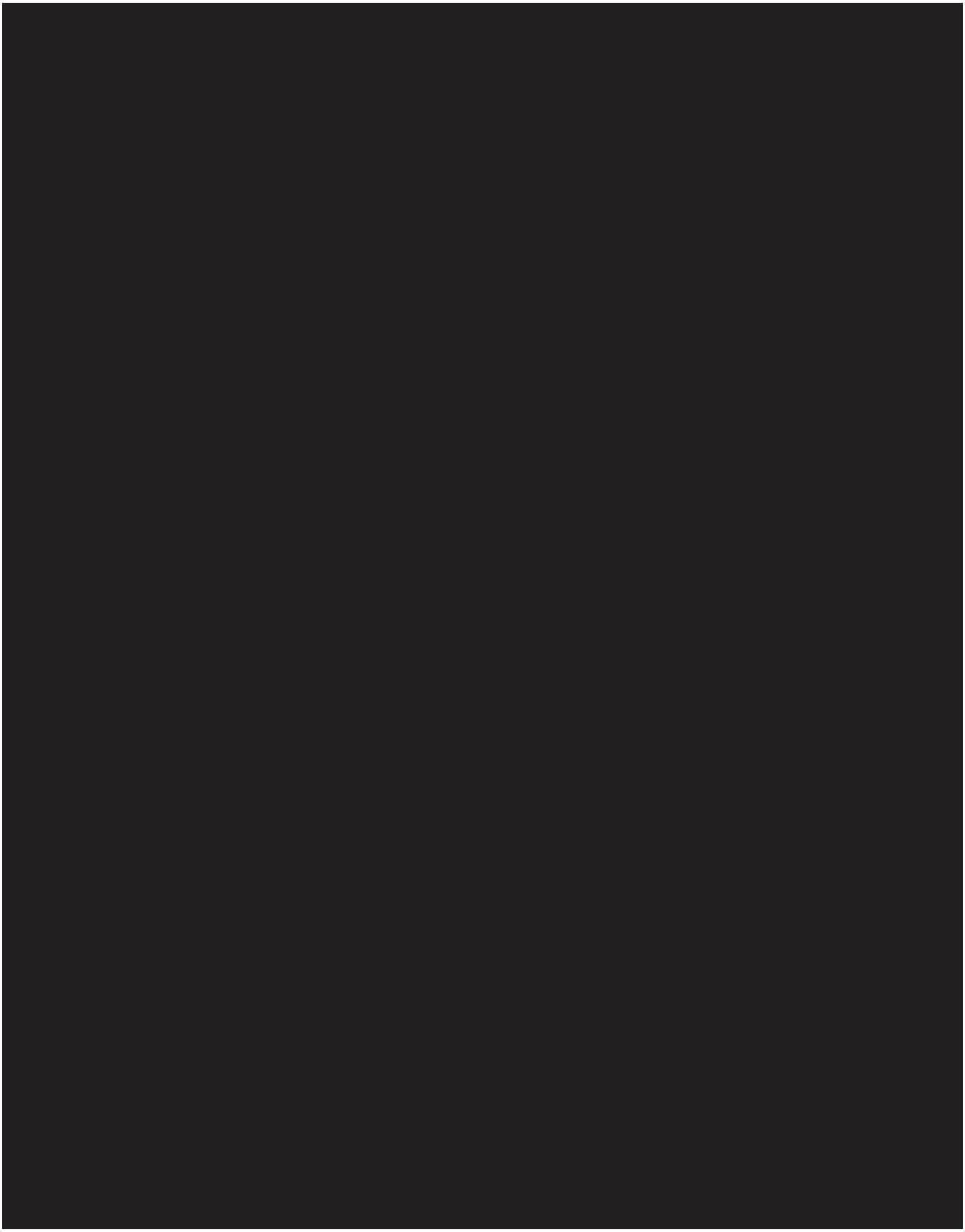

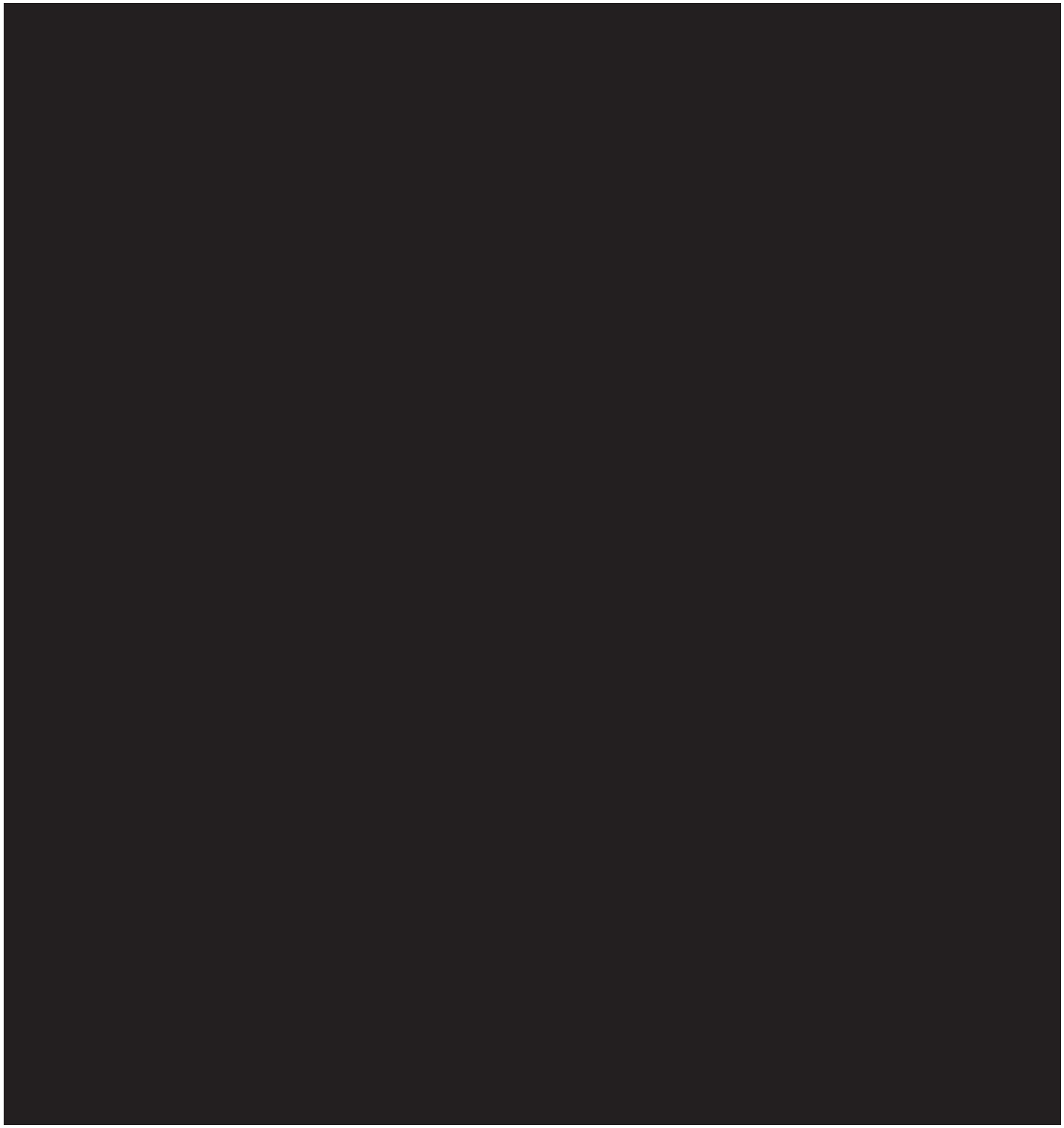

APPENDIX 11 AJCC MELANOMA STAGING

Table 1: TNM Staging Categories for Cutaneous Melanoma

Table 1. TNM Staging Categories for Cutaneous Melanoma

Classification	Thickness (mm)	Ulceration Status/Mitoses
T		
Tis	NA	NA
T1	≤ 1.00	a: Without ulceration and mitosis < 1/mm^2 b: With ulceration or mitoses ≥ 1/mm^2
T2	1.01-2.00	a: Without ulceration b: With ulceration
T3	2.01-4.00	a: Without ulceration b: With ulceration
T4	> 4.00	a: Without ulceration b: With ulceration
N	**No. of Metastatic Nodes**	**Nodal Metastatic Burden**
N0	0	NA
N1	1	a: Micrometastasis* b: Macrometastasis†
N2	2-3	a: Micrometastasis* b: Macrometastasis† c: In transit metastases/satellites without metastatic nodes
N3	4+ metastatic nodes, or matted nodes, or in transit metastases/satellites with metastatic nodes	
M	**Site**	**Serum LDH**
M0	No distant metastases	NA
M1a	Distant skin, subcutaneous, or nodal metastases	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases	Normal
	Any distant metastasis	Elevated

Abbreviations: NA, not applicable; LDH, lactate dehydrogenase.
*Micrometastases are diagnosed after sentinel lymph node biopsy.
†Macrometastases are defined as clinically detectable nodal metastases confirmed pathologically.

