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CLINICAL PROTOCOL CA043001

A Phase 1/2 First-in-human Study of BMS-986288 Alone and in Combination with Nivolumab in Advanced Malignant Tumors

Short Title: An Investigational Immunotherapy Study of BMS-986288 Alone and in Combination With Nivolumab in Advanced Solid Cancers

Protocol Amendment: 03
Incorporates Administrative Letters 03, 04, and 05

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DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Protocol Amendment 03	24-Mar-2023	The key change in this protocol amendment is the addition of a new randomized cohort of microsatellite stable colorectal cancer participants for dose expansion (Part 2C) and relevant study procedures and requirements. This protocol amendment also removes severe acute respiratory syndrome coronavirus 2 serology collection requirement, modifies biomarker sample collection plan to reduce participant burden, allows selective backfill after selected dose levels are demonstrated safe, and updates secondary and exploratory endpoints.
Administrative Letter 05	17-Jun-2022	Updated contact information for Clinical Trial Physician - Medical Monitor.
Administrative Letter 04	01-Apr-2022	Updated contact information for Clinical Trial Physician - Medical Monitor.
Administrative Letter 03	24-Sep-2021	Provided EUDRACT Number for the study.
Protocol Amendment 02	22-Jul-2021	Key changes include the addition of new dose levels for dose escalation (Part 1) and clinical outcomes assessments and new indications for dose expansion (Part 2). Other changes have been made to align dose modification criteria and immuno-oncology agent management algorithms with the current CTCAE v5, address COVID-19 infection and vaccination, clarify expectations for safety assessments, and remove male contraceptive requirements. This amendment incorporates Administrative Letter 02.
Administrative Letter 02	15-Jan-2021	Corrected a misspelling in the inclusion criteria for participants with colorectal cancer.
Revised Protocol 01	11-Jun-2019	[redacted] incorporated Administrative Letter 01, and ensured that the protocol is consistent with internal BMS policies and operating procedures.
Administrative Letter 01	15-May-2019	To add clarity to the infusion times associated with a range of doses.
Original Protocol	27-Mar-2019	Not applicable

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 03:

The key change in this protocol amendment is the addition of a new randomized cohort of microsatellite stable (MSS) colorectal cancer (CRC) participants for dose expansion (Part 2C) and relevant study procedures and requirements. This protocol amendment also removes the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) serology collection requirement, modifies the biomarker sample collection plan to reduce participant burden, allows selective backfill after selected dose levels are demonstrated safe, and updates secondary and exploratory endpoints.

Additional revisions, including revisions to the Protocol Summary, have been made to align the protocol with respect to the changes listed below. Minor formatting and typographical corrections have been made throughout and have not been summarized.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 03

Section Number & Title	Description of Change	Brief Rationale
Table 2-1: Screening Schedule of Activities for All Study Parts	• Removed manual enrollment option. • Added instruction to specify systemic and local therapy.	• To align with current enrollment process. • Added to ensure relevant data are collected for future analysis.
Table 2-1: Screening Schedule of Activities for All Study Parts Table 2-2: On-Treatment - Schedule of Activities for All Study Parts Table 2-3: Follow-up Procedural Outline for All Study Parts Section 3.3: Benefit-Risk Assessment Table 4-1: Objectives and Endpoints Section 5.1: Overall Design Figure 5.1-1: Study Design Schematic Figure 5.1-2: Study Design Schematic for Expansion Part 2C	Added Part 2C Cohort (BMS-986288 in combination with nivolumab [Arm C] or regorafenib [Arm D]) for MSS CRC participants. If more than 1 dose level is evaluated, additional participants may be enrolled in a separate arm (Arm E) in Part 2C. Participants on Arm D will have the option to transition to BMS-986288 in combination with	To explore the safety and efficacy of BMS-986288 in combination with nivolumab in MSS CRC participants based on emerging data.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.1.2: Treatment Period Section 5.1.2.3: The Expansion Phase of BMS-986288 [redacted] (Part 2A) [redacted] Nivolumab (Part 2B and Part 2C Arm C, Arm E, and Arm Z) Section 5.2: Number of Participants Section 5.4.3: Rationale for Tumor Selection in Part 2C Section 5.4.4: Rationale for Randomization in Part 2C Section 5.4.6: Rationale for Two Years Fixed Duration with Checkpoint Blockade Section 5.4.7: Rationale for Quality of Life Evaluation Section 5.4.8: Rationale for Using a [redacted] Arm Section 5.5.3: Rationale for BMS-986288 Dose Selection in Part 2C Section 5.5.4.5: Rationale for [redacted] Section 5.5.4.6: Rationale for Choice of Standard of Care Treatment in Part 2C Section 5.5.4.7: Rationale for KRAS Testing Section 5.5.4.8: Rationale for [redacted] Testing Section 5.5.4.9: Rationale for Dose Selection of Regorafenib and Line of Therapy (in 3rd/4th Line MSS CRC) Section 6.1: Inclusion Criteria	nivolumab upon progression (Arm Z).	

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 6.2: Exclusion Criteria Section 7: Treatments Administered Table 7-1: Investigational Product Description for CA043001 Table 7.1-1: Selection and Timing of Dose Section 7.1: Schedule of Dose for Each Investigational Product Section 7.2: Method of Treatment Assignment Section 7.4: Dosage Modification Section 7.4.6: Dose Modification for Regorafenib Section 7.7.2: Permitted Therapy Section 8.1: Discontinuation from Study Treatment Section 9.1: Efficacy Assessments Section 9.1.1: Imaging Assessment for the Study Section 9.1.2.2: EQ-5D-5L Section 9.2: Adverse Events Section 9.2.5: Pregnancy Section 9.3: Overdose Table 9.4.5-1: Clinical Laboratory Assessments Table 9.5-4: PK and ADA Sampling Schedule for BMS-986288 [redacted] in Combination with Nivolumab [redacted] Cohort Expansion (Part 2C		

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Arm C, Arm E, and Arm Z) [redacted] Table 9.8.3-1: Biomarker Sampling Schedule for [redacted] Dosing Schedule for Part 1, Part 2A, Part 2B, and Part 2C Arm C, Arm E, and Arm Z Table 9.8.3-2: Biomarker Sampling Schedule for [redacted] Dosing Schedule for Part 2C Arm D Section 10.1.6: The BMS-986288 in Combination with Nivolumab Cohort Expansion in MSS CRC Participants (Part 2C) Table 10.3.1-1: Efficacy - Statistical Analyses Table 10.3.8.1-1: Monitoring Boundaries for Treatment-related Toxicities Meeting DLT Criteria in Part 2		
Table 2-1: Screening Schedule of Activities for All Study Parts Table 2-2: On-Treatment - Schedule of Activities for All Study Parts Table 2-3: Follow-up Procedural Outline for All Study Parts Section 9.1.1: Imaging Assessment for the Study	Updated imaging language.	To clarify imaging modalities to be used at screening, on-treatment, and follow-up phase of the study. Clarification from which date (date of first dose) the brain imaging interval is to be calculated.
Table 2-1: Screening Schedule of Activities for All Study Parts	Removed screening, on-treatment, and follow-up SARS-CoV-2	To remove serology as the impact of SARS-CoV-2 serology status on study is no longer in the scope, due to the population having already had SARS-CoV-2 infections.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-2: On-Treatment - Schedule of Activities for All Study Parts Table 2-3: Follow-up Procedural Outline for All Study Parts Section 3.3: Benefit-Risk Assessment Table 4-1: Objectives and Endpoints Table 9.8.3-1: Biomarker Sampling Schedule for [redacted] Dosing Schedule for Part 1, Part 2A, Part 2B, and Part 2C Arm C, Arm E, and Arm Z Section 9.8.4.1: Exploratory Serum and Plasma Biomarkers Appendix 8: Schedule of Activities, Pharmacokinetics Sampling Schedule, and Biomarker Sampling Schedule for Potential Alternative Dose Schedules in CA043001	serology assessments. Section 9.8.4.1: Exploratory Serum and Plasma Biomarkers was removed.	
Table 2-2: On-Treatment - Schedule of Activities for All Study Parts Section 9.8: Biomarkers Section 9.8.3: Gut Microbiome Analysis Table 9.8.3-1: Biomarker Sampling Schedule for [redacted] Dosing Schedule for Part 1, Part 2A, Part 2B, and Part 2C Arm C, Arm E, and Arm Z Appendix 8: Schedule of Activities, Pharmacokinetics Sampling Schedule, and	Removed stool sample collection. Section 9.8.3: Gut Microbiome Analysis was removed.	To reduce study burden on participants.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Biomarker Sampling Schedule for Potential Alternative Dose Schedules in CA043001		
Table 4-1: Objectives and Endpoints	• Removed incidence of anti-drug antibody (ADA) from secondary endpoint. • Moved "To measure [redacted] and assess [redacted] change over time and in association with response" objective and endpoint from secondary to exploratory.	• To remove redundancy with exploratory endpoint of ADA incidence of nivolumab and BMS-986288, as immunogenicity characterization is an exploratory objective. • Measurement of [redacted] has been changed from a secondary to an exploratory endpoint due a lack of clear association of [redacted] with clinical response. There is no impact to study participants, as treatment decisions are not guided by the use of biomarkers.
Table 4-1: Objectives and Endpoints Section 9.8: Biomarkers [redacted]	Removed [redacted] expression and [redacted] specific genes.	To clarify that tumor specific expression is no longer in the biomarker analysis scope and has not been associated with response.
Figure 5.1-1: Study Design Schematic	Updated study design schematic.	To clarify study design and reflect Part 1B intermediate dose level and Part 2B selected dose level, and addition of the new cohort.
Section 5.1.2.1: Dose-Escalation Decisions for the BMS-986288 Monotherapy Escalation (Part 1A) and the Safety Evaluation of BMS-986288 in Combination with Nivolumab (Part 1B)	Added that Sponsor may choose to enroll only certain cancer types from dose escalation during the backfill, based on emerging data.	To allow the option to focus on indications of interest to gather more pharmacokinetic/pharmacodynamic/safety/efficacy data after the dose levels are demonstrated as tolerable.
Section 5.4.9: Rationale for Not Blinding	Added section.	To clarify that the study will be open label in order to facilitate safety monitoring by the Sponsor and to ensure adequate ability of the clinical trial physician

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
		to monitor and discuss the management of the participants with the investigators.
Table 7-1: Investigational Product Description for CA043001	Updated vial information for nivolumab.	To clarify for operational efficiency that only 100-mg vials of nivolumab will be provided for this study. There is no use for the 40-mg vials moving forward.
Section 9.1.1.1: Methods of Measurement	Added clarification that use of other imaging modalities in case of contrast contraindication is a guideline and is not mandatory.	To clarify that this section is to be used as guidance and not be considered a protocol deviation in case of the selection of a different modality based on participant-specific factors or local guidelines when a participant has an imaging contraindication.
Section 9.8.1.3: [redacted] Analysis	Added "or RNA."	To add flexibility and clarify that [redacted] receptor sequence analysis can be performed from extracted deoxyribonucleic acid or RNA material.
[redacted]		
Section 9.8.2.2: Characterization of [redacted]	Updated language regarding [redacted] may be performed on pre- and post-treatment [redacted] and/or [redacted] samples.	To represent that [redacted] technology can utilize both [redacted] material.
Table 9.8.3-1: Biomarker Sampling Schedule for [redacted] Dosing Schedule for Part 1, Part 2A, Part 2B, and Part 2C Arm C, Arm E, and Arm Z	Updated biomarker sampling schedule.	To reduce study burden on participants.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 10.3.8: Interim Analyses	Added details of the planned interim analyses.	To describe the planned interim analyses.
Appendix 2: Study Governance Considerations	Added new sections on Bristol Myers Squibb commitment to diversity in clinical trials and data protection, data privacy, and data security.	To align with BMS practice and comply with European Union Clinical Trials Regulation requirement.
Appendix 11: Country-specific Requirements/Differences	Added new appendix.	[redacted]

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1 SYNOPSIS

Protocol Title: A Phase 1/2 First-in-human Study of BMS-986288 Alone and in Combination with Nivolumab in Advanced Malignant Tumors

Short Title: An Investigational Immunotherapy Study of BMS-986288 Alone and in Combination With Nivolumab in Advanced Solid Cancers

Study Phase: Phase 1/2

Rationale:

This is a Phase 1/2, first-in-human study of BMS-986288, a non-fucosylated (NF) Probody™ variant of ipilimumab, administered alone and in combination with nivolumab in humans with select advanced solid tumors: squamous cell carcinoma of the head and neck (SCCHN), non-small cell lung cancer (NSCLC), cutaneous melanoma, triple-negative breast cancer (TNBC), renal cell carcinoma (RCC), urothelial carcinoma, gastric, esophageal, cervical, and colorectal cancer (CRC).

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 (anti-programmed cell death 1 [PD-1] mAb) results in clinically meaningful anti-tumor activity in several malignancies; however, treatment is also associated with a high frequency of immune-related adverse events (irAEs). Strategies to reduce the frequency and severity of ipilimumab-associated irAEs and increase the breadth and depth of anti-tumor activity could improve the benefit-risk of anti-CTLA-4 containing treatment regimens.

BMS-986288 is an anti-CTLA-4 NF Probody mAb (PROBODY is a trademark of CytomX Therapeutics, Inc.). Unlike ipilimumab, BMS-986288 [redacted] on the heavy chain, and is predicted to harbor a higher affinity for [redacted] and improve [redacted]. 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 mAb ipilimumab, which 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.

The properties of BMS-986288 (anti-CTLA-4 NF Probody mAb) include: [redacted] (as the Probody form) to human CTLA-4 protein compared to ipilimumab; [redacted] compared to ipilimumab; higher [redacted] activity than ipilimumab in a [redacted] assay; increased anti-tumor activity compared to ipilimumab in [redacted] tumor models; and [redacted] peripheral pharmacodynamic activity compared to ipilimumab based on analysis of extratumoral [redacted] populations. These properties support the hypothesis that BMS-986288 can potentially [redacted] the depth and breadth of response by combining CTLA-4 blockade with the [redacted] in the tumor microenvironment, while [redacted] systemic exposure to the active species and potentially reducing the risk of autoimmune side effects normally seen after ipilimumab treatment. This potentially improved [redacted] is especially important because of the promise of combination immunotherapy approaches, [redacted].

Based on this unique mechanism of action, this study will evaluate the safety and preliminary efficacy of BMS-986288 alone and in combination with nivolumab.

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 Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and have at least 1 soft tumor tissue lesion accessible for biopsy.

Objectives and Endpoints:

The objectives and endpoints for primary, secondary, and exploratory analyses for this study are shown in Table 1.

Table 1: Objectives and Endpoints

Objectives	Endpoints
For Part 1, 2A, 2B • **Primary** • To characterize the safety, tolerability, and DLTs and to determine the MTD/RP2D of BMS-986288 administered as monotherapy and in combination with nivolumab in participants with select advanced solid tumors	• Incidence of AEs, SAEs, AEs meeting protocol-defined DLT criteria, AEs leading to discontinuation, and death.
For Part 1, 2A, 2B **Secondary** • To characterize the PK of BMS-986288 when administered alone and in combination with nivolumab • To assess the preliminary efficacy of BMS-986288 alone and in combination with nivolumab in advanced solid tumors using RECIST v1.1	• Summary measures of PK parameters of BMS-986288 • ORR, DOR, PFS, and TTR per RECIST v1.1 by Investigator assessment
For Part 1, 2A, 2B **Exploratory** • To explore the potential association between anti-tumor activity and pharmacodynamic markers, such as, but not limited to, [redacted] prior to treatment and following administration of BMS-986288 alone and in combination with nivolumab • To explore the associations between BMS-986288 PK, safety, efficacy, and clinical biomarkers • To characterize the immunogenicity of BMS-986288 and nivolumab • To assess the preliminary efficacy of BMS-986288 alone and in combination with nivolumab in select advanced solid tumors using iRECIST • To assess the OS in participants treated with BMS-986288 alone and in combination with nivolumab • To assess the potential effect of BMS-986288 when administered [redacted] on the QTc interval • To characterize the PK and bioavailability of BMS-986288 when administered [redacted] • To explore the impact of treatment on NSCLC participant-reported symptoms and health-related quality of life (Part 2A and Part 2B only) • To explore participant overall perception of bother in relation to treatment-related symptomatic side effects (Part 2A and Part 2B only) • To explore overall health status (Part 2A and Part 2B only) • To measure [redacted], and assess [redacted] change over time and in association with response	• Summary measures of anti-tumor activity by pretreatment level of biomarkers of interest; correlation/measure of association of anti-tumor activity and change (or % change) from baseline in biomarkers of interest • Association measures between BMS-986288 PK levels by [redacted] select outcomes, and biomarkers of interest • Incidence of ADA to nivolumab and BMS-986288 • ORR, DOR, and PFS per iRECIST by BICR • OSR at 1 year and 2 years • Summary measures of ECG parameters and changes in QTcF (ΔQTcF) from baseline • Summary of PK parameters when BMS-986288 is administered [redacted] alone or in combination with nivolumab • Mean NSCLC-SAQ scores and change from baseline scores • Proportion of participants endorsing each response option of the FACIT GP5 • Mean EQ-5D-5L utility index scores and EQ-5D-VAS scores and change from baseline scores • Summary measures of [redacted] and correlation/ measure of association of anti-tumor activity and change (or % change) from baseline in [redacted]

Table 1: Objectives and Endpoints

Objectives	Endpoints
For Part 2C **Primary** • To compare the efficacy of BMS-986288 in combination with nivolumab vs regorafenib in the 3L/4L MSS CRC setting.	• ORR per RECIST v1.1 by BICR
For Part 2C **Secondary** • To compare the efficacy of BMS-986288 in combination with nivolumab vs regorafenib in the 3L/4L MSS CRC setting • To characterize the safety and tolerability of BMS-986288 in combination with nivolumab vs regorafenib in the 3L/4L MSS CRC setting	• DOR and PFS per RECIST v1.1 by BICR, and OS • ORR, DOR, and PFS per RECIST v1.1 by Investigator assessment • Incidence of AEs, SAEs, AEs meeting protocol-defined DLT criteria, AEs leading to discontinuation, and death
For Part 2C **Exploratory** • To compare the efficacy of BMS-986288 in combination with nivolumab vs regorafenib in the 3L/4L MSS CRC setting in subgroups of [redacted] • Explore the association between response with both baseline and pharmacodynamic markers in the [redacted] and the [redacted] • To evaluate BMS-986288 PK in the MSS CRC setting in combination with nivolumab • To evaluate immunogenicity of BMS-986288 and nivolumab when administered as combination • To explore the exposure-response relationship for BMS-986288 when given as combination with nivolumab	• ORR, DCR, DOR, PFS by BICR, and OS in the subgroups of [redacted] participants • Summary measures of change (or % change) from baseline in parameters of interest and correlation/measure of association of response and pharmacodynamic markers • Summary measures of PK parameters from population PK analysis • Summary of ADA incidence and association with PK, efficacy, hypersensitivity, and infusion-related safety events • Exposure-response relationship for efficacy endpoints including ORR and PFS. • Exposure-response relationship for safety endpoints including TRAE Grade 3+ and dose modification due to TRAE.

Abbreviations: 3L/4L = 3rd line/4th line; ADA = anti-drug antibody; AE = adverse event; BICR = blinded independent central review; BMS = Bristol-Myers Squibb; CRC = colorectal cancer; DCR = disease control rate; DOR = duration of response; DLT = dose-limiting toxicity; ECG = electrocardiogram; EQ-5D-5L = 5-Level EQ-5D; EQ-5D-VAS = EQ-5D Visual Analog Scale; FACIT GP5 = Functional Assessment of Chronic Illness Therapy, General Physical item; IgG = immunoglobulin G; iRECIST = modified RECIST in cancer immunotherapy trials; MSS = microsatellite stable; MTD = maximum tolerated dose; NSCLC-SAQ = Non-small Cell Lung Cancer Symptom Assessment Questionnaire; ORR = objective response rate; OS = overall survival; OSR = overall survival rate; 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; SAE = serious adverse event; [redacted] TRAE = treatment-related adverse event; [redacted] TTR = time to response.

Overall Design:

This is a Phase 1/2, open-label study of BMS-986288, administered as a single agent and in combination with nivolumab in participants with select advanced solid tumors (SCCHN, NSCLC, cutaneous melanoma, RCC, CRC, TNBC, urothelial carcinoma, gastric, esophageal, and cervical cancer).

The study is composed of 2 parts: dose escalation (Part 1) and initial dose expansion (Part 2). In the dose-escalation phase, BMS-986288 will be administered intravenously (IV) alone (Part 1A) or in combination with nivolumab (Part 1B). [redacted] administration of BMS-986288 as a monotherapy or in combination with nivolumab may also be evaluated [redacted]. In the initial dose-expansion phase, cohorts of BMS-986288 [redacted] (Part 2A), and in combination with nivolumab (Part 2B and Part 2C Arm C and Arm E) will be expanded to gather additional safety, tolerability, preliminary efficacy, pharmacokinetics (PK), and pharmacodynamic information in specific participant populations. In Part 2C, (randomized microsatellite stable [MSS] CRC cohort), Arm D standard of care (regorafenib) will be given. Participants in Part 2C Arm D receiving regorafenib will have the option to transition to BMS-986288 in combination with nivolumab (Part 2C Arm Z) after BICR-assessed progression. An additional dose of BMS-986288 in combination with nivolumab may be open as Arm E.

All participants will complete up to 3 study periods: Screening (up to 30 days), Treatment (up to [redacted] cycles, [redacted] days/cycle), and Follow-up (comprised of Safety [100 days], Imaging [up to 2 years], and Survival [up to 2 years] following end of treatment [EOT]). The duration of study participation will be approximately 4 years (treatment of up to 2 years and follow-up of up to 2 years).

Images will be submitted to a central imaging vendor and may undergo Blinded Independent Central Review at any time during the study. Prior to scanning first participant, sites should be qualified and understand the image acquisition guidelines and submission process as outlined in the CA043001 Imaging Manual provided by the central imaging vendor.

Number of Participants:

The approximate total number of evaluable participants will be up to [redacted], as shown below:

- Part 1 - Escalation Phase: Up to approximately [redacted] DLT-evaluable participants may be treated, including:
  - Part 1A - Safety Evaluation of BMS-986288 Monotherapy Escalation: Up to [redacted] evaluable participants
  - Part 1B - Safety Evaluation of BMS-986288 in Combination with Nivolumab: Up to [redacted] evaluable participants
  - [redacted] Evaluation of BMS-986288 as a Monotherapy and in Combination with Nivolumab: Up to [redacted] evaluable participants
- Part 2 - Initial Expansion Phase: Up to [redacted] evaluable participants may be treated, including:
  - Part 2A Cutaneous Melanoma - BMS-986288 [redacted] Cohort Expansion: Up to [redacted] participants with cutaneous melanoma
  - Part 2A NSCLC - BMS-986288 [redacted] Cohort Expansion: Up to [redacted] participants with NSCLC will be treated. If more than 1 dose level is evaluated, additional participants (up to [redacted] participants per dose level) may be enrolled, up to [redacted] participants (eg, [redacted] participants × 2 arms)
  - Part 2B - BMS-986288 in Combination with Nivolumab Cohort Expansion: Up to [redacted] participants with NSCLC will be treated. If more than 1 dose level is evaluated, additional participants (up to [redacted] participants per dose level) may be enrolled, up to [redacted] participants (eg, [redacted] participants × 2 arms)
  - Part 2C randomized MSS CRC cohort:
    - Arm C - BMS-986288 in combination with nivolumab: up to [redacted] participants will be treated.
    - Arm D - standard of care: up to [redacted] participants will be treated with regorafenib. Participants will have the option to transition to BMS-986288 in combination with nivolumab upon progression (Arm Z).
    - If more than 1 dose level is evaluated, additional participants (up to [redacted] participants) may be enrolled in a separate arm (Arm E) in Part 2C.

Treatment Arms and Duration:

Part 1: The Dose-Escalation Phase is where the dose of BMS-986288 will be administered IV alone (Part 1A) or in combination with nivolumab (Part 1B). [redacted] administration of BMS-986288 as a monotherapy (Arm A) or in combination with nivolumab (Arm B) may also be evaluated [redacted]

- The BMS-986288 Monotherapy Escalation (Part 1A) will escalate the dose of BMS-986288 to determine the monotherapy maximum tolerated dose (MTD)/recommended Phase 2 dose (RP2D). Specifically, the Part 1A dose escalation will evaluate different doses of BMS-986288 starting at [redacted] mg, followed by [redacted]. If it appears that a planned dose level is associated with an unacceptable frequency of toxicities, then an intermediate dose or alternative administration schedule may be evaluated, and will not initially exceed a dose determined to be tolerable. After preliminary evaluation of safety and PK data from these intermediate dose or alternative administration schedules, re-escalating doses of BMS-986288 may be initiated. The study will first evaluate the safety and tolerability of BMS-986288 monotherapy based on dose-limiting toxicities (DLTs), using a Bayesian Logistic Regression Model (BLRM) employing the escalation with overdose control (EWOC) principle, and overall assessment of available safety, PK, and pharmacodynamic data.
- The Safety Evaluation of BMS-986288 in Combination with Nivolumab (Part 1B) will evaluate the safety and tolerability of various doses of BMS-986288 in combination with nivolumab to determine the combination MTD/RP2D. Treatment in Part 1B will be initiated in a staggered manner relative to the BMS-986288 Monotherapy Escalation (Part 1A). Specifically, Part 1B can be initiated upon the decision to escalate when at least 2 dose levels in Part 1A have cleared the DLT period in accordance with dose escalation rules, after which dose escalation in Part 1A and Part 1B will proceed in parallel. At no point will the dose of BMS-986288 administered in combination with nivolumab in Part 1B exceed the highest safe dose in ongoing monotherapy dose escalation in Part 1A or the highest dose determined to be tolerated in Part 1A. In Part 1B, the dose of BMS-986288 will be escalated, whereas the dose of nivolumab will be [redacted]. However, if it appears that a planned dose level is associated with an unacceptable frequency of toxicities, then an intermediate dose, additional cohorts of alternative BMS-986288 administration schedules, or de-escalating doses of nivolumab may be evaluated, and potential re-escalating doses of BMS-986288 may then be initiated. The safety and tolerability of the BMS-986288 combination with nivolumab will be evaluated using a BLRM-copula employing the EWOC principle, and an overall assessment of available safety, PK, and pharmacodynamic data.
- The [redacted] Evaluation of BMS-986288 as a Monotherapy and/or in Combination with Nivolumab [redacted] may be conducted to obtain preliminary data on the safety, tolerability, PK, bioavailability, and pharmacodynamics of BMS-986288 alone or in combination with nivolumab when [redacted] will be initially composed of a single cohort for BMS-986288 monotherapy (Arm A) and/or BMS-986288 in combination with nivolumab (Arm B). The dose and administration schedule of BMS-986288 alone or in combination with nivolumab selected for [redacted] will be determined by evaluation of the available clinical safety, PK, and pharmacodynamic data from Part 1A and Part 1B, [redacted]. BMS-986288 may be combined with the [redacted] depending on the dose selected (Arm A and/or Arm B). Nivolumab in combination with [redacted] may also be administered (Arm B). The BMS-986288 dose in [redacted] will not exceed the highest dose equivalent determined to be tolerated in Part 1A and/or Part 1B. [redacted] may be used to inform [redacted] dose selection in The Initial Expansion Phase (Part 2).

Part 2: The Expansion Phase is where cohorts of BMS-986288 [redacted] (Part 2A) and Combination With Nivolumab (Part 2B) are expanded to gather additional safety, tolerability, preliminary efficacy, PK, and pharmacodynamic information in specific participant populations.

- One or more dose regimens of BMS-986288 alone and in combination with nivolumab selected for Part 2 cohort expansion will be selected from the range of doses assessed as tolerable in Part 1, and which do not exceed the MTD or highest dose administered. These dose(s) will be selected based on evaluating the recommendation from BLRM and an overall assessment of available safety, PK, pharmacodynamics, and efficacy data from Part 1.
- Part 2 is currently comprised of signal-seeking expansion cohorts in cutaneous melanoma, NSCLC, and a randomized MSS CRC cohort in comparison with regorafenib; additional tumors or potential arms will be included upon evaluation of available safety, PK, pharmacodynamic, and efficacy data from Part 1.

- In Part 2C, the efficacy and safety of BMS-986288 [redacted] with nivolumab will be assessed in participants with MSS CRC who have progressed or relapsed on at least 2 prior standard therapies. Participants must not have received prior anti-CTLA-4, anti-PD-(L)1 therapy in the advanced or metastatic setting. The dose(s) to be evaluated in Part 2C will be selected from the range of doses assessed as tolerable in Part 1B, and which do not exceed the MTD or highest dose administered that has cleared safety. The dose(s) will be selected based on the totality of available safety, tolerability, efficacy, PK, and PD data. Regardless of whether or not [redacted] status is known, all participants will be tested during screening for extended RAS (Kirsten rat sarcoma virus [KRAS] and [redacted] and [redacted] status. The Sponsor may elect to prioritize enrollment of participants based on [redacted] status as well as presence of liver metastasis at screening. In Part 2C, participants will be treated [redacted] for up to 2 calendar years regardless of treatment delays. This cohort will have a standard of care control arm using regorafenib at [redacted] mg, or in accordance with locally approved prescribing information, orally once daily for 21 days of each 28-day cycle.

Study Treatment: An overview of study treatment is shown in Table 2.

Table 2: Study Treatment for CA043001

Medication	Potency	IP/Non-IP
BMS-986288 Powder for Solution for Injection	[redacted] mg per vial	IP
Nivolumab (BMS-986558) Solution for Injection	[redacted] mg (10 mg/mL)	IP
[redacted]	[redacted] mg (1 mg/mL)	IP
Regorafenib Tablet[b]	40 mg[c]	IP

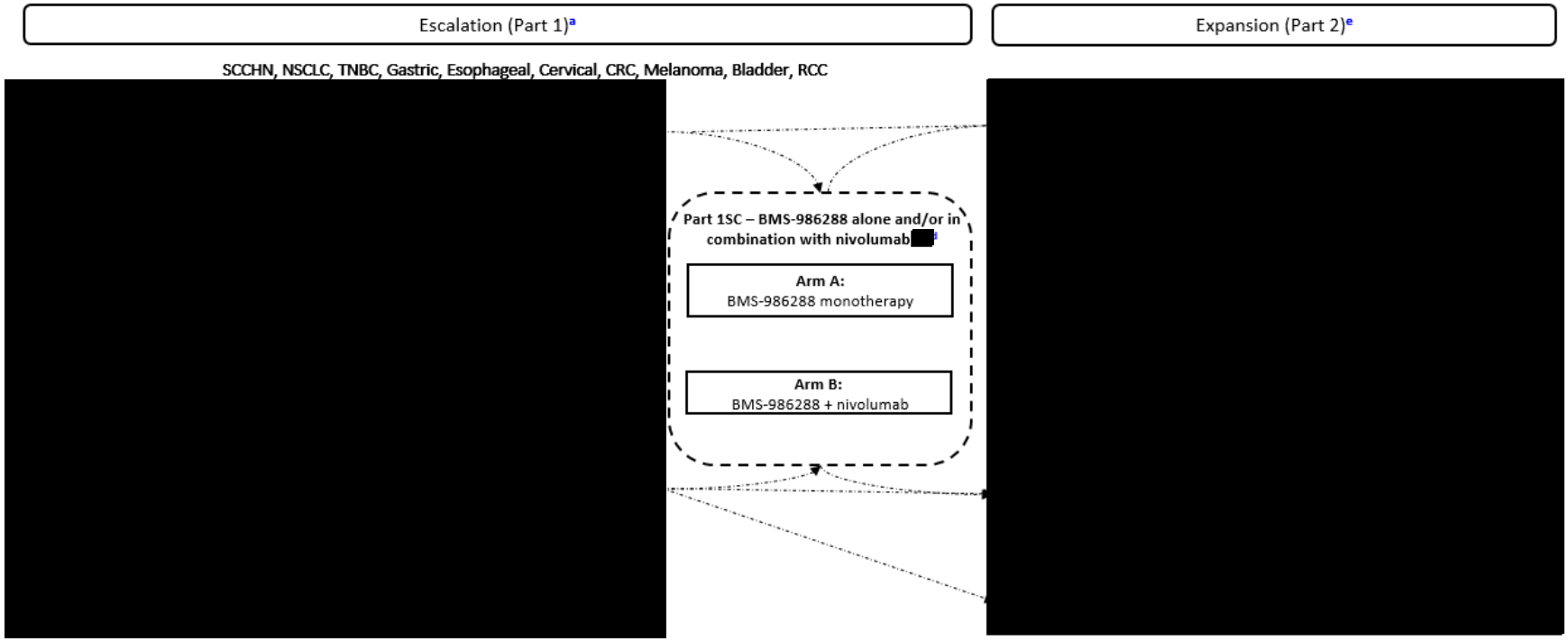
Abbreviations: IP = investigational product; [redacted].

[b] These products may be obtained by investigational sites as local commercial product in certain countries if allowed by local regulations. In these cases, products may be a different pack size/potency than listed in the table. These products should be prepared/stored/administered in accordance with the package insert or SmPC.

[c] May include other commercially available strengths.

The study design schematics are shown in Figure 1 and Figure 2.