Table 2: Anatomic Stage Groupings for Cutaneous Melanoma

Table 2. Anatomic Stage Groupings for Cutaneous Melanoma

	Clinical Staging*				Pathologic Staging†		
	T	N	M		T	N	M
0	Tis	N0	M0	0	Tis	N0	M0
IA	T1a	N0	M0	IA	T1a	N0	M0
IB	T1b	N0	M0	IB	T1b	N0	M0
	T2a	N0	M0		T2a	N0	M0
IIA	T2b	N0	M0	IIA	T2b	N0	M0
	T3a	N0	M0		T3a	N0	M0
IIB	T3b	N0	M0	IIB	T3b	N0	M0
	T4a	N0	M0		T4a	N0	M0
IIC	T4b	N0	M0	IIC	T4b	N0	M0
III	Any T	N > N0	M0	IIIA	T1-4a	N1a	M0
					T1-4a	N2a	M0
				IIIB	T1-4b	N1a	M0
					T1-4b	N2a	M0
					T1-4a	N1b	M0
					T1-4a	N2b	M0
					T1-4a	N2c	M0
				IIIC	T1-4b	N1b	M0
					T1-4b	N2b	M0
					T1-4b	N2c	M0
					Any T	N3	M0
IV	Any T	Any N	M1	IV	Any T	Any N	M1

*Clinical staging includes microstaging of the primary melanoma and clinical/radiologic evaluation for metastases. By convention, it should be used after complete excision of the primary melanoma with clinical assessment for regional and distant metastases.

†Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial (ie, sentinel node biopsy) or complete lymphadenectomy. Pathologic stage 0 or stage IA patients are the exception; they do not require pathologic evaluation of their lymph nodes.

Source: Balch CM, Gershenwald JE, Soong SJ, et al. Final Version of 2009 AJCC Melanoma Staging and Classification. J Clin Oncol 2009;27:6199-6206.

APPENDIX 12 SCHEDULE OF ACTIVITIES AND PHARMACOKINETICS SAMPLING SCHEDULE FOR POTENTIAL ALTERNATIVE DOSE SCHEDULE IN FOR PART 1 CA030001

Detailed in the tables below are the on-treatment schedule of activities and pharmacokinetic (PK) sampling schedule for potential alternative every-8-weeks (Q8W) BMS-986249 dosing administration that may be explored in The Dose Escalation Phase (Part 1) of CA030001 following evaluation of preliminary available safety, PK, and [redacted] data and upon discussion and agreement between the Investigators and Medical Monitor (or designee) (Section 5 main protocol). The alternative dosing schedule in Part 1 was initially initiated via administrative letter 03 to evaluate 1600 mg BMS-986249 Q8W monotherapy in Part 1A, and via administrative letter 04 to evaluate 800 mg BMS-986249 Q8W + 480 mg nivolumab Q4W combination therapy in Part 1B.

- Table 1: On-Treatment Schedule of Activities for BMS-986249 Q8W Dosing Schedule in the Dose Escalation Phase (Part 1) in CA030001
- Table 2: PK and ADA Sampling Schedule for Part 1A BMS-986249 Q8W Monotherapy in Dose Escalation in CA030001
- Table 3: PK and ADA Sampling Schedule for Part 1B BMS-986249 Q8W Combination in Dose Escalation in CA030001

Table 1: On-Treatment Schedule of Activities for BMS-986249 Q8W Dosing Schedule in the Dose Escalation Phase (Part 1) in CA030001

Procedure	Cycle 1 (28 days in length)				Cycle 2 (28 days in length)				Cycles 3 and Beyond (each cycle 28 days in length)	EOT[a,b]	Notes
	D1	D8 (± 2 days)	D15 (± 2 days)	D22 (± 2 days)	D1 (± 2 days)	D8 (± 2 days)	D15 (± 2 days)	D22 (± 2 days)	D1 (± 2 days)		
Safety Assessments											
ECOG Performance Status	X				X				X	X	
PE	X				X				X	X	
Symptom-directed PE		X	X	X		X	X	X			
Weight	X				X				X	X	
Vital Signs[c]	X	X	X	X	X	X	X	X	X	X	
Oxygen Saturation[c]	X				X				X		
ECG[d]	X				X				X	X	

Table 1: On-Treatment Schedule of Activities for BMS-986249 Q8W Dosing Schedule in the Dose Escalation Phase (Part 1) in CA030001

Procedure	Cycle 1 (28 days in length)				Cycle 2 (28 days in length)				Cycles 3 and Beyond (each cycle 28 days in length)	EOT[a,b]	Notes
	D1	D8 (± 2 days)	D15 (± 2 days)	D22 (± 2 days)	D1 (± 2 days)	D8 (± 2 days)	D15 (± 2 days)	D22 (± 2 days)	D1 (± 2 days)		
Laboratory Tests	X	X	X	X	X	X	X	X	X	X	There will be a 72-hour window for collection of laboratory tests on D1. If screening laboratory tests are within 72 hours of C1D1, laboratory tests performed at screening can be used for C1D1. Coagulation assessment at screening only. See Section 9.4.4 and Table 9.4.4-1.
Urinalysis	X				X				As clinically indicated; microscopic urine reflex only for urinalysis positive for blood/protein/ leukocyte esterase.		
Pregnancy Test (WOCBP only)[e]	X				X				X	X	

Table 1: On-Treatment Schedule of Activities for BMS-986249 Q8W Dosing Schedule in the Dose Escalation Phase (Part 1) in CA030001

Procedure	Cycle 1 (28 days in length)				Cycle 2 (28 days in length)				Cycles 3 and Beyond (each cycle 28 days in length)	EOT[a,b]	Notes
	D1	D8 (± 2 days)	D15 (± 2 days)	D22 (± 2 days)	D1 (± 2 days)	D8 (± 2 days)	D15 (± 2 days)	D22 (± 2 days)	D1 (± 2 days)		
Adverse Event Reporting and Concomitant Medication Assessments											
Monitor for Non-SAEs	Non-SAEs will be collected starting with the first dose of study medication and through 100 days following discontinuation of study treatment.										See Appendix 3 and Section 9.2 in the main protocol.
Monitor for SAEs	All SAEs must be collected from the date of the participant's written consent until 100 days following discontinuation of study treatment.										See Appendix 3 and Section 9.2 in the main protocol.
Concomitant Medications	X	X	X	X	X	X	X	X	X		
PK Assessments											
Serial Blood Sampling	See Table 2 for the PK and immunogenicity sampling schedule and Section 9.5 in the main protocol.										
Immunogenicity (ADA) Assessments	See Table 2 for the PK and immunogenicity sampling schedule and Section 9.5 in the main protocol.										
[redacted]											
Imaging Assessments											
Body Imaging[f]	See Section 9.1.1 in the main protocol. Tumor imaging assessments should occur every 8 weeks (± 7 days) starting from the first dose up until Week 48, and then continue every 12 weeks (± 7 days).										