Figure 1: Study Design Schematic



Abbreviations: 3L/4L = 3rd/4th line; BMS = Bristol-Myers Squibb; CRC = colorectal cancer; CTLA-4 = cytotoxic T-lymphocyte-associated protein 4; IRT = Interactive Response Technology; IV = intravenous; MSS = microsatellite stable; NSCLC = non-small cell lung cancer; PK = pharmacokinetics; [redacted] RCC = renal cell carcinoma; [redacted] RP2D = recommended Phase 2 dose; [redacted]; SCCHN = squamous cell carcinoma of the head and neck; TBD = to be determined; TNBC = triple-negative breast cancer.

a Prior anti-PD-(L)1 therapy allowed. Anti-CTLA-4 naive required.

b Additional doses and dose schedules may be explored using data obtained from [redacted] administration.

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

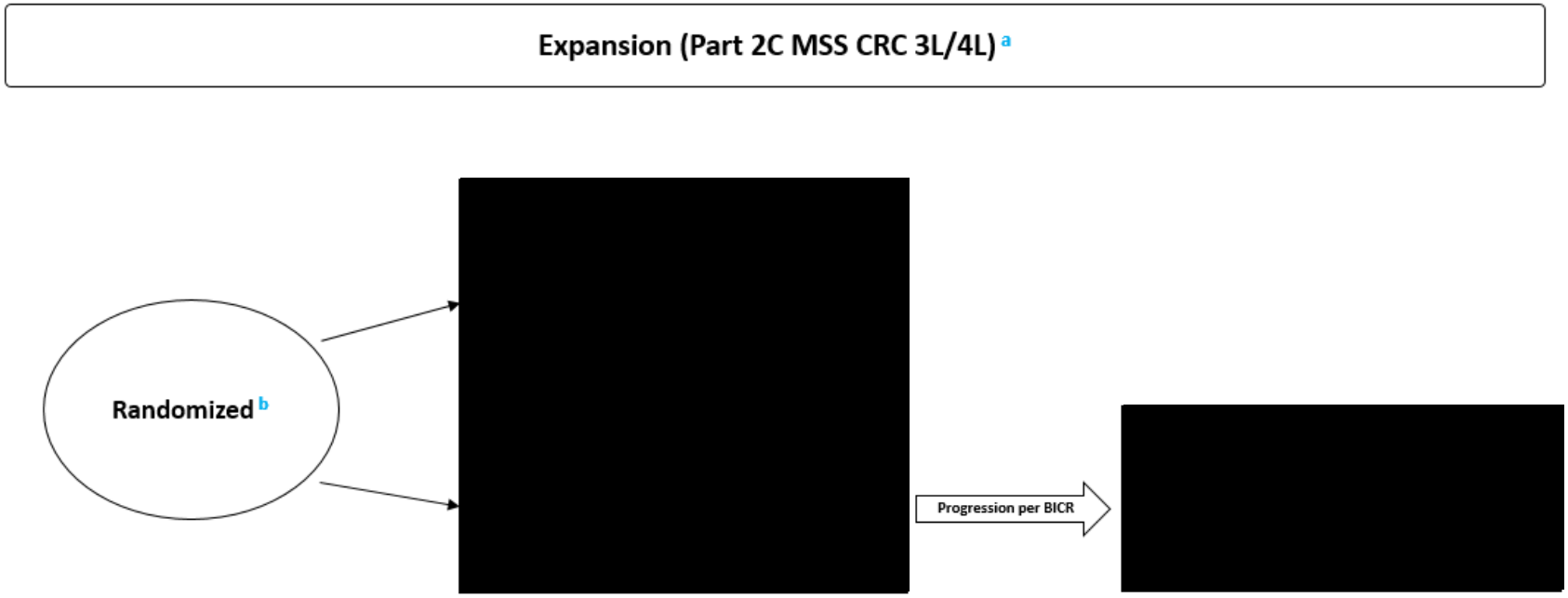
d Doses(s) will be identified upon clinical evaluation of available safety, PK, pharmacodynamics, and efficacy data in Part 1A and/or Part 1B. [redacted] may be used in combination with BMS-986288 or nivolumab, depending on the determined dose. Details will be provided through a protocol amendment.

e Part 2 will be initiated upon evaluation of available safety, PK, pharmacodynamics, and efficacy data from Part 1 and may include IV or [redacted] administration.

f Alternative assignment: In Part 2A [redacted] and Part 2B Combination Expansion, Part 2A and Part 2B may be open concurrently. In this case, treatment assignments will alternate between Part 2A and Part 2B. Multiple doses may be open concurrently in each part. In that case, treatment assignments will alternate between the dose levels, with consecutively treated participants assigned to different parts through IRT whenever possible. If there are no openings available in the dose level to which the participant would be assigned by this algorithm, then the participant will be assigned to the next open dose.

g Intermediate dose level.

Figure 2: Study Design Schematic for Expansion Part 2C



Abbreviations: 3L/4L = 3rd/4th line; BICR = blinded independent central review; CRC = colorectal cancer; IRT, Interactive Response Technology; MSS = microsatellite stable; [redacted].

a Efficacy analyses based on the treated population may be performed for interim analyses.

b Stratification by liver metastasis status and a cap of 50% participants with liver metastases in each arm. Once enrolled in IRT, participants who have met all eligibility criteria for Part 2C will be randomized in a 2:1 ratio to nivolumab in combination with BMS-986288 (Arm C) or regorafenib (Arm D) and stratified by liver metastasis status. An additional dose of BMS-986288 ([redacted] mg or [redacted] mg) in combination with nivolumab may be opened as Arm E.

[redacted]

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. 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-986288 is [redacted]. All participants will be treated for up to 2 calendar years. Continuous safety evaluation and tumor assessment occurring in Part 1 and Part 2 [redacted] of treatment and then [redacted] thereafter), 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).

- For the BMS-986288 Monotherapy Escalation (Part 1A) and the Expansion Phase BMS-986288 [redacted] (Part 2A), BMS-986288 will be infused over approximately 30 minutes.
  - Shorter infusion times may be used for the initial dose cohorts and longer infusion times (approximately [redacted]) may be used for the higher dose levels.
- For the Safety Evaluation of BMS-986288 in Combination with Nivolumab (Part 1B) and the Expansion Phase BMS-986288 in Combination with Nivolumab (Part 2B and Part 2C Arm C, Arm E, and Arm Z), BMS-986288 and nivolumab will each be infused over approximately 30 minutes.
  - When both BMS-986288 and nivolumab are given in combination, nivolumab will be given first, over [redacted] followed by BMS-986288 [redacted], beginning at least 30 minutes after completion of the infusion of nivolumab.
  - Shorter infusion times for BMS-986288 may be used for the initial dose cohorts and longer infusion times [redacted] may be used for the higher dose levels.
- Depending on the dose(s) selected for the [redacted] Evaluation of BMS-986288 as a Monotherapy and/or in Combination with Nivolumab [redacted] BMS-986288 and nivolumab may each be [redacted] with the [redacted].
  - [redacted] of study treatment should be administered [redacted]. Different [redacted] sites should be used if both BMS-986288 [redacted] and nivolumab [redacted] are being administered (Arm B), with nivolumab being given first, followed by BMS-986288. [redacted] should not occur into or around an infected or acutely inflamed area because of the danger of spreading a localized infection. Clinical judgement should be used in determining the best site for [redacted] drug administration.
- For the [redacted] BMS-986288 in combination with nivolumab portion of the study, participants will receive the [redacted] dose of [redacted] mg [redacted] with the selected BMS-986288 dose [redacted] administration will be permitted when [redacted] is not possible upon confirmation with the Sponsor. [redacted] the infusion will be the same as described below). The starting dose will be [redacted] mg of BMS-986288. A possible additional arm with a to-be-determined dose of BMS-986288 may be added based on an evaluation of the entirety of the safety, PK, PD, and anti-tumor activity data from Part 1B. When both BMS-986288 and nivolumab are given in [redacted], the infusion will be given approximately over [redacted]. For participants weighing < 40 kg, the total infusion volume will be limited to 80 mL. For the [redacted] Arm D, the participants will receive regorafenib at [redacted] mg orally once daily for 21 days of each [redacted]-day cycle until disease progression, toxicity, withdrawal of consent, or death, whichever occurs first.
- Refer to the Pharmacy Manual for additional dose preparation details for BMS-986288, nivolumab, [redacted], and regorafenib (if applicable).
- Tumor progression and response endpoints will be assessed using RECIST v1.1.

Follow-up:

- Safety Follow-up Period:
  - Upon completion of study therapy (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.
  - All participants will be evaluated for any new AEs for at least 100 days after the EOT visit. Follow-up visits should occur at Days 30, 60, and 100 (± 7 days for all study visits) after the EOT visit. All participants should

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

- Imaging Follow-up Period:
  - Participants will continue to have radiologic and clinical tumor assessments after treatment discontinuation. Imaging assessments will continue to occur [redacted] (± 1 week) from the date of first treatment until Week 48, then continue [redacted] (± 1 week) thereafter. The duration of the Imaging Follow-up Period will be for a total of 2 years following EOT, or until initiation of another anti-cancer treatment, or death, 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.
- 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 (± 2 weeks) from EOT for 2 years or until death, loss to follow-up, withdrawal of consent, or conclusion of the study, whichever comes first. 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.

Data Monitoring Committee: No.

BMS has developed a multi-layered process to ensure safety monitoring through close collaboration of study site Investigators, the BMS study team, and the BMS Worldwide Patient Safety (WWPS)-led Safety Management Team (SMT). This collaborative process constitutes the Data Safety Monitoring Plan for the study. To support safety oversight, BMS has established ongoing processes for collection, review, analysis, and submission of individual adverse event reports and their aggregate analyses. Because this is an open-label study, WWPS, the BMS Medical Monitor, and the Investigators will have access to all data necessary for safety evaluation.

BMS WWPS is an internal group that operates independently from the clinical team to monitor safety across all BMS protocols, and analyze all data in an unblinded fashion. Within BMS, an SMT is established for investigational therapies under clinical development, and a member of WWPS chairs this team. In addition, signal detection is performed at least monthly and ad hoc throughout the study by the SMT composed, at a minimum, of the WWPS medical safety assessment physician (Chairman of the SMT) and WWPS single-case review physician, the study Medical Monitor(s) (or designee), the study biostatistician, and epidemiologist, all of whom analyze the data in an unblinded fashion. Furthermore, the SMT routinely monitors for actual or potential issues related to participant safety that could result in a significant change in the medical benefit-risk balance associated with the use of study treatment(s).

2 SCHEDULE OF ACTIVITIES

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

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 drug 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), pharmacodynamic, and safety profiles of BMS-986288 are being elucidated; modifications to the procedures (ie, reduction in PK, pharmacodynamic 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.

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

Procedure	Screening Visit (Days -30 to -1)	Notes
Eligibility Assessments		
Informed Consent	X	A participant is considered enrolled only when a protocol-specific ICF is signed.
IRT Participant Assignment	X	After the participants meet all eligibility criteria, sites will use IRT for participant number assignment. Subsequent visits will be registered into the IRT system for drug supply (see Section 5.1.1).
Inclusion/Exclusion Criteria	X	See Section 6.1 and Section 6.2.
Medical History	X	Include all medical history relevant to the disease under study (including, but not limited to, liver metastasis status of Part 2C participants), any toxicities or allergies related to previous treatments, and SARS-CoV-2 vaccines more than 30 days prior to first study treatment.
Prior Cancer Therapies	X	Specify systemic and local therapy, particularly local liver-directed therapy for Part 2C participants.
Concomitant Medications	X	Within 14 days prior to treatment assignment. Vaccine use within 30 days prior to first study treatment.
ECOG Performance Status	X	ECOG Performance Status of 0 or 1 is required for eligibility.
Safety Assessments		
PE	X	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.
Physical Measurements	X	Includes height and weight.
Vital Signs	X	Includes body temperature, respiratory rate, and seated/supine blood pressure and heart rate. Blood pressure and heart rate should be measured after the participant has been resting quietly for at least 5 minutes.
Oxygen Saturation	X	Pulse oximetry collected at rest.
ECG	X	ECGs should be recorded after the participant has been supine for at least 5 minutes and prior to blood draws (see Section 9.4.4).
[redacted]		

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

Procedure	Screening Visit (Days -30 to -1)	Notes
[redacted]		
Laboratory Tests	X	See Clinical Laboratory Assessments in Section 9.4.5 and Table 9.4.5-1.
Urinalysis	X	Microscopic urine reflex only for urinalysis positive for blood/protein/leukocytes.
Serology	X	Includes hepatitis C Ab, hepatitis B surface antigen, and HIV-1 and HIV-2 antibody (see Section 9.4.5 and Table 9.4.5-1).
Pregnancy Test	X	For WOCBP only. Serum to be collected at screening and within 24 hours prior to dosing. 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.
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.
Adverse Event Reporting		
Assessment of Signs/Symptoms/ Clinical Complaints	X	
Monitor for SAEs	X	All SAEs must be collected from the date of participant's written consent until 100 days after discontinuation of dosing. All AEs (SAEs or nonserious AEs) associated with SARS-CoV-2 infection collected from time of consent.
Tumor Assessments		
Body Imaging	X	Contrast-enhanced CT of the chest, abdomen, pelvis, and all other known and/or suspected sites of disease, within 30 days prior to first dose. For participants with cancer of the head and neck, a CT or MRI of the neck is required. For participants with TNBC without measurable lesions outside of the breast, contrast-enhanced MRI of the breasts should be performed. See Section 9.1.1 for further details.

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

Procedure	Screening Visit (Days -30 to -1)	Notes
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 drug administration. Refer to imaging assessment details in Section 9.1.1.
Bone Scan	X	As clinically indicated per local standards (see Section 9.1.1).
Biomarker Assessment		
Collection of [redacted]	X	**All study parts: Consent for [redacted] is required for enrollment. [redacted] are optional for Part 2C regorafenib Arm D and Arm Z participants. For participants in Part 2C Arm D who elect to crossover to Arm Z, [redacted] are mandatory in order to provide pre-treatment information.** [redacted] obtained within 3 months prior to the initiation of study treatment (without any intervening systemic anti-cancer therapy during that time) must be submitted to the central laboratory. [redacted] Instructions for the collection and processing [redacted] will be provided in the Laboratory Manual.

Abbreviations: AE = adverse event; BMS = Bristol-Myers Squibb; C1D1 = Cycle 1 Day 1; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FSH = follicle stimulating hormone; HIV = human immunodeficiency virus; ICF = informed consent form; IgG = immunoglobulin G; IRT = Interactive Response Technology; MRI = magnetic resonance imaging; PE = physical examination; SAE = serious adverse event; 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 All Study Parts

Procedure	Cycle 1 ([redacted] days in length)				Cycle 2 ([redacted] days in length)				Cycles 3 and Beyond (each cycle [redacted] days in length)	EOT[a,b]	Notes
	D1	[redacted]							D1 (± 2 days)		
		(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)			
Safety Assessments											
ECOG Performance Status	X				X				X	X	
PE	X				X				X	X	[redacted]
Symptom-directed PE		X	X	X		X	X	X			
Weight	X				X				X	X	
Vital Signs[d]	X	X	X	X	X	X	X	X	X	X	
Oxygen Saturation[d]	X				X				X		
ECG[e]	X				X				X	X	Triplicate ECGs performed at predose and EOI on C1D1 and C4D1 for Part 1A only. Single safety ECGs to be performed for all other time points and cohorts.

Table 2-2: On-Treatment - Schedule of Activities for All Study Parts

Procedure	Cycle 1 [redacted] days in length)				Cycle 2 ([redacted] days in length)				Cycles 3 and Beyond (each cycle [redacted] days in length)	EOT[a,b]	Notes
	D1	[redacted]							D1 (± 2 days)		
		(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)			
[redacted]											
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 9.4.5 and Table 9.4.5-1.
Urinalysis	X				X				As clinically indicated		Microscopic urine reflex only for urinalysis positive for blood/protein/leukocyte esterase.
Pregnancy Test (WOCBP only)[h]	X				X				X	X	
Adverse Event Reporting and Concomitant Medication Assessments											
Monitor for Non-SAEs	Non-SAEs will be collected continuously starting with the first dose of study medication and through 100 days following last dose of study treatment.										See Appendix 3 and Section 9.2. All AEs (SAEs or nonserious AEs) including

Table 2-2: On-Treatment - Schedule of Activities for All Study Parts

Procedure	Cycle 1 [redacted] days in length)				Cycle 2 ([redacted] days in length)				Cycles 3 and Beyond (each cycle [redacted] days in length)	EOT[a,b]	Notes
	D1	[redacted] (± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	D1 (± 2 days)		
											those associated with SARS-CoV-2 infection must be collected continuously during the treatment period.
Monitor for SAEs	All SAEs must be collected continuously from the date of the participant's written consent until 100 days following last dose of study treatment.										See Appendix 3 and Section 9.2. All AEs (SAEs or nonserious AEs) including those associated with SARS-CoV-2 infection must be collected continuously during the treatment period.
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	
PK Assessments											
[redacted]	[redacted].										
Immunogenicity (ADA) Assessments	See Table 9.5-2, Table 9.5-3, and Table 9.5-4 for the PK and immunogenicity sampling schedule and Section 9.5.										
[redacted]	See Table 9.8.3-1 and Table 9.8.3-2 for the biomarker sampling schedule and Section 9.8.										

Table 2-2: On-Treatment - Schedule of Activities for All Study Parts

Procedure	Cycle 1 ([redacted] days in length)				Cycle 2 ([redacted] days in length)				Cycles 3 and Beyond (each cycle [redacted] days in length)	EOT[a,b]	Notes
	D1	[redacted]							D1 (± 2 days)		
		(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)			
Imaging Assessments											
Body Imaging[i]	Contrast-enhanced CT of the chest, abdomen, pelvis, and all other known and/or suspected sites of disease should occur [redacted] (± 7 days) starting from the first dose up until Week 48. Imaging assessments should then occur [redacted] (± 7 days). For participants with cancer of the head and neck, a CT or MRI of the neck is required. For participants with TNBC without measurable lesions outside of the breast, contrast-enhanced MRI of the breasts should be performed. See Section 9.1.1 for further details.										
Brain Imaging	Participants with history of brain metastasis should have surveillance MRI performed approximately every 12 weeks from first dose or sooner if clinically indicated. CT of the brain without and with contrast can be performed if MRI is contraindicated. See Section 9.1.1.1 for further details.										
Bone Scan	As clinically indicated per local standards (see Section 9.1.1).										
Biomarker Assessments											See Section 9.5, Section 9.8, and Table 9.8.3-1 and Table 9.8.3-2.
[redacted]						X					Mandatory [redacted] must be performed at C2[redacted] (± 3 days), except for Part 2C participants enrolled in the regorafenib arm (Part 2C Arm D) and cross-over (Part 2C Arm Z).

Table 2-2: On-Treatment - Schedule of Activities for All Study Parts

Procedure	Cycle 1 [redacted] days in length)				Cycle 2 ([redacted] days in length)				Cycles 3 and Beyond (each cycle [redacted] days in length)	EOT[a,b]	Notes
	D1	[redacted] (± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	D1 (± 2 days)		
[redacted]	A [redacted] is required, if medically feasible, upon confirmation of PD (within 7 days) except for: 1) participants who have an [redacted] 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 [redacted]; 3) participants who consent to be treated beyond progression will require the [redacted] only at the subsequent confirmation of progression; and 4) participants in Part 2C, unless the participant elects to crossover to Arm Z.										[redacted]
[redacted] Sampling	See Table 9.8.3-1 and Table 9.8.3-2 for details of biomarker assessments.										See Section 9.5, Section 9.8, Table 9.8.3-1, and Table 9.8.3-2 and refer to Laboratory Manual.
Exploratory Biomarker Assessments											See Section 9.5, Section 9.8, Table 9.8.3-1, and Table 9.8.3-2.
Clinical Treatment Supplies											
BMS-986288 Planned Administration [redacted][k]	X				X				X		BMS-986288 to be supplied by BMS. Does not apply for Part 2C Arm D.
Nivolumab Administration [redacted] (Part 1B, [redacted] Arm B, Part 2B, Part 2C Arm C, Arm E, and Arm Z)	X				X				X		Nivolumab to be supplied by BMS.

Table 2-2: On-Treatment - Schedule of Activities for All Study Parts

Procedure	Cycle 1 ([redacted] days in length)				Cycle 2 ([redacted] days in length)				Cycles 3 and Beyond (each cycle [redacted] days in length)	EOT[a,b]	Notes
	D1	[redacted] (± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	D1 (± 2 days)		
Regorafenib ([redacted] mg) Part 2C Arm D1	See notes										Orally, once daily for the first 21 days (D1 to D21) of each [redacted]-day cycle.
[redacted]											
Clinical Outcomes Assessments (Part 2A and Part 2B Only)											
NSCLC-SAQ	X				X				X	X	Clinical outcomes assessments to be administered in Part 2A and Part 2B only. NSCLC-SAQ will only be administered to NSCLC participants. Data will be collected using electronic devices. See Section 9.1.2.
FACIT GP5	X	X	X	X	X	X	X	X	X	X	
EQ-5D-5L	X				X				X	X	

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; EQ-5D-5L = 5-Level EQ-5D; FACIT GP5 = Functional Assessment of Chronic Illness Therapy, General Physical item; hCG = human chorionic gonadotropin; IgG = immunoglobulin G; MRI = magnetic resonance imaging; NSCLC = non-small cell lung cancer; NSCLC-SAQ = Non-small Cell Lung Cancer Symptom Assessment Questionnaire; PD = progressive disease; PE = physical examination; PK = pharmacokinetic; [redacted] RECIST = Response Evaluation Criteria in Solid Tumors; [redacted] SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; [redacted] 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] [redacted]

[d] Vital signs will be obtained before the IV infusion of BMS-986288 and then every 15 minutes (± 5 minutes) until 60 minutes after completion of the infusion for first 3 doses of study treatment on C1D1, C2D1, and C3D1; oxygen saturation to also be performed in conjunction with vital signs monitoring on these days. For all cycles after C3 and for the 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.

[e] ECGs should be recorded after the participant has been supine for at least 5 minutes and prior to blood draws (see Section 9.4.4).

[redacted]

[g] Eye exam is to be performed as clinically indicated, starting with Cycle 3 (ie, Cycle 3, Cycle 5, etc.) and at EOT.

[h] 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).

[i] 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.

[j] Pre-treatment screening [redacted] can be performed on C1D1. Mandatory [redacted] must be performed at C2D8 (± 3 days), except for the Part 2C participants enrolled in the regorafenib arm (Part 2C Arm D). Bone lesion [redacted] are unacceptable for submission. [redacted]

[k] Refer to Appendix 8 (if applicable) for potential alternative schedules that may be explored following evaluation of preliminary safety, PK, and pharmacodynamic data from [redacted] administration. Decisions to initiate exploration of these alternative dose schedules will be made after discussion and agreement between the Investigators and the BMS 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 [redacted] dosing schedule and will not exceed a dose equivalent determined to be tolerable. 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.

[1] For participants who transition from regorafenib (Part 2C Arm D) to receive BMS-986288 in combination with nivolumab, PK, biomarker, physical examinations, vital sign measurements, and clinical laboratory evaluations will be performed on the same schedule of combination therapy starting at C1D1 and moving forward. A biomarker sample should be collected at the time of initial documented disease progression as the requirement at EOT visit and will be treated as screening sample in Part 2C Arm Z. Efficacy and safety data obtained after starting the combination therapy will be analyzed separately; however, safety data from these participants will be considered among the totality of data used for safety evaluation.

Table 2-3: Follow-up Procedural Outline for All Study Parts

Procedure	Safety Follow-up (relative to the last dose of study treatment or date of discontinuation, whichever is later)			Imaging Follow-up	Survival Follow-up (assessed every 12 weeks for 2 years from EOT)	Notes
	Follow-up 1 30 Days (± 7 Days)	Follow-up 2 60 Days (± 7 Days)	Follow-up 3 100 Days (± 7 Days)			
Safety Assessments						
PE	X	X	X			
Vital Signs	X	X	X			Includes body temperature, seated/supine blood pressure, and heart rate.
Laboratory Tests	X	X	X			Laboratory tests also as clinically indicated. See laboratory assessments in Section 9.4.5 and Table 9.4.5-1.
Urinalysis	As clinically indicated (see Section 9.4.5).					
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).
Adverse Event Reporting and Concomitant Medication Assessments						
Monitor for Non-SAEs	X	X	X		See Notes	Nonserious AEs will be collected continuously starting with the first dose of study treatment and through 100 days after last dose of study treatment (see Appendix 3 and Section 9.2).
Monitor for SAEs	X	X	X		See Notes	All SAEs must be collected continuously from the date of the participant's written consent until 100 days after last dose of study treatment (see Appendix 3 and Section 9.2).
Monitor for SARS-CoV-2-related	X	X			See Notes	Participants will be followed for all SAEs and all AEs (SAEs and nonserious AEs) associated with confirmed or suspected

Table 2-3: Follow-up Procedural Outline for All Study Parts

Procedure	Safety Follow-up (relative to the last dose of study treatment or date of discontinuation, whichever is later)			Imaging Follow-up	Survival Follow-up (assessed every 12 weeks for 2 years from EOT)	Notes
	Follow-up 1 30 Days (± 7 Days)	Follow-up 2 60 Days (± 7 Days)	Follow-up 3 100 Days (± 7 Days)			
Nonserious AEs and SAEs						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.
Concomitant Medications	X	X	X			
Sample Collection						
PK Assessments	See Table 9.5-2, Table 9.5-3, and Table 9.5-4 for the PK and immunogenicity sampling schedule and Section 9.5.					
Immunogenicity (ADA) Assessments	See Table 9.5-2, Table 9.5-3, and Table 9.5-4 for the PK and immunogenicity sampling schedule and Section 9.5.					
Efficacy Assessments						
Body Imaging	Contrast-enhanced CT of the chest, abdomen, pelvis, and all other known and/or suspected sites of disease should occur [redacted] (± 7 days) starting from the first dose, up until Week 48. Imaging assessments should then occur [redacted] (± 7 days). The duration of the Imaging Follow-up Period will be for a total of 2 years following EOT, initiation of another anti-cancer treatment, or death, whichever occurs first. For participants with cancer of the head and neck, a CT or MRI of the neck is required. For participants with TNBC without measurable lesions outside of the breast, contrast-enhanced MRI of the breasts should be performed. See Section 9.1.1 for further details.					

Table 2-3: Follow-up Procedural Outline for All Study Parts

Procedure	Safety Follow-up (relative to the last dose of study treatment or date of discontinuation, whichever is later)			Imaging Follow-up	Survival Follow-up (assessed every 12 weeks for 2 years from EOT)	Notes
	Follow-up 1 30 Days (± 7 Days)	Follow-up 2 60 Days (± 7 Days)	Follow-up 3 100 Days (± 7 Days)			
Brain Imaging	Participants with a history of brain metastasis should have surveillance MRI performed approximately every 12 weeks from first dose 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.					
Bone Scan	See Section 9.1.1. As clinically indicated per local standards.					
Subsequent Treatments (anti-cancer)	X	X	X		X	
Assessment of Participant Survival Status					X	Participant status will be assessed by any documented clinic visit or telephone contact every 12 weeks.
Clinical Outcomes Assessments (Part 2A and Part 2B Only)						
NSCLC-SAQ	X	X	X		X	Clinical outcomes assessments to be administered in Part 2A and Part 2B only. NSCLC-SAQ will only be administered to NSCLC patients. Data will be collected using electronic devices, and EQ-5D-5L data can be collected via telephone for the Survival Follow-up Period. See Section 9.1.2.
EQ-5D-5L	X	X	X		X	
FACIT GP5	X	X	X		X	

Abbreviations: ADA = anti-drug antibody; AE = adverse event; CT = computed tomography; EOT = end of treatment; EQ-5D-5L = 5-Level EQ-5D; FACIT GP5 = Functional Assessment of Chronic Illness Therapy, General Physical item; hCG = human chorionic gonadotropin; IgG = immunoglobulin G; MRI = magnetic resonance imaging; NSCLC-SAQ = Non-small Cell Lung Cancer Symptom Assessment Questionnaire; PE = physical examination; PK = pharmacokinetics; SAE =

serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TNBC = triple-negative breast cancer; WOCBP = women of childbearing potential.

In the event of 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.

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 (anti-programmed cell death 1 [PD-1] mAb) results in clinically meaningful anti-tumor activity in several malignancies; however, treatment is also associated with a high frequency of immune-related adverse events (irAEs). Strategies to reduce the frequency and severity of ipilimumab-associated irAEs and increase the breadth and depth of anti-tumor activity could improve the benefit-risk of anti-CTLA-4 containing treatment regimens. CA043001 is a Phase 1/2, first-in-human (FIH) study of BMS-986288, a non-fucosylated (NF) Probody™ variant of ipilimumab, administered alone and in combination with nivolumab, in humans with select advanced solid tumors: squamous cell carcinoma of the head and neck (SCCHN), non-small cell lung cancer (NSCLC), cutaneous melanoma, triple-negative breast cancer (TNBC), renal cell carcinoma (RCC), urothelial carcinoma, gastric, esophageal, cervical, and colorectal cancer (CRC).

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 melanoma adjuvant treatment setting. Blockade of CTLA-4 by ipilimumab has demonstrated anti-tumor activity in other malignancies, including lung cancer, prostate cancer, and RCC. However, no significant activity as a monotherapy was observed in urothelial carcinoma, colorectal, esophageal, gastric, and triple-negative breast cancer. 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. Benefit with the combination has also been observed in NSCLC, RCC, and microsatellite instability high (MSI-H) CRC, and is currently under evaluation in several other malignancies. 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 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. Developing a new anti-CTLA-4 antibody with a more manageable AE profile and an [redacted] breadth and depth of response could improve the [redacted] of anti-CTLA-4 containing treatment regimens.

BMS-986288 is an anti-CTLA-4 NF Probody mAb (PROBODY is a trademark of CytomX Therapeutics, Inc.). 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 mAb ipilimumab. These amino acids form a masking peptide with a protease-cleavable linker containing sites for specific enzymes that are more 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 a 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 where clinical utility is limited by significant on-target toxicities caused by antibody binding to target outside of the tumor. The hypothesis that a Probody version of ipilimumab (BMS-986249) will have a more tolerable safety profile than ipilimumab is currently being tested in a Phase 1 clinical trial (clinicaltrials.gov, NCT03369223).

The rest of the BMS-986288 amino acid sequence is exactly the same as ipilimumab; however, BMS-986288 is expressed in a [redacted], and therefore [redacted]. In addition to the CTLA-4 blocking activity of ipilimumab, BMS-986288, via this [redacted], is predicted to harbor [redacted]. Data from [redacted] models suggests that [redacted] increases the anti-tumor efficacy of CTLA-4 antibodies.[1] Indeed, [redacted] studies with BMS-986288 show [redacted] compared to ipilimumab, correlating with more profound [redacted] at the tumor site (but not the periphery). [redacted] play an important role in [redacted] the anti-tumor immune response by [redacted] in the tumor microenvironment. [redacted] present in tumors express higher levels of CTLA-4, and part of ipilimumab's mechanism of action may be related to [redacted] triggered by [redacted]; however, the data supporting this potential functionality is currently inconclusive. The hypothesis that a [redacted] version of ipilimumab (BMS-986218) will have increased anti-tumor activity to ipilimumab is currently being tested in a Phase 1 clinical trial (clinicaltrials.gov, NCT03110107).

The properties of BMS-986288 (anti-CTLA-4 NF Probody mAb) are summarized below:

- [redacted] (as the Probody form) to human [redacted] (masking efficiency of 30×) compared to ipilimumab
- Comparable binding to [redacted] compared to ipilimumab
- [redacted] activity than ipilimumab in a [redacted] assay
- Increased anti-tumor activity compared to ipilimumab in [redacted] tumor models

- [redacted] peripheral pharmacodynamic activity compared to ipilimumab based on analysis of extratumoral [redacted]

The above properties support the hypothesis that BMS-986288 can potentially [redacted] the depth and breadth of response by combining CTLA-4 blockade with the [redacted] in the tumor microenvironment, while [redacted] systemic exposure to the active species and potentially reducing the risk of autoimmune side effects normally seen after ipilimumab treatment. This potentially improved [redacted] is especially important because of the promise of combination immunotherapy approaches, [redacted].

Based on this unique mechanism of action, this study will evaluate the safety and preliminary efficacy of BMS-986288 alone and in combination with nivolumab.