Table 1: On-Treatment Schedule of Activities for BMS-986249 Q8W Dosing Schedule in the Dose Escalation Phase (Part 1) in CA030001

Procedure	Cycle 1 (28 days in length)				Cycle 2 (28 days in length)				Cycles 3 and Beyond (each cycle 28 days in length)	EOT[a,b]	Notes
	D1	D8 (± 2 days)	D15 (± 2 days)	D22 (± 2 days)	D1 (± 2 days)	D8 (± 2 days)	D15 (± 2 days)	D22 (± 2 days)	D1 (± 2 days)		
Brain Imaging	See Section 9.1.1 in the main protocol. Participants with history of brain metastasis should have surveillance MRI performed approximately every 12 weeks or sooner if clinically indicated. CT of the brain without and with contrast can be performed if MRI is contraindicated.										
Bone Scan	See Section 9.1.1 in the main protocol. Required for participants with prostate cancer only (PCWG3 Assessment). For participants with prostate cancer, bone scans should occur every 8 weeks starting from the first dose (± 7 days).up until Week 48, and then continue every 12 weeks (± 7 days). Others only as clinically indicated per local standards.										
Biomarker Assessments											See Section 9.5 and Section 9.8 in the main protocol and Table 2 in Appendix 12
On-treatment Tumor Biopsy[g]						X					Mandatory tumor biopsies must be performed at [redacted]; specimens may be collected within 3 days of the time point.
Required Post-progression Tumor Biopsy	A tumor biopsy is required upon confirmation of PD (within 7 days) except for: 1) participants who have an on-treatment biopsy and progress within 4 cycles; 2) participants who will be imminently (within 4 weeks) enrolling in a subsequent clinical research study that requires a screening biopsy; and 3) participants who consent to be treated beyond progression will require the biopsy only at the subsequent confirmation of progression.										See Section 9.8.2 in the main protocol.

[redacted]

Table 1: On-Treatment Schedule of Activities for BMS-986249 Q8W Dosing Schedule in the Dose Escalation Phase (Part 1) in CA030001

Procedure	Cycle 1 (28 days in length)				Cycle 2 (28 days in length)				Cycles 3 and Beyond (each cycle 28 days in length)	EOT[a,b]	Notes
	D1	D8 (± 2 days)	D15 (± 2 days)	D22 (± 2 days)	D1 (± 2 days)	D8 (± 2 days)	D15 (± 2 days)	D22 (± 2 days)	D1 (± 2 days)		
Exploratory Biomarker Assessments											See Section 9.5 and Section 9.8 in the main protocol and Table 3
Clinical Treatment Supplies											
BMS-986249 Administration Q8W (Part 1A and Part 1B)	X								X (Every other cycle starting at Cycle 3 [eg, C3, C5, C7, etc])		BMS-986288 to be supplied by BMS.
Nivolumab Administration Q4W (Part 1B)	X				X				X		Nivolumab to be supplied by BMS.

Abbreviations: ADA = anti-drug antibody; BMS = Bristol-Myers Squibb; C = cycle; CT = computed tomography; CXDY = Cycle X Day Y, as an example; D = day; DLT = dose-limiting toxicity; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOI = end of infusion; EOT = end of treatment; hCG = human chorionic gonadotropin; MRI = magnetic resonance imaging; NSCLC = non-small cell lung cancer; PD = progressive disease; PE = physical examination; PK = pharmacokinetic; Q8W = every 8 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; WOCBP = women of childbearing potential.

[a] EOT is defined as the visit where the decision is made to discontinue the participant from treatment. Evaluations will be performed prior to study discharge, or for participants who are prematurely discontinued.

[b] For participants who complete all scheduled cycles of therapy, the EOT visit will be the same as the last scheduled and completed on-treatment visit (eg, C26D1) and the start of the safety follow-up period. For participants who do not complete all scheduled cycles of therapy, the EOT visit will be the most recent on-treatment visit (with all available safety and response data); it does not need to be repeated and will be considered as the start of the safety follow-up period.

[c] Vital signs will be obtained before the infusion BMS-986249 and then every 15 minutes (± 5 minutes) until 60 minutes after completion of the infusion; oxygen saturation to also be performed in conjunction with vital signs monitoring on these days. For all cycles after C5 and for nivolumab infusion, vital signs and oxygen saturation are to be taken before the infusion and at the end of infusion. If any vital sign is abnormal (based upon clinician assessment) at the final check, the participant must be observed further for a period of time, as clinically indicated.

[d] ECGs should be recorded after the participant has been supine for at least 5 minutes and prior to blood draws. For Part 1A, triplicate ECGs are performed at predose and EOI on C1D1 and C5D1. Single predose safety ECGs to be performed for all other time points. For Part 1B, single predose ECGs are performed for all time points and also at EOI for C1D1 & C5D1. See Section 9.4.3 of the main protocol).

[e] Serum/urine to be collected within 24 hours prior to BMS-986249 or nivolumab dosing. For Part 1A this would be collected prior to D1 of odd cycles (e.g. C1, C3, C5, etc), for Part 1B this would be collected prior to D1 of all cycles Pregnancy test may be completed on the first day of treatment, provided the results are available before the start of study therapy. Serum or urine pregnancy test must be performed within 24 hours prior to administration of study treatment (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG).

[f] The same imaging modality is to be used for all assessments, per RECIST v1.1 (Appendix 5). Tumor assessment to be performed prior to initiating next cycle of treatment.

[g] Pre-treatment (screening) biopsy can be performed optionally on C1D1. Mandatory tumor biopsies must be performed at [redacted]; specimens may be collected within 3 days of the time point and must be obtained prior to administration of study treatments. Bone lesion biopsies are unacceptable for submission. See Section 9.8.2 of the main protocol.

Table 2: PK and ADA Sampling Schedule for Part 1A BMS-986249 Q8W Monotherapy in Dose Escalation in CA030001

Study Day of Sample Collection (1 cycle = 4 weeks)	Event	Time (Relative To Start of BMS-986249 Infusion) Hour: Min	BMS-986249 PK Plasma Sample	BMS-986249 ADA Serum Samples
C1D1	Predose[a]	0:00	X	X
	EOI	See note[b]	X	
		4:00	X	
C1D2		24:00	X	
C1D4 (± 1 days)		72:00	X	
C1D8 (± 2 days)		168:00	X	
C1D15 (± 2 days)		336:00	X	
C1D22 (± 2 days)		504:00	X	
C2D1		672:00	X	
C2D8[c] (± 3 days)		840:00	X	
C3D1	Predose[a]	0:00	X	X
	EOI	See note[b]	X	
C4D1		672:00	X	
C4D2		696:00	X	
C4D4 (± 1 days)		744:00	X	
C4D8 (± 2 days)		840:00	X	

Table 2: PK and ADA Sampling Schedule for Part 1A BMS-986249 Q8W Monotherapy in Dose Escalation in CA030001

Study Day of Sample Collection (1 cycle = 4 weeks)	Event	Time (Relative To Start of BMS-986249 Infusion) Hour: Min	BMS-986249 PK Plasma Sample	BMS-986249 ADA Serum Samples
C4D15 (± 2 days)		1008:00	X	
C4D22 (± 2 days)		1176:00	X	
C5D1 (± 2 days)	Predose[a]	0:00	X	X
	EOI	See note[b]	X	
C7D1 (± 2 days)	Predose[a]	0:00	X	X
Every fourth cycle after C7 until EOT (C11D1, C15D1, C19D1, etc until EOT)	Predose[a]	0:00	X	X
EOT			X	X
30-day follow-up			X	X
60-day follow-up			X	X
100-day follow-up			X	X
Grade 3+ Infusion Reaction			X	X

Abbreviations: C = cycle; D = day.

[a] Predose: All predose samples should be taken within 30 minutes prior to the start of the infusion.

[b] EOI samples should be collected immediately after stopping the infusion (preferably within 2 minutes). Refer to Table 7.1.1-1 for infusion duration. If the EOI is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.

[c] To align with the scheduled tumor biopsy, the time window can be the same as tumor biopsy collection (± 3 days)

Table 3: PK and ADA Sampling Schedule for Part 1B BMS-986249 Q8W Combination in Dose Escalation in CA030001

Study Day of Sample Collection (1 cycle = 4 weeks)	Event	Time (Relative To Start of nivolumab Infusion) Hour:Min	BMS-986249 PK Plasma Sample	nivolumab PK Serum Sample	BMS-986249 ADA Serum Samples	nivolumab ADA Serum Samples
C1D1	Predose[a]	0:00	X	X	X	X
	EOI	See note[b]	X	X		
		4:00	X			
C1D2		24:00	X			
C1D4 (± 1 day)		72:00	X			
C1D8 (± 2 days)		168:00	X			
C1D15 (± 2 days)		336:00	X			
C1D22 (± 2 days)		504:00	X			
C2D1	Predose[a]	0:00	X	X	X	X
C2D8[c] (± 3 days)		168:00	X			
C3D1	Predose[a]	0:00	X	X	X	X
	EOI	See note[b]	X	X		
C4D1	Predose[a]	0:00	X	X	X	X
C4D2		24:00	X			
C4D4 (± 1 days)		72:00	X			
C4D8 (± 2 days)		168:00	X			
C4D15 (± 2 days)		336:00	X			
C4D22 (± 2 days)		504:00	X			

Table 3: PK and ADA Sampling Schedule for Part 1B BMS-986249 Q8W Combination in Dose Escalation in CA030001

Study Day of Sample Collection (1 cycle = 4 weeks)	Event	Time (Relative To Start of nivolumab Infusion) Hour:Min	BMS-986249 PK Plasma Sample	nivolumab PK Serum Sample	BMS-986249 ADA Serum Samples	nivolumab ADA Serum Samples
C5D1 (± 2 days)	Predose[a]	0:00	X	X	X	X
	EOI	See note[b]	X	X		
C7D1 (± 2 days)	Predose[a]	0:00	X	X	X	X
Every fourth cycle after C7 until EOT (C11D1, C15D1, C19D1, etc until EOT)	Predose[a]	0:00	X	X	X	X
EOT			X	X	X	X
30-day follow-up			X	X	X	X
60-day follow-up			X	X	X	X
100-day follow-up			X	X	X	X
Grade 3+ Infusion Reaction			X	X	X	X

Abbreviations: C = cycle; D = day

[a] Predose: All predose samples should be taken within 30 minutes prior to the start of the infusion.

[b] EOI samples should be collected immediately after stopping the infusion (preferably within 2 minutes). Refer to Table 7.1.1-1 for infusion duration. For co-administration visits, separate EOI samples (1 each for BMS-986249 and nivolumab) should be collected following co-administration of BMS-986249 and nivolumab and recorded as having the same collection time, if applicable. If the EOI is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.

[c] To align with the scheduled tumor biopsy, the time window can be the same as tumor biopsy collection (± 3 days)

APPENDIX 13 CHILD-PUGH SCORE

Score	Points
Child-Pugh A	5 - 6
Child-Pugh B	7 - 9
Child-Pugh C	> 9

Scoring

	Score		
Measure	1 Point	2 Points	3 Points
Ascites	Absent	Slight	Moderate
Serum bilirubin (mg/dL)	< 2.0	2.0 - 3.0	> 3.0
Serum albumin (g/dL)	> 3.5	2.8 - 3.5	< 2.8
PT prolongation or INR	< 4 sec < 1.7	4 - 6 sec 1.7 - 2.3	> 6 sec > 2.3
Encephalopathy grade	None	1 - 2	3 - 4

Encephalopathy Grading

Encephalopathy Grade	Clinical Definition
Grade 0	Normal consciousness, personality, and neurological examination
Grade 1	Restless, sleep disturbed, irritable/agitated, tremor, and impaired handwriting
Grade 2	Lethargic, time-disoriented, inappropriate, asterixis, and ataxia
Grade 3	Somnolent, stuporous, place-disoriented, hyperactive reflexes, and rigidity
Grade 4	Unrousable coma, no personality/behavior, decerebrate

APPENDIX 14 COUNTRY SPECIFIC REQUIREMENTS/DIFFERENCES

Country/Location Requirement	Original Language/Section Number	Country-specific Language or Differences
Argentina, Germany, Romania	Section 6.2 : Exclusion Criteria Exclusion criterion 3)e)xii)	"Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)" to be replaced with "Positive test for HIV" OR Standard language in exclusion criterion add "Countries where exclusion of HIV positive participants is locally mandated."

APPENDIX 15 REVISED PROTOCOL SUMMARY OF CHANGE HISTORY

Overall Rationale for Protocol Amendment 08, 22-Feb-2022

The primary reasons for Protocol Amendment 08 are to update and/or clarify the inclusion criteria to align with the current disease state and treatment landscape based on investigator feedback for Part 2.

Additional revisions, including in sections of the Protocol Synopsis, have been made to align the protocol with respect to these changes. This amendment incorporates the changes from approved Administrative Letters 05 and 06, which are indicated in the Document History but not listed in the Summary of Key Changes below.

Summary of key changes for Protocol Amendment 08		
Section Number & Title	**Description of Change**	**Brief Rationale**
Figure 5.1-2: Study Design Schematic - Part 2, the BMS-986249 Cohort Expansion Combination Therapy Phase Section 5.4.9: Rationale for Selecting HCC, CRPC, and TNBC in Part 2B Expansion	Updated the study design figure to include participants with intermediate hepatocellular carcinoma (HCC) in Part 2B Cohort 1 and updated the section on rationale for expanding participant population to intermediate HCC in Part 2B Expansion.	To align with current disease state and treatment landscape.
Section 6.1: Inclusion Criteria	• Clarified Inclusion Criterion 2)a).	• To clarify measurability for Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 vs Prostate Cancer Working Group 3 (PCWG3) criteria.
	• Clarified Inclusion Criterion 2)e)ii)1) and 2).	• To support melanoma participants given recent changes in adjuvant standard of care.
	• Modified Inclusion Criterion 2)f)i)2) and 3).	• To support HCC participants given recent changes in first-line treatment landscape.
	• Updated Inclusion Criterion 2)f)i)10).	• To create consistency across Bristol Myers Squibb (BMS)-sponsored protocols.
	• Modified Inclusion Criterion 2)f)ii)3).	• To allow for radiotherapy in alignment with recent treatment landscape.
	• Added new Inclusion Criterion 2)f)ii)3)**c**.	• To increase clarity.
	• Inclusion Criterion 2)f)ii)6) was marked "Not Applicable per Protocol Amendment 08."	• To allow for inclusion of Part 2B castration-resistant prostate cancer (CRPC) participants with liver

Summary of key changes for Protocol Amendment 08		
Section Number & Title	**Description of Change**	**Brief Rationale**
		metastasis based on investigator feedback.
Section 7.4.1: Dose-limiting Toxicities	Modified text in this section.	For increased clarity.
Section 7.7.2: Permitted Therapy	• Addition of text indicating that non-live COVID-19 vaccines are allowed. • Addition of a COVID-19 vaccine benefit/risk statement.	To clarify COVID-19 vaccination language.
Section 8.2.1: Individual Discontinuation Criteria Section 9.8.4: Additional Research Collection	Added new section and revised text.	To increase clarity.
Appendix 2: Study Governance Considerations Appendix 3: Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow up and Reporting	• Updated text in Monitoring and Source Documents sections. • Added new sections "Study and Site Start and Closure" and "Dissemination of Clinical Study Data." • Updated contact information for reporting of SAEs.	To increase clarity.
Appendix 9: Management Algorithms	Updated formatting of HCC-specific management algorithm.	To align with other BMS-sponsored HCC studies.
All	Minor formatting, clarification, and typographical corrections; additional amendments to align the protocol with respect to the key changes outlined above.	Corrections for clarity and consistency within the document were minor, and therefore have not been summarized.

Overall Rationale for the Revised Protocol 07, 15-Nov-2020

This is a revised protocol to modify the treatment arms in the Part 2A Expansion Phase and define the Part 2B Expansion Phase. The Part 2A Expansion Phase will now include concurrent evaluation of 3 treatment arms in a randomized setting in melanoma (2 different dose regimens of BMS-986249 in combination with nivolumab and 1 standard-of-care reference arm) rather than the previously defined 5 treatment arms. The Part 2B Expansion Phase will evaluate a single-dose regimen of BMS-986249 in combination with nivolumab in 3 tumor tumor-specific cohorts. This protocol revision also includes global changes to reduce redundancies and increase readability; incorporates updated learnings for BMS-986249, nivolumab, and ipilimumab; and adds language around COVID-19.