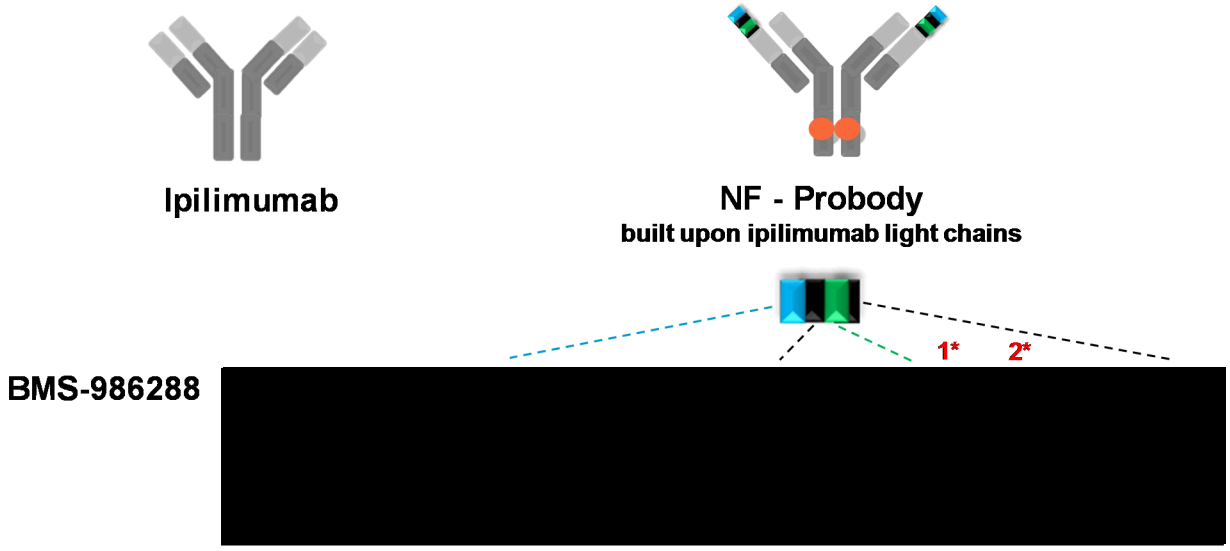
3.2 Background

A detailed description of the chemistry, pharmacology, efficacy, and safety of BMS-986288 is provided in the Investigator's Brochure (IB).[2]

3.2.1 BMS-986288

BMS-986288 has shown promising characteristics as a combination of both of the Probody (BMS-986249) and NF (BMS-986218) second generation anti-CTLA-4 strategies and may decrease irAEs while maximizing clinical benefits. The masked antibody exhibits reduced binding to CTLA-4 and [redacted] functional activity in vitro. When tested in [redacted] syngeneic tumor models, BMS-986288 has [redacted] systemic pharmacodynamic markers of anti-CTLA-4 activity, such as Ki-67 and ICOS upregulation on [redacted] and [redacted] in peripheral lymphoid organs. At the same time, BMS-986288 has consistently shown [redacted] anti-tumor activity to BMS-986218, and [redacted] levels of [redacted] at the tumor site. These data confirm the ability of the Probody to preferentially target the tumor site for antigen binding activity and [redacted] while reducing the systemic exposure to active antibody and serves as the basis for BMS-986288, the Probody version of the fully human anti-CTLA-4 NF mAb, BMS-986218, and is shown in Figure 3.2.1-1.

Figure 3.2.1-1: Schematic of BMS-986288



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

BMS-986288 was selected for dosage form development and is also referred to as BMS-986288-01 or anti-CTLA-4 NF Probody mAb. BMS 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. Hence, BMS-986288 has a masking peptide attached to the N-terminus of the 2 light chains of the anti-CTLA-4 NF mAb, BMS-986218. BMS-986218 is therefore the parent molecule and active form of BMS-986288. BMS-986288 is produced from cell culture using a [redacted].

3.2.1.2 BMS-986288 Nonclinical Pharmacology

BMS-986288 binds CTLA-4 with an approximately [redacted]-fold [redacted] (ie, less potent) half-maximal effective concentration (EC50) than the parent molecule BMS-986218, when the masking peptide is intact.[3] The [redacted] in binding affinity also results in a [redacted] in functional activity. In a human [redacted] functional assay using [redacted] to stimulate interleukin (IL)-2 production, BMS-986218 induced approximately [redacted]-fold [redacted] levels of IL-2 compared to BMS-986288 at the highest concentration tested.[4] [redacted] induced by BMS-986288 was also [redacted] compared to BMS-986218.[5]

In the [redacted] syngeneic tumor model, dose titrations of both BMS-986218 and BMS-986288 [redacted] tumor growth to a similar extent at all 3 identical dose levels ([redacted] µg) examined, and resulted in [redacted] tumor regressions [redacted] at the 2 highest dose levels.[6] At the lowest dose level examined, BMS-986288 treatment resulted in a [redacted] regressions than BMS-986218 [redacted]. A similar trend was observed between ipilimumab and BMS-986249, with comparable inhibition of tumor growth at the 2 highest dose levels and reduced anti-tumor activity of BMS-986249 at the lowest dose level. At the [redacted]-µg dose level, BMS-986218 and BMS-986288 exhibited a more robust anti-tumor activity compared to ipilimumab and BMS-986249. Immune monitoring of [redacted] populations

indicated that BMS-986288 [redacted] similarly to BMS-986218, with a [redacted] and [redacted] reduction, respectively. Systemic pharmacodynamic markers of CTLA-4 activity, such as increased Ki-67 and ICOS levels on [redacted] subsets in the spleen, were [redacted]. BMS-986288, therefore, has been shown to [redacted] anti-tumor activity and tumoral pharmacodynamic effects while [redacted] systemic pharmacodynamic effects.[7]

In summary, the in vitro and in vivo data indicate that BMS-986288 has [redacted] activity outside of the tumor site compared to ipilimumab and the parent molecule BMS-986218, while preserving the [redacted] of BMS-986218, supporting the development of this antibody for the treatment of cancer.

3.2.1.3 BMS-986288 Nonclinical Pharmacokinetics

The PK properties of BMS-986288, a Probody of BMS-986218 (NF-ipilimumab), were evaluated in mice and cynomolgus monkeys.

In human CTLA-4 [redacted] tumors, following a [redacted]-mg/kg IP dose of BMS-986288, the area under the concentration-time curve from 0 to 7 days (AUC[0-7d]) for total antibody in [redacted] was [redacted] µg•h/mL, comparable to that of the parent molecule BMS-986218 ([redacted] µg•h/mL) administered at the same dose. The active species were formed over time, and the AUC(0-7d) of the active species was determined to be [redacted] µg•h/mL. As a result, the AUC(0-7d) ratio between the active species and the total antibody in mice up to 7 days post IP dose was [redacted].

Similar to mice, after [redacted]-mg/kg weekly IV doses to monkeys for [redacted], the [redacted] concentration-time profile of the total antibody superimposed on that of BMS-986218 given at the same dose. The AUC(0-7d) ratio between the active species and the total antibody after the first dose was [redacted], with the active species increasing following subsequent doses on a [redacted] schedule. PK modeling of monkey repeat-dose data revealed that the total body [redacted] clearance (CLT) of the intact Probody was [redacted] mL/d/kg, [redacted] than that of the total antibody ([redacted] mL/d/kg), suggesting that the Probody undergoes protease-mediated clearance in addition to the typical mAb elimination. The steady-state volume of distribution (Vss, [redacted] mL/kg) was estimated to be the same for the intact Probody and the total antibody. As a result, the estimated terminal half-life of the intact Probody [redacted], based on the PK model, was ~2-fold shorter than that of the total antibody [redacted]. In addition, after a single IV dose, the AUC (INF) ratio of the intact Probody, [redacted] species vs total antibody in monkeys, estimated using the PK model, was [redacted], respectively, demonstrating the conversion of the Probody to [redacted] species.

Anti-drug antibody (ADA) formation was observed in [redacted] monkeys; however, the formation of ADAs did not appear to affect the PK of BMS-986288 in monkeys. Furthermore, the tissue concentrations of the total antibody and the active species were evaluated in monkeys on Day 21 after the first IV dose. The concentrations of the total antibody in the liver, spleen, and colon were similar and [redacted] lower than the [redacted] concentration. The active species were detected in these tissue samples, with the concentrations being [redacted] of the total antibody.

3.2.1.4 BMS-986288 Nonclinical Toxicology

In a 1-month toxicity study in monkeys [redacted] at weekly doses of [redacted] mg/kg [redacted], [redacted] mg/kg [redacted], or [redacted] mg/kg [redacted] U/mL [redacted]) of BMS-986288 resulted in profound dose-dependent [redacted] of [redacted] activation (ranging from [redacted]) was observed at all doses following [redacted] consistent with the pharmacology of BMS-986288.[8] BMS-986288 was clinically tolerated by monkeys when administered [redacted] once [redacted] for 1 month at [redacted] mg/kg/week (mean AUC[0-T] = [redacted] µg•h/mL) with findings generally limited to minimal lymphohistiocytic [redacted]. At [redacted] mg/kg/week [redacted] (mean AUC[0-T] = [redacted] µg•h/mL or [redacted] µg•h/mL, respectively), BMS-986288 administration resulted in [redacted] on Days [redacted], due to [redacted] clinical condition, primarily resulting from [redacted] (correlating with increased BUN, creatinine, and chloride), [redacted]. In addition, there were mild to marked decreases in [redacted] and [redacted] [redacted] mg/kg/week [redacted] BMS-986288 was [redacted]. With the exception of the [redacted] recovery monkeys that required [redacted] during the recovery period, most BMS-986288-related changes were partially or fully reversible. Based on tolerability and lack of severe toxicity at the low dose, the highest non-severely toxic dose (HNSTD) in this study was considered to be [redacted] mg/kg/week ([redacted] µg•h/mL).

In comparison, the HNSTD for BMS-986218 in a similar 1-month IV monkey toxicity study was [redacted] mg/kg/week ([redacted] µg•h/mL), with moribundity occurring at the next highest dose level of [redacted] mg/kg/week ([redacted] µg•h/mL).[9] Thus, BMS-986288 appeared to reduce the systemic immune toxicities of BMS-986218 in both a [redacted]-dependent manner. BMS-986288 administration also resulted in reduced toxicological effects compared to ipilimumab over a comparable dose range. Although the HNSTD of ipilimumab was also [redacted] mg/kg/week (mean AUC[0-168h] = [redacted] µg•h/mL) in a similar 1-month study, there was a higher incidence and wider tissue distribution of inflammatory infiltrates in the ipilimumab groups compared to BMS-986288 groups across and within studies.[10,11] These results were consistent with the proposed masking properties of the Probody linker on BMS-986288 and support the potential of BMS-986288 to offer an improved and/or differentiated safety profile relative to BMS-986218 and ipilimumab.

The BMS-986288 HNSTD corresponds to exposure (AUC) multiples of approximately [redacted] µg•h/mL) and highest projected dose for the FIH study ([redacted] mg [redacted] µg•h/mL), respectively.

In vitro incubation of human PBMCs with dry-coated BMS-986218 as well as an isotype-matched control mAb (anti-KLH IgG1nf) led to significant [redacted] activation (as measured by increased CD25 and CD69 expression) at [redacted] µg/well.[12,13] Additionally, [redacted] of IL-1β, IL-6, IL-8, interferon gamma (IFN-γ), and tumor necrosis factor alpha (TNF-α) relative to the phosphate-buffered saline (PBS) control occurred in a [redacted] of incubation with either dry-coated BMS-986218 or anti-KLH IgG1nf, due to non-target mediated engagement of the NF Fc tail. Despite the [redacted] and [redacted] observed with BMS-986218 and the isotype control under these superphysiologic conditions, clinical trial data from BMS-986218 and similar NF IgG1 constructs indicate that these antibodies do not have significant non-target related cytokine release in humans. No adverse cytokine release has been noted following IV administration of BMS-986218 at up to [redacted] mg/dose every [redacted] in patients with advanced cancers.[14] [redacted]
Furthermore, in physiologically relevant whole-blood assays, clinically relevant concentrations of BMS-986218 in solution induced a [redacted] activation in a few donors at concentrations [redacted] µg/mL, and [redacted] cytokine release potential similar to that of ipilimumab.[12,13,16,17] Therefore, BMS-986288 is also not expected to elicit adverse cytokine release in humans.

Overall, BMS-986288 has demonstrated an acceptable pharmacologic, nonclinical PK, pharmacodynamics, and risk profile to support initiation of a FIH clinical study in cancer patients.

3.2.2 Nivolumab

Nivolumab is a fully human, IgG4 (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). 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.[18]

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-986288 and nivolumab have not been conducted and are not required by the International Council on Harmonisation (ICH) S9 Note for Guidance on Nonclinical Evaluation for Anticancer Pharmaceuticals.[19] The safety of the combination will be carefully monitored in the planned clinical trial.

The overall clinical safety experience with nivolumab, as either monotherapy or in combination with other therapeutics, is based on experience in approximately 17,700 participants.[18] Nivolumab monotherapy is approved in multiple regions, including the United States (US) and Europe (EU), for unresectable or metastatic melanoma, previously treated metastatic NSCLC, previously treated advanced RCC, previously treated relapsed or refractory classical Hodgkin lymphoma, previously

treated advanced or metastatic urothelial carcinoma, and for the treatment of previously treated recurrent or metastatic SCCHN; it is also approved for previously treated CRC, previously treated hepatocellular carcinoma (HCC), and the adjuvant treatment of melanoma in the US. In addition, nivolumab has been approved for use in combination with ipilimumab for RCC in the US and unresectable melanoma in multiple countries, including the US and EU.[18]

Details on the clinical safety and PK profile of nivolumab, including results from other clinical studies, are summarized in the nivolumab IB.[18]

3.2.3 Ipilimumab

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 T-regulatory cell (Treg) function, which may contribute to a general increase in T-cell responsiveness, including the anti-tumor response.

Ipilimumab (BMS-734016, MDX010, and MDX-CTLA-4) is a fully human monoclonal IgG1κ specific for human CTLA-4 (CD152). Ipilimumab is a mAb that binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Ipilimumab has been administered to more than 22,571 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.

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-related adverse events (irAEs) 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 patients 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 or 2) and treatment was discontinued for adverse reactions in 10% of participants.

Dose-dependent toxicity as well as the relative efficacy of ipilimumab 3 mg/kg vs 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 patients treated with 10 mg/kg and 11.53 months in patients treated with 3 mg/kg. Ipilimumab 10 mg/kg demonstrated statistically a significant improvement in OS (primary efficacy endpoint) compared with ipilimumab 3 mg/kg (HR = 0.84: 95% CI: 0.70, 0.99;

P-value = 0.0400). Best overall response rate 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.[20]

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.[21]

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 triple-negative breast tumors are summarized in the ipilimumab and nivolumab IBs.[18,21]

3.2.4 Nivolumab Combined with Ipilimumab

Multiple clinical studies have evaluated nivolumab (OPDIVO®) combined with ipilimumab (YERVOY®) at different doses and schedules. Based on phase 3 data showing improved survival over standard of care therapies, nivolumab combined with ipilimumab has been approved in multiple countries for the treatment of patients with unresectable or metastatic melanoma, intermediate or poor risk, previously untreated advanced renal cell carcinoma (RCC), malignant pleural mesothelioma, NSCLC (PD-L1 ≥ 1%), and microsatellite instability-high or mismatch repair deficient metastatic colorectal cancer (mCRC). Details of the clinical activity in these various malignancies are provided in the USPI and summary of product characteristics (SmPC).

The combination of ipilimumab and nivolumab is currently FDA approved at 2 different dosing regimens: 1) 3 mg/kg ipilimumab and 1 mg/kg nivolumab Q3W for 4 doses in patients with unresectable or metastatic melanoma; and 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 microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) mCRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.[22]

In CA209032 (CheckMate 032), a Phase 1/2, open-label study of nivolumab monotherapy or nivolumab combined with ipilimumab in participants with advanced or metastatic solid tumors, the safety and anti-cancer efficacy of N3 Q2W, N+I at N1I1, N1I3, and I3N1 Q3W × 4 followed by N3 Q2W were evaluated in 216 participants with SCLC who had received at least 1 prior platinum-containing regimen. Responses were seen in 10 (10%) of 98 participants treated with N3, 1 (33%) of 3 treated with N1I1, 14 (23%) of 61 who received N1I3 and 10 (19%) of 54 who received N3I1. Grade 3 or 4 treatment-related AEs occurred in 13 (13%) participants in the N3 cohort, 18 (30%) in the N1I3 cohort, and 10 (19%) in the N3I1 cohort; none of the 3 participants treated with N1I1 experienced treatment-related Grade 3 or higher AEs.[23]

CA209016 (CheckMate 016) was a Phase 1 study of nivolumab plus sunitinib, pazopanib, or ipilimumab in participants with metastatic renal cell carcinoma (RCC). Three different N+I regimens were assessed: N3I3, N1I3, and N3I1 given Q3W for 4 cycles followed by N3 Q3W. The N3I3 arm was closed due to poor tolerance. The N3I1 and the N1I3 arm accrued 47 participants each, and Grade 3 to 4 treatment-related AEs were reported in 38.3% and 61.7%

of the participants in the N3I1 and N1I3 arms, respectively. At a median follow-up of 22.3 months, the confirmed objective response rate (ORR) was 40.4% in both arms, with ongoing responses in 42.1% and 36.8% of participants in the N3I1 and N1I3 arms, respectively. The 2-year OS was 67.3% and 69.6% in the N3I1 and N1I3 arms, respectively.[24]

Based on CheckMate 016, a randomized trial (CA209214; CheckMate 214) of nivolumab combined with ipilimumab (N3I1 Q3W × 4 followed by N3 Q2W) vs sunitinib monotherapy was conducted in participants with previously untreated, advanced, or metastatic RCC. After a minimum follow up of 17.5 months, improved ORRs (41.6% vs 26.5%, $p < 0.0001$) and median PFS (11.6 vs 8.4 months, $p = 0.0331$) were seen in intermediate and high-risk RCC participants treated with nivolumab and ipilimumab (n = 425) compared to sunitinib (n = 422), respectively. Drug-related AEs in the entire study population (including participants with low risk RCC) were observed in 509 of 547 participants (93% any Grade, 46% Grade 3 to 4) with nivolumab + ipilimumab vs 521 of 535 participants (97% any Grade, 63% Grade 3 to 5) with sunitinib. Death occurred in 159 N+I participants (7 [1%] drug-related) and 202 sunitinib participants (4 [1%] drug-related).[25]

CA209012 (CheckMate 012) was a Phase 1, multiple-cohort study of nivolumab as monotherapy, in combination with ipilimumab, or in combination with chemotherapy or targeted therapy, in chemotherapy-naive adult (≥ 18 years) participants with stage IIIB/IV NSCLC or recurrent disease, assessing the safety, tolerability, ORR, and PFS rate (PFSR) at 24 weeks based on immune-related response criteria assessment. Cohort P included 38 participants who received nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg every 12 weeks (Q12W), while Cohort Q included 39 participants who received nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg every 6 weeks (Q6W). Confirmed objective responses were achieved in 18 (47% [95% CI: 31, 64]) participants in the ipilimumab Q12W cohort and 15 (38% [95% CI: 23, 55]) participants in the ipilimumab Q6W cohort. Median duration of response (DOR) was not reached in either cohort, with median follow-up times of 12.8 months (interquartile range [IQR]: 9.3, 15.5 months) in the ipilimumab Q12W cohort and 11.8 months (IQR: 6.7, 15.9 months) in the ipilimumab Q6W cohort. The safety profiles in Cohorts P and Q were similar; no new types of AEs were observed and AEs were manageable with established algorithms. There were no deaths due to study drug toxicity. The rate of treatment-related AEs in the Q12W (82%) and Q6W (72%) arms were comparable to monotherapy (69%). In the study, Grade 3 to 4 treatment related AEs were 37%, 33%, and 19% for the Q12W, Q6W, and nivolumab monotherapy arms, respectively. Treatment-related SAEs occurred in 32% and 28% of participants in the Q12W and Q6W cohorts, respectively, compared to 19% to nivolumab monotherapy.[26,27]

When nivolumab 1 mg/kg was administered in combination with ipilimumab 3 mg/kg, the clearance (CL) of nivolumab was increased by 29%, and the CL of ipilimumab was unchanged compared to nivolumab administered alone. When nivolumab 3 mg/kg was administered in combination with ipilimumab 1 mg/kg, the CL of nivolumab and ipilimumab were unchanged. When nivolumab was administered in combination with ipilimumab, the presence of anti-

nivolumab antibodies increased the CL of nivolumab by 20% and the CL of ipilimumab was unchanged in the presence of anti-ipilimumab antibodies.