Summary of key changes for Revised Protocol 07		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title page	Updated names, titles, and contact information.	To comply with new protocol model document.
Section 2, Schedule of Activities, Tables 2-1 through 2-5	Relocated instructions for when multiple procedures are required at a single time point. Updated activities related to Part 2A and Part 2B. Removed stool sample collection from required activities. Added EORTC-QLQ-C30, EQ-5D-3L, FACIT GP5, and PRO-CTCAE requirements to EOT visit. Added requirement for assessment of participant survival status to Follow-up 1, 2, and 3.Restructured and condensed table headings and rows.	To increase readability. To include and support the modified Part 2A design and introduction of Part 2B. To align with current nivolumab essential protocol elements (EPE).
Section 2.1, Schedule of Activities, Tables 2-1 through 2-5, Table 4-2, Table 4-3, Section 6.2, Exclusion Criteria, Section 6.4.1, Retesting During Screening Section 7.4.3, Dose Delays due to Toxicity, Section 7.4.3.1, Criteria to Resume Treatment, Section 9.2.1, Time Period and Frequency for Collecting AE and SAE Information and Section 9.2.3, Follow-up of AEs and SAEs Criteria to Resume Treatment, Section 9.8.1.6, Other Assessment, Table 9.8.3-1, Biomarker Sampling Schedule for All Study Parts	Added language around SARS-CoV-2 and COVD-19.	To align with proposed COVID-19 language for oncology protocols.
Section 3.2.1.5, BMS-986249 Clinical Pharmacokinetics	Updated systemic exposure data for BMS-986249	To update with most recent analysis to support Part 2A and Part 2B.
Table 4-2, Objectives and Endpoints for Part 2A	Removed Arm A and Arm B from the objectives and added Arm F.	To support Part 2A modified design.
Table 4-3, Objectives and Endpoints for Part 2B	Added primary, secondary, and exploratory objectives for Part 2B.	To support incorporation of Part 2B.
Section 5.1, Overall Design	Added addendum per Revised Protocol 07. Added treatment dosing and schedule for Part 2B participants. Updated Figure 5.1-2 and 5.1-3.	To support Part 2A modified design. To support incorporation of Part 2B.
Section 5.1.1, Screening Period	Added instructions for if a participant exceeds the 30-day screening period due to a study-related procedure.	To increase participant/site convenience.

Summary of key changes for Revised Protocol 07		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.1.2.4, The BMS-986249 Cohort Expansion Combination Therapy (Part 2)	Clarified instructions for clinical evaluation of toxicity events.	To support Part 2A modified design. To support incorporation of Part 2B.
Section 5.1.5.2, Imaging Follow-up Period	Removed tumor assessment schedule and added a reference to Section 2.	To increase readability.
Section 5.2, Number of Participants	Adjusted sample sizes for Part 2A and added information on the number of participants for Part 2B.	To support modification of Part 2A design and introduction of Part 2B.
Old Section 5.4.7, Rationale for Evaluating Different Dose Levels and Schedules of BMS-986249 in Combination with Nivolumab in Part 2A	Relocated to Section 5.5.4.	To increase readability.
Section 5.4.7.2, Rationale for Nivolumab Monotherapy as a Reference	Updated language around stopping enrollment/randomization into Part 2A Arm E as of Revised Protocol 07.	To provide rationale for modified Part 2A design.
Section 5.4.9, Rationale for Selecting HCC, CRPC, and TNBC in Part 2B Expansion	Added rationale for selecting HCC, CRPC, and TNBC in Part 2B.	To provide rationale to support Part 2B design.
Section 5.5.4, Rationale for Evaluating Different Dose Levels and Schedules of BMS-986249 in Combination with Nivolumab in Part 2A	Relocated from Section 5.4.7. Added language around recent analysis resulting in decision to modify enrollment/randomization into Part 2A.	To increase readability. To provide rationale for modified Part 2A design.
Section 5.5.5, Rationale for Q3W Dosing of BMS-986249 and Nivolumab in Part 2A Arm A	Added statement that as of Revised Protocol 07, no further enrollment/randomization will occur for Part 2A Arm A.	To provide rationale for modified Part 2A design.
Section 5.5.6, Rationale for Dose Selection in Part 2B	Added rationale for dose selection in Part 2B.	To provide rationale to support Part 2B design.
Section 6.1, Inclusion Criteria and Section 6.2, Exclusion Criteria	Added inclusion/exclusion criteria specific for participants with HCC, CRPC, and TNBC in Part 2B. Added that WOCBP must agree not to donate eggs for reproduction. Removed leptomeningeal metastasis as an exclusion criterion. Changed window for botanical preparations from within 4 weeks to prior to treatment to within 2 weeks prior to treatment. Clarified exclusion criterion regarding a positive test for hepatitis B virus. Updated exclusion criterion regarding a positive test for HIV.	To support introduction of Part 2B. To align with current nivolumab EPE.

Summary of key changes for Revised Protocol 07		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 7.1.1-1, Selection and Timing of Dose for All Study Parts	Added footnote b, clarifying infusion time for participants < 35 kg receiving 1,200 mg BMS-986249 + 480 mg nivolumab. Added footnote e regarding flushing of the IV line.	To increase participant convenience while maintaining safe infusion limits for those with low weight. To align with current nivolumab EPE.
Section 7.2, Method of Treatment Assignment	Added that as of Revised Protocol 07, enrollment/randomization into Part 2A Arms A, B, and E is closed and method of IRT assignment for Part 2B.	To support modification of Part 2A design and introduction of Part 2B.
Section 7.4.1.2, Hepatic Dose-limiting Toxicity	Added hepatic DLT criteria for participants with HCC.	To support HCC population in Part 2B.
Section 7.7.1, Prohibited and/or Restricted Treatments and Section 7.7.2, Permitted Therapy	Added prohibited and permitted therapies for HCC, TNBC, and CRPC participants. Added non-palliative radiation therapy as a prohibited treatment.	To support introduction of Part 2B patient populations. To align with current nivolumab EPE.
Section 9.1.1, Imaging Assessment for the Study	Removed imaging assessment schedule and added reference to Section 2. Added and moved language to support HCC, TNBC, and CRPC.	To increase readability. To support introduction of Part 2B patient populations.
Section 9.2.8, Potential Drug-induced Liver Injury	Added potential DILI criteria for HCC participants.	To support Part 2B HCC patient population.
Table 9.4.4-1, Clinical Laboratory Assessments	Added assessments to align with Section 2 Schedule of Activities.	To support introduction of Part 2B.
Section 9.5, Pharmacokinetics and Immunogenicity Assessments Table 9.5-5, PK and ADA Sampling Schedule for Part 2A Arm B and Arm C	Modified Tables 9.5-4, 9.5.-5 and 9.5-6 and footnotes (as applicable) to align with biomarker sample collection. Added Tables 9.5-8 and 9.5-9 and corresponding footnotes.	To support modification of Part 2A design and introduction of Part 2B.
Section 9.8.2, Tumor Samples	Updated tumor specimen language for Part 2A and added for Part 2B.	To support modification of Part 2A design and introduction of Part 2B.
Section 9.8.3, Gut Microbiome Analysis	Removed entire section and requirement for stool collection.	To increase participant convenience.
Table 9.8.3-1, Biomarker Sampling Schedule for All Study Parts	Removed stool collection, modified Part 2A biopsy timing, and added Part 2B biopsy collection.	To support modification of Part 2A design, introduction of Part 2B, and increased participant convenience.
Section 9.9, Patient-reported Outcomes	Added that PROs will be collected for Part 2B participants.	To support introduction of Part 2B.
Section 10.1.2.2, Changes to Sample Size Assumptions for Revised Protocol 07	Added changes to sample size assumptions for Part 2A in Revised Protocol 07.	To support modification of Part 2A design.