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 advanced melanoma, NSCLC, RCC, SCCHN, and other tumors. Treatment-related AEs include those associated with autoimmune activation, such as colitis, pneumonitis, thyroiditis, hepatitis, and adrenal insufficiency.

There is no prior human experience with BMS-986288; 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 clinical studies with BMS-986288, the 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-986288 in monkeys (Section 3.2.1), and clinical evidence from ipilimumab therapy. In addition, BMS is evaluating an anti-CTLA-4 NF mAb (clinical trials.gov, NCT03110107) and an anti-CTLA-4 Probody mAb (clinicaltrials.gov, NCT03369223) in separate clinical trials. Emerging data from these programs may inform the safety profile of BMS-986288.

The nonclinical assessment based on Good Laboratory Practice (GLP) toxicology studies of BMS-986288 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-986288 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 17,700 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.[18,21] Unanticipated side effect events may also occur.

The proposed clinical studies of BMS-986288 have been designed to minimize the overall risk to participants; measures will include those described below.

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 serious adverse events (SAEs) will be reviewed on an ongoing basis by the BMS Medical Monitor (or designee) and Worldwide Patient Safety (WWPS) representatives to monitor for any safety signals or trends. As BMS-986288 is an experimental agent, it is possible that unforeseen, unknown, or unanticipated reactions may occur. However, based on the nonclinical safety profile of BMS-986288 built into the planned starting dose of [redacted] mg (equivalent to approximately [redacted] mg/kg), the potential safety risks are expected to be minimized.

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. In addition to conventional safety measures for infusion of biologic agents, all participants administered study drug IV 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. [redacted] 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, neurologic, and cardiac systems are included in the protocol (see Appendix 6).

Participants who develop imAEs may require prolonged treatment with high-dose corticosteroids and other immunosuppressive agents. This could increase the risk of opportunistic infections. The imAE management algorithms in the protocol recommend antibiotic prophylaxis against opportunistic infections in such situations.

Complete blood counts (CBCs) and chemistry (including liver enzyme) tests will be carried out prior to administration of study therapy and on a weekly basis during the first [redacted] weeks of treatment in monotherapy and the first [redacted] weeks of the combination between BMS-986288 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 [redacted] weeks of treatment. [redacted] Safety assessments are outlined in Section 2 and Section 9.4. 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 [redacted] pose limited risk to the participant and include discomfort, pain, and bleeding. [redacted] gives guidance on lesions that are appropriate for a [redacted], and participants where a [redacted] is attempted but who are not able to undergo the [redacted] with an acceptable risk can participate in some situations and upon agreement with the Study Director/Medical Monitor (or designee). Because of the need for development of predictive

biomarkers for participants treated with BMS-986288 in future studies or the clinical setting, the limited risk of a [redacted] in selected (low-risk) participants is considered appropriate in an early phase research setting.

The amount of [redacted] 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/ADAs, and biomarker needs and is below the recommended daily limits for each treatment day.

Patients with mCRC after progression on 2 lines of standard systemic chemotherapy have a very poor prognosis.[30] There is a need to develop treatments that can be effective in later lines of therapy. Nivolumab as a monotherapy is not an effective treatment for proficient mismatch repair (pMMR)/microsatellite stable (MSS) colon cancer, but has demonstrated safety and activity in multiple solid tumors including MSI-H colon cancer.[31] The combination of nivolumab and BMS-986288 has the potential to allow treatment in the broader group of MSS mCRC patients and tolerable over the Part 1B dose range in a variety of solid tumors, including mCRC. The available evidence supports the safe addition of a randomized Phase 2 expansion cohort in MSS CRC participants (see Section 5.4.3). In Part 1B, current data indicate that the combination of BMS-986288 with nivolumab is safe and the overall benefit/risk assessment for this study is favorable.[2] Regorafenib is approved globally for the treatment of mCRC and is recognized standard of care treatment for 3rd/4th line treatment of mCRC.[32,33] This will be used as the comparator in the expansion cohort. To mitigate risks associated with the use of regorafenib, the protocol allows for dose adjustment. A weekly hepatic laboratory value and more frequent international normalized ratio (INR) monitoring in warfarin-treated participants is recommended as per institutional guidelines to minimize potential risk to study participants.

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, objective response, 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-986288 both as a single agent and in combination with nivolumab in this Phase 1/2 clinical study with the risk mitigation described above.

More detailed information about the known and expected benefits and risks and reasonably anticipated AEs of BMS-986288 may be found in the IB.[2]

The global coronavirus disease 2019 (COVID-19) pandemic has been identified as a potential risk to clinical trial participants in general. Whether administration of BMS-986288 alone or in combination with nivolumab increases the risk for contracting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or increases the severity or duration of symptoms is currently unknown. This unknown risk must be considered when enrolling a participant.

No additional safety monitoring or routine screening tests will be required due to the SARS-CoV-2 pandemic. Participants with recent or acute infections will be excluded or delay start of treatment as defined in Section 6.2 and Section 7.4. If a participant has a confirmed SARS-CoV-2 infection

while on study treatment, dose delay or interruption of study treatment is required as described in Section 7.4.

The study has been designed with study visits that allow for close monitoring of participants' safety throughout the clinical trial (Section 2), and participants are encouraged to contact the investigator if an intercurrent illness develops between study visits. Testing for SARS-CoV-2 to inform decisions about clinical care during the study should follow local standard practice.

Non-live SARS-CoV-2 vaccination is considered a simple concomitant medication within the study. However, the efficacy and safety of non-live vaccines (including non-live SARS-CoV-2 vaccines) in participants receiving BMS-986288 or nivolumab is unknown.

4 OBJECTIVES AND ENDPOINTS

The objectives and endpoints for this study are shown in Table 4-1.

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
For Part 1, 2A, 2B • **Primary** • To characterize the safety, tolerability, and DLTs and to determine the MTD/RP2D of BMS-986288 administered as monotherapy and in combination with nivolumab in participants with select advanced solid tumors	• Incidence of AEs, SAEs, AEs meeting protocol-defined DLT criteria, AEs leading to discontinuation, and death.
For Part 1, 2A, 2B **Secondary** • To characterize the PK of BMS-986288 when administered alone and in combination with nivolumab • To assess the preliminary efficacy of BMS-986288 alone and in combination with nivolumab in advanced solid tumors using RECIST v1.1	• Summary measures of PK parameters of BMS-986288 • ORR, DOR, PFS, and TTR per RECIST v1.1 by Investigator assessment
For Part 1, 2A, 2B **Exploratory** • To explore the potential association between anti-tumor activity and pharmacodynamic markers, such as, but not limited to, [redacted] prior to treatment and following administration of BMS-986288 alone and in combination with nivolumab • To explore the associations between BMS-986288 PK, safety, efficacy, and clinical biomarkers • To characterize the immunogenicity of BMS-986288 and nivolumab • To assess the preliminary efficacy of BMS-986288 alone and in combination with nivolumab in select advanced solid tumors using iRECIST • To assess the OS in participants treated with BMS-986288 alone and in combination with nivolumab • To assess the potential effect of BMS-986288 when administered [redacted] on the QTc interval • To characterize the PK and bioavailability of BMS-986288 when [redacted] • To explore the impact of treatment on NSCLC participant-reported symptoms and health-related quality of life (Part 2A and Part 2B only) • To explore participant overall perception of bother in relation to treatment-related symptomatic side effects (Part 2A and Part 2B only) • To explore overall health status (Part 2A and Part 2B only)	• Summary measures of anti-tumor activity by pretreatment level of biomarkers of interest; correlation/measure of association of anti-tumor activity and change (or % change) from baseline in biomarkers of interest • Association measures between BMS-986288 PK levels by [redacted], select outcomes, and biomarkers of interest • Incidence of ADA to nivolumab and BMS-986288 • ORR, DOR, and PFS per iRECIST by BICR • OSR at 1 year and 2 years • Summary measures of ECG parameters and changes in QTcF (ΔQTcF) from baseline • Summary of PK parameters when BMS-986288 is [redacted] alone or in combination with nivolumab • Mean NSCLC-SAQ scores and change from baseline scores • Proportion of participants endorsing each response option of the FACIT GP5

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
• To measure [redacted], and assess [redacted] change over time and in association with response	• Mean EQ-5D-5L utility index scores and EQ-5D-VAS scores and change from baseline scores • Summary measures of [redacted] and correlation/ measure of association of anti-tumor activity and change (or % change) from baseline in [redacted]
For Part 2C **Primary** • To compare the efficacy of BMS-986288 in combination with nivolumab vs regorafenib in the 3L/4L MSS CRC setting.	• ORR per RECIST v1.1 by BICR
For Part 2C **Secondary** • To compare the efficacy of BMS-986288 in combination with nivolumab vs regorafenib in the 3L/4L MSS CRC setting • To characterize the safety and tolerability of BMS-986288 in combination with nivolumab vs regorafenib in the 3L/4L MSS CRC setting	• DOR and PFS per RECIST v1.1 by BICR, and OS • ORR, DOR, and PFS per RECIST v1.1 by Investigator assessment • Incidence of AEs, SAEs, AEs meeting protocol-defined DLT criteria, AEs leading to discontinuation, and death
For Part 2C **Exploratory** • To compare the efficacy of BMS-986288 in combination with nivolumab vs regorafenib in the 3L/4L MSS CRC setting in subgroups of [redacted] and mutant tumors • Explore the association between response with both baseline and pharmacodynamic markers in the [redacted] • To evaluate BMS-986288 PK in the MSS CRC setting in combination with nivolumab • To evaluate immunogenicity of BMS-986288 and nivolumab when administered as combination • To explore the exposure-response relationship for BMS-986288 when given as combination with nivolumab	• ORR, DCR, DOR, PFS by BICR, and OS in the subgroups of [redacted] and [redacted] participants • Summary measures of change (or % change) from baseline in parameters of interest and correlation/measure of association of response and pharmacodynamic markers • Summary measures of PK parameters from population PK analysis • Summary of ADA incidence and association with PK, efficacy, hypersensitivity, and infusion-related safety events • Exposure-response relationship for efficacy endpoints including ORR and PFS. • Exposure-response relationship for safety endpoints including TRAE Grade 3+ and dose modification due to TRAE.

Abbreviations: 3L/4L = 3rd line/4th line; ADA = anti-drug antibody; AE = adverse event; BICR = blinded independent central review; BMS = Bristol-Myers Squibb; CRC = colorectal cancer; DCR = disease control rate; DOR = duration of response; DLT = dose-limiting toxicity; ECG = electrocardiogram; EQ-5D-5L = 5-Level EQ-5D; EQ-5D-VAS = EQ-5D Visual Analog Scale; FACIT GP5 = Functional Assessment of Chronic Illness Therapy, General Physical item; IgG = immunoglobulin G; iRECIST = modified RECIST in cancer immunotherapy trials; MSS = microsatellite

stable; MTD = maximum tolerated dose; NSCLC-SAQ = Non-small Cell Lung Cancer Symptom Assessment Questionnaire; ORR = objective response rate; OS = overall survival; OSR = overall survival rate; 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; SAE = serious adverse event; [redacted] TRAE = treatment-related adverse event; [redacted] TTR = time to response.

5 STUDY DESIGN

5.1 Overall Design

This is a Phase 1/2, open-label study of BMS-986288 administered as a single agent and in combination with nivolumab in participants with select advanced solid tumors (SCCHN, NSCLC, cutaneous melanoma, RCC, CRC, TNBC, urothelial carcinoma, gastric, esophageal, and cervical cancer). The study is composed of 2 parts: dose escalation and initial dose expansion.

Part 1: The Dose-Escalation Phase is where the dose of BMS-986288 will be administered IV alone (Part 1A) or in combination with nivolumab (Part 1B). [redacted] administration of BMS-986288 as a monotherapy (Arm A) or in combination with nivolumab (Arm B) may also be evaluated [redacted].

- The BMS-986288 Monotherapy Escalation (Part 1A) will escalate the dose of BMS-986288 to determine the monotherapy maximum tolerated dose (MTD)/recommended Phase 2 dose (RP2D). Specifically, the Part 1A dose escalation will evaluate different doses of BMS-986288 starting at [redacted] mg, followed by [redacted]. If it appears that a planned dose level is associated with an unacceptable frequency of toxicities, then an intermediate dose or alternative administration schedule may be evaluated, and will not initially exceed a dose determined to be tolerable. After preliminary evaluation of safety and PK data from these intermediate dose or alternative administration schedules, re-escalating doses of BMS-986288 may be initiated (see Table 2-2 and Appendix 8). The study will first evaluate the safety and tolerability of BMS-986288 monotherapy based on dose-limiting toxicities (DLTs), using a Bayesian Logistic Regression Model (BLRM) employing the escalation with overdose control (EWOC) principle [redacted], and overall assessment of available safety, PK, and pharmacodynamic data.
- The Safety Evaluation of BMS-986288 in Combination with Nivolumab (Part 1B) will evaluate the safety and tolerability of various doses of BMS-986288 in combination with nivolumab to determine the combination MTD/RP2D. Treatment in Part 1B will be initiated in a staggered manner relative to the BMS-986288 Monotherapy Escalation (Part 1A). Specifically, Part 1B can be initiated upon the decision to escalate when at least 2 dose levels in Part 1A have cleared the DLT period in accordance with dose escalation rules, after which dose escalation in Part 1A and Part 1B will proceed in parallel (see Section 7.2). At no point will the dose of BMS-986288 administered in combination with nivolumab in Part 1B exceed the highest safe dose in ongoing monotherapy dose escalation in Part 1A or the highest dose determined to be tolerated in Part 1A. In Part 1B, the dose of BMS-986288 will be escalated, whereas the dose of nivolumab will be [redacted] mg [redacted]. However, if it appears that a planned dose level is associated with an unacceptable frequency of toxicities then an intermediate dose level, additional cohorts of alternative BMS-986288 administration schedules, or de-escalating doses of nivolumab may be evaluated, and potential re-escalating doses of BMS-986288 may then be initiated (see Table 2-2 and Appendix 8).The safety and tolerability of the BMS-986288 combination with nivolumab will be evaluated using a BLRM-copula employing the EWOC principle, and an overall assessment of available safety, PK, and pharmacodynamic data.

- The [redacted] of BMS-986288 as a Monotherapy and/or in Combination with Nivolumab [redacted] may be conducted to obtain preliminary data on the safety, tolerability, PK, bioavailability, and pharmacodynamics of BMS-986288 alone or in combination with nivolumab when [redacted] will be initially composed of a single cohort for BMS-986288 monotherapy (Arm A) and/or BMS-986288 in combination with nivolumab (Arm B). The dose and administration schedule of BMS-986288 alone or in combination with nivolumab selected for [redacted] will be determined by evaluation of the available safety, PK, and pharmacodynamic data from Part 1A and Part 1B, [redacted]. BMS-986288 may be combined with [redacted] depending on the dose selected (Arm A and/or Arm B). Nivolumab in combination with [redacted] may also be administered (Arm B). The BMS-986288 dose in [redacted] will not exceed the highest dose equivalent determined to be tolerated in Part 1A and/or Part 1B. [redacted] may be used to inform [redacted] dose selection in The Initial Expansion Phase (Part 2).

Part 2: The Expansion Phase is where cohorts of BMS-986288 [redacted] (Part 2A) and Combination with Nivolumab (Part 2B) are expanded to gather additional safety, tolerability, preliminary efficacy, PK, and pharmacodynamic information in specific participant populations.

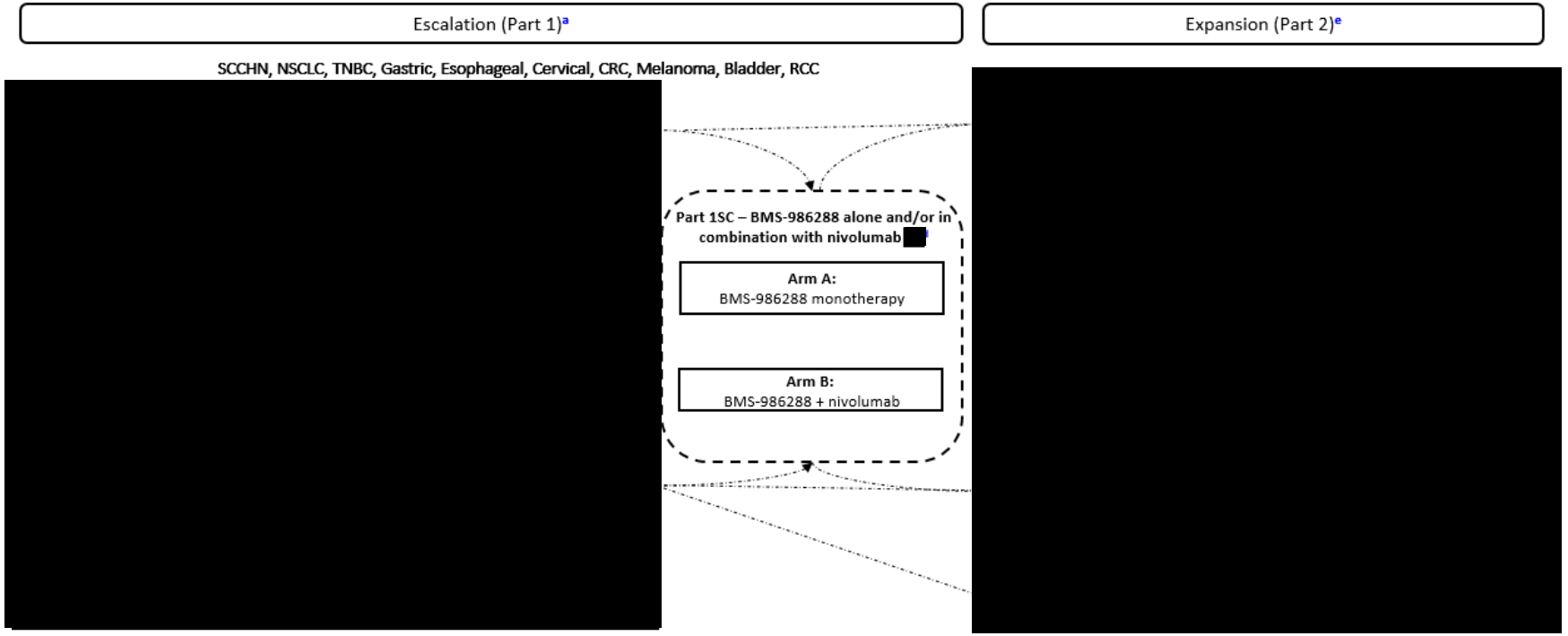
- One or more dose regimens of BMS-986288 alone and in combination with nivolumab selected for Part 2 cohort expansion will be selected from the range of doses assessed as tolerable in Part 1, and which do not exceed the MTD or highest dose administered. These dose(s) will be selected based on evaluating the recommendation from BLRM and an overall assessment of available safety, PK, pharmacodynamic, and efficacy data from Part 1.
- Part 2 is currently comprised of signal-seeking expansion cohorts in cutaneous melanoma, NSCLC, and a randomized MSS CRC cohort in comparison with regorafenib; additional tumors or potential arms will be included upon evaluation of available safety, PK, pharmacodynamic, and efficacy data from Part 1.

All participants will complete up to 3 study periods: Screening (up to 30 days), Treatment (up to [redacted] cycles, [redacted] days/cycle), and Follow-up (comprised of Safety [100 days], Imaging [up to 2 years], and Survival [up to 2 years] following end of treatment [EOT]). The duration of study participation will be approximately 4 years (treatment of up to 2 years and follow-up of up to 2 years).

Images will be submitted to a central imaging vendor and may undergo blinded independent central review (BICR) at any time during the study. Prior to scanning first participant, sites should be qualified and understand the image acquisition guidelines and submission process as outlined in the CA043001 Imaging Manual provided by the central imaging vendor.

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

Figure 5.1-1: Study Design Schematic



Abbreviations: 3L/4L = 3rd/4th line; BMS = Bristol-Myers Squibb; CRC = colorectal cancer; CTLA-4 = cytotoxic T-lymphocyte-associated protein 4; IRT = Interactive Response Technology; MSS = microsatellite stable; NSCLC = non-small cell lung cancer; PK = pharmacokinetics; RCC = renal cell carcinoma; RP2D = recommended Phase 2 dose; SCCHN = squamous cell carcinoma of the head and neck; TBD = to be determined; TNBC = triple-negative breast cancer.

[a] Prior anti-PD-(L)1 therapy allowed. Anti-CTLA-4 naive required.

[b] Additional doses and dose schedules may be explored using data obtained from administration.

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

[d] Doses(s) will be identified upon clinical evaluation of available safety, PK, pharmacodynamics, and efficacy data in Part 1A and/or Part 1B. may be used in combination with BMS-986288 or nivolumab, depending on the determined dose. Details will be provided through a protocol amendment.

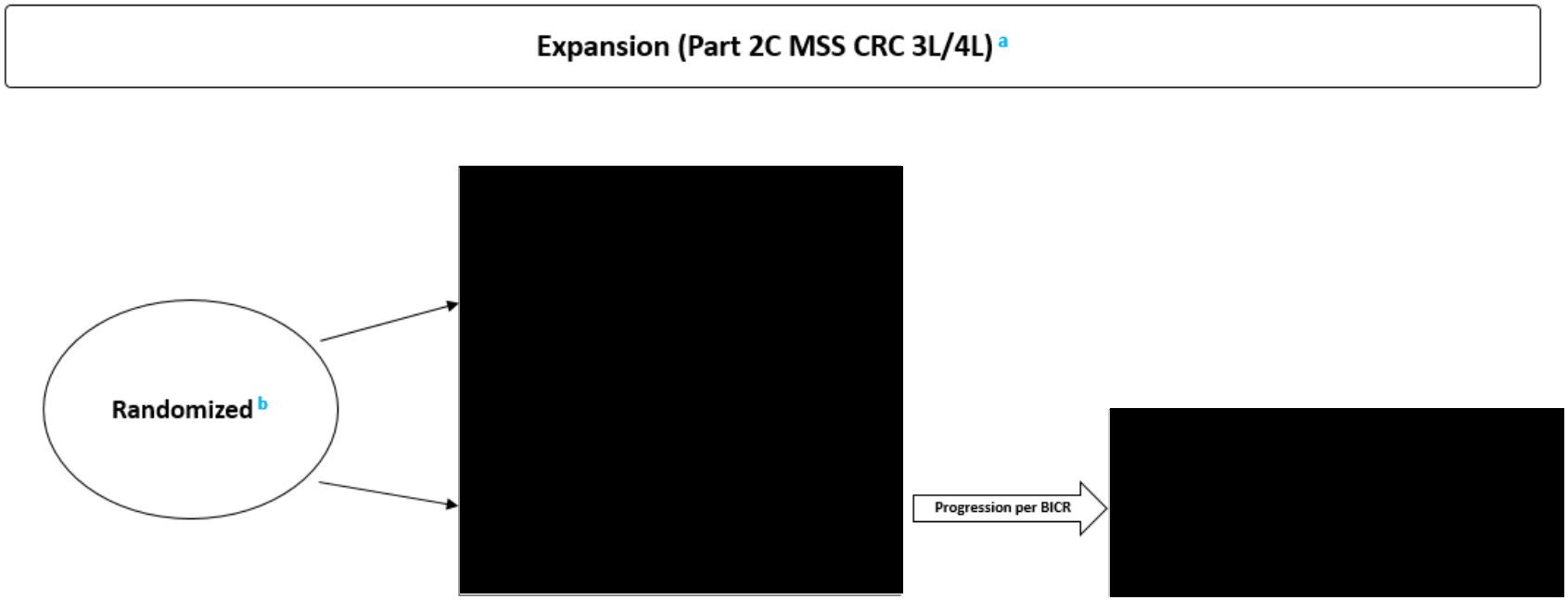
[e] Part 2 will be initiated upon evaluation of available safety, PK, pharmacodynamics, and efficacy data from Part 1 and may include administration.

[f] Alternative assignment: In Part 2A and Part 2B Combination Expansion, Part 2A and Part 2B may be open concurrently. In this case, treatment assignments will alternate between Part 2A and Part 2B. Multiple doses may be open concurrently in each part. In that case, treatment assignments will alternate

between the dose levels, with consecutively treated participants assigned to different parts through IRT whenever possible. If there are no openings available in the dose level to which the participant would be assigned by this algorithm, then the participant will be assigned to the next open dose.

[g] Intermediate dose level (Section 5.1.2.1).

Figure 5.1-2: Study Design Schematic for Expansion Part 2C



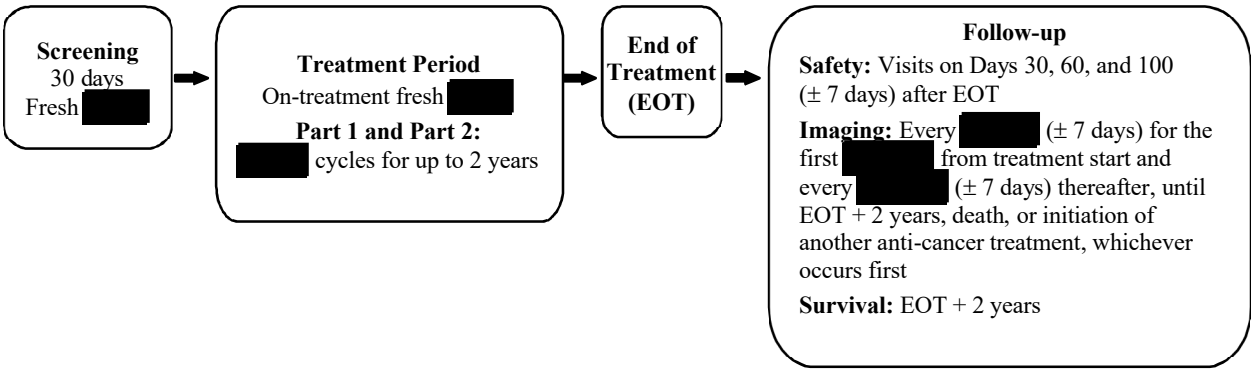
Abbreviations: 3L/4L = 3rd/4th line; BICR = blinded independent central review; CRC = colorectal cancer; IRT, Interactive Response Technology; MSS = microsatellite stable; [redacted].

a Efficacy analyses based on the treated population may be performed for interim analyses (see further details in Section 10).

b Stratification by liver metastasis status and a cap of 50% participants with liver metastases in each arm. Once enrolled in IRT, participants who have met all eligibility criteria for Part 2C will be randomized in a 2:1 ratio to nivolumab in combination with BMS-986288 (Arm C) or regorafenib (Arm D) and stratified by liver metastasis status. An additional dose of BMS-986288 ([redacted] mg or [redacted] mg) in combination with nivolumab may be opened as Arm E.

[redacted] (see further details in Section 5.4.8).

Figure 5.1-3: Study Period and Participant Flow



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 [redacted] or waiting for a study-related laboratory value), the participant must be re-consented, but does not 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. Within a given disease type, participants meeting all eligibility criteria will be enrolled in the study using an Interactive Response Technology (IRT) according to the part and treatment arm availability.

5.1.2 Treatment Period

The initial dosing regimen of BMS-986288 is [redacted]. Continuous safety evaluation and tumor assessment occurring in Part 1 and Part 2 ([redacted] until Week 48 of treatment and then [redacted] thereafter), 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 for the first 8 weeks after the first dose of study treatment for the BMS-986288 Monotherapy Escalation (Part 1A), the Safety Evaluation of BMS-986288 in Combination with Nivolumab (Part 1B), the [redacted] of BMS-986288 as a Monotherapy and in Combination with Nivolumab [redacted], and the Initial Expansion Phase (Part 2), followed by study visits [redacted] thereafter. During the treatment period for all study parts, additional study visits to collect samples for intensive PK, ADA, and cytokine assessments will be required at Cycles 1-6, and every fourth cycle after Cycle 6 until EOT. See Section 9.5 for further details.

For the BMS-986288 Monotherapy Escalation (Part 1A) and the Expansion Phase BMS-986288 [redacted] (Part 2A), BMS-986288 will be infused over approximately [redacted]. Shorter infusion times may be used for the initial dose cohorts and longer infusion times (approximately [redacted]) may be used for the higher dose levels.

For the Safety Evaluation of BMS-986288 in Combination with Nivolumab (Part 1B) and the Expansion Phase BMS-986288 in Combination with Nivolumab (Part 2B and Part 2C Arm C, Arm

E, and Arm Z), BMS-986288 and nivolumab will each be infused over approximately 30 minutes. When both BMS-986288 and nivolumab are given in combination, nivolumab will be given first, over 30 minutes, followed by BMS-986288 over [redacted], beginning at least 30 minutes after completion of the infusion of nivolumab. Shorter infusion times for BMS-986288 may be used for the initial dose cohorts and longer infusion times (approximately [redacted]) may be used for the higher dose levels.

For the Part 2C BMS-986288 in combination with nivolumab portion of the study, participants will receive the [redacted] with the selected BMS-986288 dose [redacted] is not possible upon confirmation with the Sponsor. [redacted], the infusion will be the same as described below). The starting dose will be [redacted] mg of BMS-986288. A possible additional arm with a to-be-determined dose of BMS-986288 may be added based on an evaluation of the entirety of the safety, PK, PD, and anti-tumor activity data from Part 1B. When both BMS-986288 and nivolumab are given [redacted], the infusion will be given approximately over [redacted]. For participants weighing < 40 kg, the total infusion volume will be limited to 80 mL. For the Part 2C Arm D, the participants will receive regorafenib at [redacted] mg orally once daily for 21 days of each [redacted]-day cycle until disease progression, toxicity, withdrawal of consent, or death, whichever occurs first (see Section 5.5.4.9 for details).

Depending on the dose(s) selected for the [redacted] of BMS-986288 as a Monotherapy and/or in Combination with Nivolumab [redacted], BMS-986288 and nivolumab may each be [redacted] with the [redacted] of study treatment should be administered in the abdomen or alternatively in the thigh. Different [redacted] sites should be used if both BMS-986288 [redacted] and nivolumab [redacted] are being administered (Arm B), with nivolumab being given first, followed by BMS-986288. [redacted] should not occur into or around an infected or acutely inflamed area because of the danger of spreading a localized infection. Clinical judgement should be used in determining the best site for [redacted] drug administration.

See Table 2-2 for the on-treatment Schedule of Activities and Table 7.1-1 for a list of dose selection and timing. Refer to the Pharmacy Manual for additional dose preparation details for BMS-986288, nivolumab, and [redacted] (if applicable).

Sentinel Participant

During the Dose-Escalation Phase (Part 1), a staggered dosing (sentinel participant) approach will be used. The first participant to be dosed at Cycle 1 Day 1 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 5.1.2.1 and Section 7.4.1.

5.1.2.1 Dose-Escalation Decisions for the BMS-986288 Monotherapy Escalation (Part 1A) and the Safety Evaluation of BMS-986288 in Combination with Nivolumab (Part 1B)

The Dose-Escalation Phase (Part 1) of the study will evaluate the safety and tolerability of BMS-986288, given alone or in combination with nivolumab, based on DLTs, using a BLRM for both Part 1A and Part 1B. The DLT period will be 5 weeks.

During the monotherapy (Part 1A) and combination therapy (Part 1B) dose-escalation phases, a set of approximately 3 participants will be treated at each specified dose level. If the potential DLT occurring in the third evaluable participant regarding the specific dose level does not influence the dose escalation decision by BLRM, the next dose level may proceed without waiting for the third participant to complete the corresponding DLT observation period. In this situation, cohort tolerability assessment and subsequent dose recommendation may occur when at least [redacted] evaluable participants within a cohort have completed a 5-week DLT period, after discussion and agreement between the Sponsor and Investigators. 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 7.4.1.