Summary of key changes for Revised Protocol 07		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 10.1.3, Additional Tumor Cohort Expansion (Part 2B)	Added sample size assumptions for Part 2B. Added Figures 10.1.3-1 and 10.1.3-2.	To support introduction of Part 2B.
Section 10.3, Statistical Analyses	Modified analysis details for Part 2A and added details for Part 2B.	To support modification of Part 2A design and introduction of Part 2B.
Appendix 9, Management Algorithms	Modified Appendix 9.	To support HCC participants in Part 2B.
Appendix 13, Child-Pugh Score	Added Appendix 13.	To support HCC participants in Part 2B.
Appendix 14, Country-specific Requirements/Differences	Added Appendix 14.	To support local and country-specific requirements.

Overall Rationale for the Revised Protocol 06, 05-Aug-2019

This is a revised protocol that defines the selected BMS-986249 + nivolumab doses and schedules for Part 2A Arms A - C, updates modified intermediate dose levels in Part 1B, and incorporates other minor clarifying edits.

Summary of key changes for Revised Protocol 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
Synopsis	Text in synopsis updated	Synopsis was updated to reflect the changes made in the protocol
Section 2 Schedule of Activities	Arm B reference removed from Table 2-2 and Table 2-3 and added to Table 2-4.	Updated to align and support the selected BMS-986249 + nivolumab doses and schedules for Part 2A Arms A - C.
Section 3.2.1.5 BMS-986249 Clinical Pharmacokinetics; Section 3.2.1.6 Clinical Safety Summary Section 5.4.7 Rationale for Evaluating Different Dose Levels and Schedules of BMS-986249 in Combination with Nivolumab in Part 2A Section 5.5.1.7 Rationale for Q3W dosing of BMS-986249 and Nivolumab in Part 2A Arm A	Sections updated	
Section 5.1 Overall Design; Section 5.1.2 Treatment Period; Section 5.1.2.4 The BMS-986249 Cohort Expansion Combination Therapy (Part 2)	• Updated Figure 5.1-3 • Doses and schedules for Part 2A Arms A - C defined	

Summary of key changes for Revised Protocol 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 7.1.1 Schedule of Dose for Each Investigational Product	Table 7.1.1-1 updated	
Section 7.2 Method of Treatment Assignment	Clarification added to prioritize participants in Part 2.	
Section 9.5: Pharmacokinetics and Immunogenicity Assessments	Arm B reference removed from Table 9.5-4 and added to 9.5-5	
Section 5.1 Overall Design	Updated Figure 5.1-2	Study design updated to include modified intermediate dosing cohorts in Part 1B
All	Minor formatting, typographical changes, and edits were made for consistency and clarity	Minor, therefore have not been summarized

Overall Rationale for the Revised Protocol 05, 01-May-2019

This is a revised protocol to explicitly mention encephalitis as an example of a possible neurological adverse event, updates management algorithms for immuno-oncology agents, updates PD-L1 stratification criteria for Part 2A, clarifies screening biopsy criteria for Part 2A, and incorporates other clarifying modifications.

Summary of key changes for Revised Protocol 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
Schedule of Activities Table 2-2	For Part 2A, fresh screening biopsy is optional as long as archival tissue is available and fulfills specific criteria	Align with clinical practice
Section 3.2.1.6: Clinical Safety Summary	Section added	Provide summary of Part 1 BMS-986249 doses explored and clinical safety
Section 7.4.1.5 Other Dose-limiting Toxicities	DLT criteria updated	Address protocol inconsistency and align with BMS standard language
Section 7.4.2 and Appendix 9: Management Algorithms for Immuno-oncology Agents	Added encephalitis as an example of a neurological irAE and cardiac management algorithms	Provide clarity and align with BMS standard language for increased patient safety
Schedule of Activities Table 2-2, Sections 5.1.2.4, 5.4.8.2, 5.4.8.3, 6.1, 7.2, and 9.8.2	Changed PD-L1 stratification for Part 2A from 5% to 1%	1% may be closer to medium cutoff based on prevalence
Appendix 2	Updated Serious Breach Definition	Clarity and alignment with updated SOP

Summary of key changes for Revised Protocol 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
	Updated Clinical Study Report and Scientific Publication	Updated BMS Publication Policy
All	Minor typographical errors were corrected and edits were made for consistency and clarity	Minor, therefore have not been summarized

Overall Rationale for the Revised Protocol 04, 01-Mar-2019

This is a revised protocol to define the Part 2A Expansion Phase, which includes concurrent evaluation of three different dose regimens of BMS-986249 in combination with nivolumab in relation to two standard of care reference arms in a randomized setting in melanoma. The expansion design allows for a more comprehensive understanding of the safety, efficacy, and [redacted] profile of the BMS-986249 + nivolumab combination. This may also allow for the identification of an optimized combination regimen with 1) a high exposure of BMS-986249 with nivolumab that has an acceptable safety profile and potentially increased efficacy, and 2) a lower BMS-986249 exposure in combination with nivolumab that has a potentially optimal safety and tolerability profile without a change in efficacy. This protocol revision also updates DLT criteria, updates inclusion/exclusion criteria, changes the on-treatment biopsy timing, and provides clarifications around planned dose level modifications/intermediate dose levels, and incorporates other clarifying modifications.

Summary of key changes for Revised Protocol 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 2: Schedule of Activities: All tables	Updated Section 2 Schedule of Activities to incorporate activities for Part 2A	Updated to include and support the BMS-986249 Cohort Expansion Combination Therapy Phase (Part 2) study design, especially in relation to defining the BMS-986249 in Combination with Nivolumab Randomized Cohort Expansion in Melanoma (Part 2A)
Section 3.2: Background	Added Section 3.2.2.1: Clinical Pharmacokinetics of Nivolumab and Section 3.2.4: Nivolumab Combined with Ipilimumab	
Table 4-2: Objectives and Endpoints: The Dose Expansion Phase in Melanoma (Part 2A)	Added Objectives and Endpoints for Part 2A	

Summary of key changes for Revised Protocol 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.1: Overall Design	Added figures supporting Part 2A. Updated details in the treatment period, overall design, Imaging, and added description of activities in Part 2A. Study design also updated to represent intermediate dose levels evaluated in Part 1 escalation.	
Section 5.2: Number of Participants	The number of participants was increased in Part 1, added information on the number of participants for Part 2.	
Section 5.4: Scientific Rationale for Study Design	Added individual Sections to include: • Rationale for Selecting Melanoma in Part 2A Expansion • Rationale for Testing Three Different Dose Exposures of BMS-986249 in Combination with Nivolumab in Part 2A • Rationale for Part 2A Expansion Reference Arms • Rationale for Ipilimumab and Nivolumab Combination Therapy as a Reference • Rationale for Nivolumab Monotherapy as a Reference • Rationale for Part 2A Stratification by M-Staging and PD-L1 Status • Rationale for Quality of Life Evaluation	
Section 5.5: Justification for Planned Dose Selection	Added Section 5.5.1.7: Rationale for Q3W dosing of BMS-986249 and Nivolumab in Part 2A Arm A and Arm B	
Table 7.1-1: Study Treatments for CA030001	Ipilimumab included	
Table 7.1.1-1: Selection and Timing of Dose for All Study Parts	Updated table numbering and added Timing of Dose for Part 2A	
Section 7.2: Method of Treatment Assignment	Added method of treatment assignment and randomization for Part 2A	
Section 8.1: Discontinuation from Study Treatment	Added discontinuation criteria for Part 2A	

Summary of key changes for Revised Protocol 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 9.1.1: Imaging Assessment for the Study	Added imaging details for Part 2A	
9.3: Overdose	Ipilimumab and nivolumab added	
Section 9.5: Pharmacokinetics and Immunogenicity Assessments	Tables: 9.5-4, 9.5-5, 9.5-6 and 9.5-7 added	
Section 9.8: Biomarkers	Added details of tumor collection for Part 2A, gut microbiome analysis, and updated Table 9.8.4-1.	
Section 9.9: Health Economics	Added individual Sections to include: • Patient Reported Outcomes • EORTC QLQ-C30 • EQ-5D-3L • FACIT GP5 • PRO-CTCAE	
Section 10.1: Sample Size Determination	Added Section 10.1.2: Cohort Expansion and Table 10.1.2-1 for Part 2A	
Table 10.2-1: Populations of Analyses	Added randomization for Part 2A and details about patient-reported outcome.	
Section 10.3: Statistical Analyses	Added analyses details for the randomized population for Part 2A, and updated analysis details for Part 1	
Section 10.3.8: Interim Analyses	Section updated	
Section 6.1: Inclusion Criteria	Added criteria for participants with RCC and for Part 2A. . Laboratory test findings updated.	Updated to provide clarity in enrollment criteria. Updated to support the Part 2 study design.
Section 6.2: Exclusion Criteria	Criteria regarding interstitial lung disease added. Section updated to include Part 2	
Section 7.4.1: Dose-limiting Toxicities	DLT criteria updated in Sections 7.4.1.1, 7.4.1.3, and 7.4.1.5	Modified to align with BMS standard language for increased patient safety.
Section 7.7.3: Palliative Local Therapy	Section added	Provide clarity around allowed palliative local therapy.
Section 7.7.1: Prohibited and/or Restricted Treatments	Details regarding botanical preparations added	Align with BMS standard language.
	Details regarding live/attenuated vaccine was added	
Section 9.2: Adverse Events	Updated Section 9.2.2 and Section 9.2.5	

Summary of key changes for Revised Protocol 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 9.5-3: Pharmacokinetics and Immunogenicity Assessments	Updated to include event of a Grade 3+ infusion reaction or hypersensitivity reaction	
Appendix 03: AE and SAE (Definitions and procedures for Recording, Evaluating, Follow-up, and Reporting)	Appendix was updated	Appendix was updated as part of an update to BMS protocol standards
Appendix 4: Women of Childbearing Potential Definitions and Methods of Contraception	Updated contraception guidance for female and male participants	Updated to align with revisions to the Part 2 study design and align with BMS standard language
Appendix 12: Schedule of Activities and pharmacokinetics sampling schedule for potential alternative dose schedule in CA030001	Appendix 12 was added	Dose modification language clarified throughout protocol and Appendix 12 added for increased completeness
All	Minor typographical errors were corrected and edits were made for consistency and clarity.	Minor, therefore have not been summarized.

Overall Rationale for the Revised Protocol 03, 25-May-2018

This is a revised protocol to reduce the DLT period from 8 to 5 weeks, incorporate clinic visit windows, revise participant cohort assignment, and provide clarifying modifications.

Summary of key changes for Revised Protocol 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	Title page was updated.	EUDRACT number was added.
Section 2: Schedule of Activities, Table 2-2: On Treatment - Schedule of Activities for the BMS-986249 Monotherapy Escalation (Part 1A), the Safety Evaluation of Combination Doses of BMS-986249 with Nivolumab (Part 1B), Section 5.1.2.6: Window Visits, Table 9.5-2: Pharmacokinetic and ADA Sampling Schedule for BMS-986249 Q4W Monotherapy in Dose Escalation (Part 1A), Table 9.5-3: Pharmacokinetic and ADA Sampling Schedule for BMS-986249 Q4W in Combination with Nivolumab Q4W in Dose Escalation (Part 1B), Table 9.8.3-1: Biomarker Sampling Schedule for All Study Parts	Window visits were added to permit a 2-day window for clinic visits.	Accommodate participant schedules and emerging data.
Section 3.2.1.5: BMS-986249 Clinical Pharmacokinetics, Section 5.1.2.1: The BMS-986249 Monotherapy Escalation (Part 1A), Section 5.1.2.2: The Safety Evaluation of Combination Doses of BMS-986249 with Nivolumab (Part 1B), Section 5.1.2.3: Dose Escalation Decisions for the BMS-986249 Monotherapy Escalation (Part 1A) and the Safety Evaluation of Combination Doses of BMS-986249 with Nivolumab (Part 1B), Section 7.5.1: Dose-limiting Toxicities, Section 10.1.1: Dose Escalation, [redacted]	Sections were updated to reduce DLT period from 8 to 5 weeks.	Supported by the known ipilimumab safety profile and new clinical BMS-986249 safety and pharmacokinetic data.
Section 7.3: Method of Treatment Assignment	Section was updated to change treatment assignments to prioritize Part 1B in participants eligible for both Part 1A and Part 1B.	Enable enrollment to Part 1B.

Summary of key changes for Revised Protocol 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Appendix 06: PCWG3 Guidelines (with Modified RECIST Criteria for Soft Tissue Lesion Assessment)	Appendix was updated.	Appendix was updated as part of an update to BMS protocol standards.
All	Minor typographical errors were corrected and edits were made for consistency and clarity.	Minor, therefore have not been summarized.

Overall Rationale for the Revised Protocol 02, 24-Jan-2018

This is a revised protocol to enable co-administration of BMS-986249 and nivolumab in Part 1B, expand Part 1B eligible tumor types, adjust imaging assessments, adjust biomarker requirements, and provide clarifying modifications.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Synopsis	Synopsis was updated.	Synopsis was updated to reflect the changes made to the protocol.
Table 2-1: Screening Schedule of Activities for All Study Parts	Bone scan and consent for post-progression tumor biopsy were updated.	Bone scan was updated to clarify the requirement for prostate cancer only. Consent for post-progression tumor biopsy was updated as mandatory.
Table 2-2: On Treatment - Schedule of Activities for the BMS-986249 Monotherapy Escalation (Part 1A), the Safety Evaluation of Combination Doses of BMS-986249 with Nivolumab	Body imaging, bone scan, and post-progression tumor biopsy were updated.	Body imaging was updated to clarify the change in frequency of scans up to Week 48 versus thereafter. Bone scan was updated to clarify the requirement for prostate cancer only. Post-progression tumor biopsy was updated as mandatory.
Table 2-3: Follow-up Procedural Outline for All Study Parts	Response Follow-up was changed to Imaging Follow-up. Tumor/response assessments was updated.	Response Follow-up was changed to Imaging Follow-up to clarify the follow-up period. Tumor/response assessments was updated to clarify the change in frequency of scans.
Table 4-1: Objectives and Endpoints	Objectives and endpoints were updated.	Secondary objective was updated to clarify use of RECIST v1.1 and PCWG3 and exploratory objective was updated to clarify use of iRECIST and PCWG3.
Figure 5.1-1: Study Design Schematic	Study design schematic was updated.	Study design schematic was updated to include Part 1B expansion tumor types.
Figure 5.1-2: Study Period and Participant Flow	Study period and participant flow schematic was updated.	Study period and participant flow schematic was changed from response follow-up to imaging follow-up to clarify the follow-up period.
Section 5.1.2: Treatment Period	Treatment period was updated.	Treatment period was updated to correct the cycle during the treatment period and for Part 1B to utilize co-administration of BMS-986249 + nivolumab and clarify the frequency of tumor assessments.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.1.2.1: The BMS-986249 Monotherapy Escalation (Part 1A)	Number of participants was updated.	Number of participants was updated to align with the protocol.
Section 5.1.2.2: The Safety Evaluation of Combination Doses of BMS-986249 with Nivolumab (Part 1B)	Imaging assessments were updated.	Imaging was updated to clarify the change in frequency of scans up to Week 48 versus thereafter.
Section 5.1.2.5: Treatment Beyond Progression	Tumor progression and response endpoints were updated.	Tumor progression and response endpoints were updated to add PCWG3 for prostate cancer.
Section 5.1.3.2: ImagingFollow-up Period	Imaging follow-up period was updated.	Imaging follow-up period was updated to clarify the follow-up period and the change in frequency of scans up to Week 48 versus thereafter.
Section 5.4.3: Rationale for Tumor Selection for Part 1B	Rationale for tumor selection for Part 1B was added.	Rationale for tumor selection for Part 1B was added for tumor expansion.
Section 5.4.4: Rationale for Treatment Duration	Rationale for treatment duration was updated.	Rationale for treatment duration was updated to address 2 year treatment duration.
Section 5.5.1.5: Rationale for BMS-986249 and Nivolumab 30-minute Infusion	Rationale for 30-minute infusion was updated.	Rationale for 30-minute infusion was updated ton indicate that nivolumab is currently approved for IV administration over 30 minutes for select indications.
Section 5.5.1.6: Rationale for BMS-986249 and Nivolumab Co-administration	Rationale for BMS-986249 and nivolumab co-administration was added.	Rationale for BMS-986249 and nivolumab co-administration was added to address the advantages and overall safety profile.
Section 6.1: Inclusion Criteria	Inclusion criterion 1)b), 2)a), and 4)g) were updated and criterion 2)d)i), 2)d)ii), 2)d)ii)1), 2)d)iii)1-2), 2)d)v)1-3), 2)d)vi)1-2), and 2)d)vii)1-2 were added.	Inclusion criteria 1)b) was updated to make progression tumor biopsy samples mandatory, 2)a) was updated to add PCWG3 for prostate cancer, and 4)g) was updated to remove WOCBP exemption. Criterion 2)d)i), 2)d)ii), 2)d)ii)1), 2)d)iii)1-2), 2)d)v)1-3), 2)d)vi)1-2), and 2)d)vii)1-2 were added or updated for Part 1B tumor expansion.
Section 6.2: Exclusion Criteria	Exclusion criteria 2)b)i) was added.	Exclusion criteria 2)b)i) was added for Part 1B tumor expansion.
Table 7.2-1: Selection and Timing of Dose for All Study Parts	Selection and timing of dose for all study parts was updated.	Selection and timing of dose for all study parts was updated to add co-

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
		administration of BMS-986249 + nivolumab.
Section 7.5.3: Dose Delays Due to Toxicity	Imaging assessments were updated.	Imaging was updated to clarify the change in frequency of scans up to Week 48 versus thereafter.
Section 7.6: Preparation/ Handling/Storage/Accountability	Section was updated to remove ipilimumab.	Section was updated to remove ipilimumab to reflect the protocol.
Section 7.8.1: Prohibited and/or Restricted Treatments	Concurrent anti-neoplastic therapy was updated.	Concurrent anti-neoplastic therapy was updated to address Part 1B tumor expansion in CRPC.
Section 8.1: Discontinuation from Study Treatment	Documented disease progression was updated.	Documented disease progression was updated to add PCWG3 for prostate cancer.
Section 8.1.1: Treatment Beyond Progression	Documented disease progression was updated.	Documented disease progression was updated to add PCWG3 for prostate cancer.
Section 8.1.1.1: Discontinuation Due to Further Progression (Confirmed Progression)	Follow-up scan and subsequent scans were updated and addressing new lesions was added.	Follow-up scan and subsequent scans were updated to clarify that the scans should be performed until further progression is determined and address new lesions and PCWG3 was added for prostate cancer.
Section 9.1: Efficacy Assessments	Efficacy assessments were updated.	Efficacy assessments were updated to add PCWG3 for prostate cancer and use of iRECIST using BICR as an exploratory objective.
Section 9.1.1: Imaging Assessment for the Study	Imaging assessments were updated.	Imaging was updated to clarify the change in frequency of scans up to Week 48 versus thereafter and prostate cancer requirements.
Section 9.2.1: Time Period and Frequency for Collecting AE and SAE Information	SAEs occurring after the start of a new anti-neoplastic therapy was updated.	SAEs occurring after the start of a new anti-neoplastic therapy was updated from ‘will’ to ‘should.’
Section 9.5: Pharmacokinetic and Immunogenicity Assessments	PK and ADA samples for co-administration of BMS-986249 + nivolumab were added.	PK and ADA samples for co-administration of BMS-986249 + nivolumab were added.
Table 9.5-2: Pharmacokinetic and ADA Sampling Schedule for BMS-986249 Q4W Monotherapy in Dose Escalation (Part 1A)	Table was updated.	Table was updated to clarify the time was relative to the start of infusion.
Table 9.5-3: Pharmacokinetic and ADA Sampling Schedule for BMS-986249 Q4W in	Table was updated.	Table was updated to clarify the time was relative to the start of

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Combination with Nivolumab Q4W in Dose Escalation (Part 1B)		infusion and sample schedule was updated.
Section 9.8: Biomarkers	Biomarker measures were updated.	Biomarker measures were updated to add upon disease progression.
Section 9.8.2: Tumor Samples	Tumor samples were updated.	Tumor samples were updated to add screening and upon disease progression fresh biopsy specimens and add tumor biopsy requirements.
Table 9.8.3-1: Biomarker Sampling Schedule for All Study Parts	Table was updated.	Sample schedule was updated and plasma sample analysis was clarified.
Table 10.3.1-1: Efficacy - Statistical Analyses	Table was updated.	Table was updated to add PCWG3 for prostate cancer.
Section 10.3.3: Pharmacokinetic Analysis for BMS-986249	Section was updated to remove ipilimumab.	Section was updated to remove ipilimumab to reflect the protocol.
Appendix 1: Abbreviations	Abbreviations were updated.	New abbreviations were added.
Appendix 6: PCWG3 Guidelines (with Modified RECIST Criteria for Soft Tissue Lesion Assessment)	Appendix was added.	Appendix was added for Part 1B tumor expansion into prostate cancer.
All	Minor typographical use of the words participants, patients, and subjects were made for consistency and clarity.	Minor, therefore have not been summarized

Overall Rationale for the Revised Protocol 01, 20-Nov-2017

The revised protocol addresses questions provided by the US FDA and fixes some typographical errors present in the original protocol. These apply to all participants.

Summary of key changes of Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
6.1: Inclusion Criteria, 2), d), iii)	Inclusion criteria updated: urothelial carcinoma patients must have received, and then progressed, relapsed, been intolerant to, or ineligible for, at least 1 platinum-containing chemotherapy regimen.	Inclusion criteria was updated to ensure that patients received appropriate prior therapy.
6.1: Inclusion Criteria, 2), c), ii)	Inclusion criteria updated: breast cancer patients must have received or been intolerant to, all approved standard systemic treatments that have shown a documented benefit in overall survival per product label.	Inclusion criteria was updated to ensure that patients received appropriate prior therapy.
Synopsis, 5.1.2: Treatment Period, Table 7.2-1	Added specific infusion times for specific doses of BMS-986249	Infusion times for escalating doses need to be increased because of endotoxin limitations
7.5.1.1: Gastrointestin-al Dose Limiting Toxicity	Added Grade 4 diarrhea or colitis, regardless of duration	Added for participant safety
7.5.1.3: Hematologic Dose Limiting Toxicity	Changed to neutropenic fever of any duration	Added for participant safety
7.5.1.5: Other Dose Limiting Toxicities	Added any death not clearly due to the underlying disease or extraneous causes	Added for participant safety
7.5.1.5: Other Dose Limiting Toxicities	The following Grade 3 or 4 events will not be considered DLTs: grade 3 fatigue lasting < 1 week	Added for participant safety
7.5.1.5: Other Dose Limiting Toxicities	Section has been revised and text has been added to provide general guidance for management of potential ocular adverse events	Added for participant safety
7.5.4: Exceptions to Permanent Discontinua-tion Criteria	The following event will not lead to permanent discontinuation: Grade 3 fatigue < 1 week	To be consistent with comment above for Section 7.5.1.5
8.1: Discontinua-tion from Study Treatment	Provide guidance for investigators to help distinguish adverse events due to BMS-986249 from those due to nivolumab.	General guidance and specific imAE and AE profiles were added

Summary of key changes of Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
9.8.2: Tumor Samples	Added fresh tumor biopsy specimens will be obtained prior to treatment to characterize immune cell populations and expression of selected tumor markers including dMMR and MSI-H.	Further clarify which tumor markers will be investigated
Tables 2-2 and 2-3 and Section 9.1.1 Imaging Assessment for the Study	Corrected imaging assessment timing to Q8W and inserted: and at the Sponsor's discretion, may be reviewed by blinded independent central review at a later date or at any time during the study, for image review	Corrected typographical errors and added clarifying language
Tables 2-2, 9.8.3-1, and 9.8.4-1	Corrected on-treatment biopsy timing [redacted]	Corrected typographical errors
All	Minor formatting and typographical corrections	Minor, therefore have not been summarized