Continuous reassessment of dose recommendation, by BLRM in the BMS-986288 Monotherapy Dose Escalation (Part 1A) and in the Safety Evaluation of BMS-986288 in Combination with Nivolumab (Part 1B), will be carried out for each dose level. The planned dose regimens are shown in the study design schematic in Figure 5.1-1.

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 (during the DLT evaluation) in order to obtain additional experience or to investigate dose levels intermediate to those defined in the protocol (hereon referred to as “backfill”). The Sponsor may choose to enroll only participants with certain cancer types and certain criteria, from dose escalation during backfill, based on emerging data. Planned dose levels may be modified (eg, alternative administration schedule, Appendix 8), or intermediate dose levels added, based upon the BLRM analysis and clinical evaluation of available safety, PK, and pharmacodynamic data in Part 1A and Part 1B. Dose escalation in the alternative schedule may be performed; cohort tolerability assessment and subsequent dose recommendation will follow the same principles as outlined for the planned administration schedule of [redacted].

5.1.2.2 [redacted] Evaluation of BMS-986288 as a Monotherapy and in Combination with Nivolumab [redacted]

Up to a total of [redacted] evaluable participants may be treated in the BMS-986288 monotherapy (Arm A) and/or combination (Arm B) [redacted] cohort(s) [redacted] will be initiated [redacted] once an appropriate BMS-986288 monotherapy (Part 1A) or combination dose (Part 1B) is identified from clinical evaluation of available preliminary safety, PK, pharmacodynamic, and efficacy data (eg, MTD/RP2D). The dose(s) selected for [redacted] will not

exceed the dose equivalent determined to be safe and tolerable in Part 1A and/or Part 1B. Depending on the dose selected, BMS-986288 may be [redacted] with the [redacted] (as a monotherapy [Arm A] or in combination [Arm B] with nivolumab [redacted]). Participants receiving [redacted] stration will be different from those receiving [redacted] administration, not crossed over. Treatment will be for up to [redacted] calendar years.

5.1.2.3 The Expansion Phase of BMS-986288 [redacted] (Part 2A) [redacted] Nivolumab (Part 2B and Part 2C Arm C, Arm E, and Arm Z)

The purpose of the BMS-986288 cohort expansions is to gather preliminary efficacy information in specific patient populations regarding BMS-986288 alone and in combination with nivolumab. In addition, safety, tolerability, PK, and pharmacodynamics data will be evaluated.

The Initial Expansion Phase (Part 2) will be initiated once an appropriate BMS-986288 monotherapy (Part 1A) or combination dose (Part 1B) is identified based on recommendations from the BLRM and an overall assessment of available preliminary safety, PK, pharmacodynamic, and efficacy data (eg, MTD/RP2D). The Part 2 route of administration [redacted] may be informed from an overall assessment of available preliminary safety, PK, pharmacodynamic, and efficacy data from Part 1A, Part 1B, or [redacted]. Any BMS-986288 dose selected for use in Part 2A will not exceed the highest dose determined to be safe in monotherapy (Part 1A). Similarly, any BMS-986288 dose selected for use in Part 2B and Part 2C will not exceed the highest dose determined to be safe in combination therapy (Part 1B). A safe dose selected for use in Part 2 in either part of the study requires a minimum of [redacted] safety-evaluable participants in the selected dose level in Part 1.

The Expansion Phase of BMS-986288 [redacted] (Part 2A) will initially involve signal-seeking expansion cohorts in participants with advanced cutaneous melanoma and NSCLC with disease relapse/recurrence or progression after prior immunotherapy treatment with an anti-PD-(L)1 containing regimen. Participants with cutaneous melanoma must not have received prior anti-CTLA-4 therapy.

The Expansion Phase of BMS-986288 in Combination with Nivolumab (Part 2B) will initially involve signal seeking expansion cohorts in participants with advanced NSCLC with disease relapse/recurrence or progression after prior immunotherapy treatment with an anti-PD-(L)1 containing regimen.

In Part 2C, the efficacy and safety of BMS-986288 [redacted] with nivolumab will be assessed in participants with MSS CRC who have progressed or relapsed on at least 2 prior standard therapies. Participants must not have received prior anti-CTLA-4, anti-PD-(L)1 therapy in the advanced or metastatic setting. The dose(s) to be evaluated in Part 2C will be selected from the range of doses assessed as tolerable in Part 1B, and which do not exceed the MTD or highest dose administered that has cleared safety. The dose(s) will be selected based on the totality of available safety, tolerability, efficacy, PK, and PD data. Regardless of whether or not [redacted] mutation status is known, all participants will be tested during screening for [redacted]

and [redacted] status. The Sponsor may elect to prioritize enrollment of participants based on mutation status as well as presence of liver metastasis at screening. In Part 2C, participants will be treated [redacted] for up to 2 calendar years regardless of treatment delays. This cohort will have a standard of care control arm using regorafenib at [redacted] mg, or in accordance with locally approved prescribing information, orally once daily for 21 days of each [redacted]-day cycle.

Additional tumor types considered may include those in which ipilimumab monotherapy has failed to prove sufficient efficacy, in participants who have progressed or relapsed after anti-PD-(L)1 therapy, or tumors in which a high level of [redacted] correlates with worse prognosis.

Participants with unconfirmed progressive disease (PD), stable disease (SD), partial response (PR), or complete response (CR) at the end of a given cycle will continue to the next treatment cycle. 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
- PD defined by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (Appendix 5), unless participants meet criteria for treatment beyond progression (Section 5.1.4)
- 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

5.1.2.4 Visit Windows

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.

5.1.3 Follow-up

5.1.3.1 Safety Follow-up Period

Upon completion of study therapy (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.

All participants will be evaluated for any new AEs for at least 100 days after the EOT visit. Follow-up visits should occur at Days 30, 60, and 100 (± 7 days for all study visits) after the EOT visit. All participants should complete the 3 clinical safety follow up visits regardless of whether new anti-cancer therapy is started, except those participants who will withdraw consent for study participation. Refer to Table 2-2 and Table 2-3.

5.1.3.2 Imaging Follow-up Period

Participants will continue to have radiologic and clinical tumor assessments after treatment discontinuation. Imaging assessments will continue to occur [redacted] (± 1 week) from the date of first treatment until Week 48, then continue [redacted] (± 1 week) thereafter. The duration of the Imaging Follow-up Period will be for a total of 2 years following EOT, or until initiation of another anti-cancer treatment, or death, 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.

5.1.3.3 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 (± 2 weeks) from EOT for 2 years or until death, loss to follow-up, withdrawal of consent, or conclusion of the study, whichever comes first. 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.

5.1.4 Treatment Beyond Progression

Tumor progression and response endpoints will be assessed using RECIST v1.1 criteria (Appendix 5). Treatment beyond progression may be allowed in selected participants with initial RECIST v1.1 defined PD after discussion and agreement with the BMS Medical Monitor (or designee), if the benefit-risk assessment favors continued administration of study treatment. Participants will be permitted to continue treatment beyond initial RECIST v1.1 defined progressive disease (PD), as assessed by the Investigator, as long as the following criteria are considered:

- Investigator-assessed clinical benefit.
- Tolerance of study drug.
- Stable performance status.
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, central nervous system [CNS] metastases).

Participants must be re-consented with an ICF addendum or similar document to continue treatment beyond progression and prior to receiving additional treatment with the study drug regimen. All other elements of the main consent including description of reasonably foreseeable risks or discomforts, or other alternative treatment options will still apply. Continue radiographic assessment/scan(s) in accordance with the Section 2 Schedule of Activities for the duration of the treatment beyond progression and submit to the central imaging vendor. Balance the assessment of clinical benefit with clinical judgment as to whether the participant is clinically deteriorating and unlikely to receive any benefit from continued treatment with study regimens.

If the Investigator feels that the participant continues to achieve clinical benefit by continuing treatment, the participant could remain on the trial and should continue to receive monitoring according to the Section 2 (Schedule of Activities). Radiographic assessment, by compute tomography (CT; preferred) or magnetic resonance imaging (MRI) described in Section 5.1.4.1 and Section 9.1.1, is required when participants continue post-progression treatment and should

be performed for the duration of the treatment beyond progression and should be submitted to the central imaging vendor. Participants in Part 2C Arm D receiving regorafenib will have the option to transition to BMS-986288 in combination with nivolumab (Part 2C Arm Z) after BICR-assessed progression.

5.1.4.1 Discontinuation Due to Further Progression (Confirmed Progression)

Participants that meet the above criteria and continue on study therapy beyond initial PD must discontinue BMS-986288 (and nivolumab, if part of the combination cohorts) upon the next documented event of PD.

A follow-up scan should be performed within 6 weeks ± 5 days of original progressive disease to determine whether there has been a decrease in the tumor size, or continued progression of disease. For participants who continue study therapy beyond progression, further progression is defined as an additional 10% increase in tumor burden with a minimum of 5 mm absolute increase from time of initial PD. This includes an increase in the sum of diameters of all target lesions and/or the diameters of new measurable lesions compared to the time of initial PD. Study treatment should be discontinued permanently upon documentation of further progression.

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

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

5.1.5 Criteria for Transition From Regorafenib (Part 2C Arm D) to BMS-986288 in Combination with Nivolumab

Participants in the regorafenib arm (Part 2C Arm D) may receive BMS-9864288 in combination with nivolumab provided that the criteria below are met:

- The participant has PD per RECIST v1.1 (as assessed by BICR).
- The participant has completed at least 2 cycles of regorafenib.
- At least [redacted] days have elapsed since the last dose of regorafenib.
- AEs have returned to ≤ Grade 1 or baseline, except clinically insignificant laboratory values which must have returned to ≤ Grade 2 or to baseline.
- Provided participants still meet physical and laboratory test findings inclusion criteria (see Section 6.1 Inclusion Criterion 3)).
- Participant does not have any condition, including active or uncontrolled infection, or the presence of laboratory abnormalities, which places the participant at unacceptable risk.

- Participant provides written informed consent prior to receiving additional treatment.

For Part 2C Arm D participants who elect to crossover to Part 2C Arm Z to receive BMS-986288 in combination with nivolumab, a collection [redacted] is mandatory in order to provide pre-treatment information. These participants may continue treatment at the next scheduled treatment visit and will be followed on study for up to 2 years from the last dose of study intervention.

5.1.6 Data Monitoring Committee and Other External Committees

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 WWPS-led Safety Management Team (SMT). This collaborative process constitutes the Data Safety Monitoring Plan for the study, as detailed below.

Study safety is evaluated continuously by representatives of BMS WWPS, who operate independently from the clinical team and monitor safety across all BMS protocols. AEs are monitored continuously by WWPS. Signal detection is performed at least monthly and ad hoc throughout the study by the SMT composed, at a minimum, of the WWPS medical safety assessment physician (Chairman of the SMT) and WWPS single-case review physician, the study Medical Monitor(s) (or designee), the study biostatistician, and epidemiologist. The SMT 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 treatment(s). 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 [redacted] 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 BMS 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.

Relative to the exploratory nature of this Phase 1/2 study and the robust experience that already exists around use of ipilimumab, BMS has elected not to use a Data Monitoring Committee (DMC) for this study. In addition to the comprehensive safety monitoring plan outlined above, 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).

- 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-986288 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.
- For the combination therapy with nivolumab management algorithms for immune-related events are well established based on the clinical experiences from the over 17,700 patients who were exposed to nivolumab as either monotherapy or in combination with other agents, in the past as well as in ongoing studies.

5.2 Number of Participants

The approximate total number of evaluable participants treated will be up to [redacted], as shown below:

- Part 1 - Escalation Phase: Up to approximately [redacted] DLT-evaluable participants may be treated, including:
  - Part 1A - Safety Evaluation of BMS-986288 Monotherapy Escalation: Up to [redacted] evaluable participants
  - Part 1B - Safety Evaluation of BMS-986288 in Combination with Nivolumab: Up to [redacted] evaluable participants
  - [redacted] of BMS-986288 as a Monotherapy and in Combination with Nivolumab: Up to [redacted] evaluable participants
- Part 2 - Initial Expansion Phase: Up to [redacted] evaluable participants may be treated, including:
  - Part 2A - BMS-986288 [redacted] Cohort Expansion
    - Part 2A Cutaneous Melanoma: Up to [redacted] participants with cutaneous melanoma
    - Part 2A NSCLC: Up to [redacted] participants with NSCLC will be treated. If more than 1 dose level is evaluated, additional participants (up to [redacted] participants per dose level) may be enrolled, up to [redacted] participants (eg, [redacted] participants × 2 arms)
  - Part 2B - BMS-986288 in Combination with Nivolumab Cohort Expansion: Up to [redacted] participants with NSCLC will be treated. If more than 1 dose level is evaluated, additional participants (up to [redacted] participants per dose level) may be enrolled, up to [redacted] participants (eg, [redacted] participants × 2 arms).
  - Part 2C randomized MSS CRC cohort:
    - Arm C - BMS-986288 in combination with nivolumab: up to [redacted] participants will be randomized.
    - Arm D - standard of care: up to [redacted] participants will be randomized to receive regorafenib. Participants will have the option to transition to BMS-986288 in combination with nivolumab upon progression (Arm Z).

- If more than 1 dose level is evaluated, additional participants (up to [redacted] participants) may be treated in a separate arm (Arm E) in Part 2C.

For additional details on sample size determination, see Section 10.1.

5.3 End of Study Definition

The start of the study for the trial is defined as the first visit for the first participant screened. The end of the study for the trial is defined as the last visit or scheduled procedure shown in the Schedule of Activities (see 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.

A participant is considered to have completed the study if he/she has completed the last procedure shown in the Schedule of Activities.

5.4 Scientific Rationale for Study Design

BMS-986288 is being investigated as a monotherapy and in combination with nivolumab in humans with select advanced solid tumors (SCCHN, NSCLC, cutaneous melanoma, RCC, CRC, TNBC, urothelial carcinoma, gastric, esophageal, and cervical cancer). These indications were chosen based on a higher prevalence of [redacted] and [redacted] (internal data at BMS). [redacted] play an important role in impairing the anti-tumor immune response by [redacted] function. NF increases the affinity of BMS-986288 for [redacted], enhancing [redacted] of target expressing cells; this increase in effector function may mediate specific [redacted] at the tumor site. CTLA-4 is expressed on a subset of activated T cells on which it acts as a negative regulator of [redacted] activity. Blockade of CTLA-4 has been shown to augment [redacted] activation and proliferation, including the activation and proliferation of tumor infiltrating T-effector cells. Inhibition of CTLA-4 signaling can also reduce [redacted] function, which may contribute to a general increase in [redacted] responsiveness. The amount of [redacted] and CTLA-4 expression in tumor samples will be assessed in this study. The study design includes the following:

- 30-day screening period
- Up to 2 calendar year treatment period
- Dose-escalation phases in monotherapy and combination with nivolumab
- Cohort-expansion phase
- Safety follow-up period of 100 days from EOT
- Imaging/survival follow-up period of up to [redacted] years from EOT

The rationale for the individual elements of the study design are given below.

5.4.1 Rationale for BMS-986288 Monotherapy Dose Escalation (Part 1A) and the Safety Evaluation of BMS-986288 in Combination with Nivolumab (Part 1B)

The safety of CTLA-4 blockade with ipilimumab has been extensively characterized in more than 22,571 participants with different cancer types (refer to the ipilimumab IB for further details[21]). Modifying the ipilimumab structure with enhanced [redacted] may result in a different dose/effect relationship and AE profile; however, the addition of the protease cleavable masking peptide may abrogate the affinity for CTLA-4 and minimize systemic effects. BMS is evaluating an anti-CTLA-4 NF mAb (clinical trials.gov, NCT03110107) and an anti-CTLA-4 Probody mAb (clinicaltrials.gov, NCT03369223) in separate clinical trials. Emerging data from these programs may help inform the dose effect and AE profile of BMS-986288. In addition, in nonclinical experiments, BMS-986288 was tolerated at doses up to [redacted] mg/kg, with evidence of pharmacodynamic effects at all doses. The [redacted] mg ([redacted] mg/kg) of BMS-986288 in the monotherapy dose escalation (Part 1A) is lower than the dose safely tested in animals, and will allow an accurate evaluation of the tolerability of BMS-986288.

Furthermore, the study plans to evaluate different dose escalations of BMS-986288 in combination with nivolumab (Part 1B). The combination of ipilimumab and nivolumab is approved for RCC in the US and unresectable melanoma in multiple countries, including the US and EU. Information regarding safety and efficacy can be found in the nivolumab IB.[18] The combination of nivolumab and ipilimumab is also currently under investigation in various doses, schedules of administration, and additional tumor types. Different doses and schedules of administration were evaluated with different outcomes in terms of safety, tolerability, and efficacy depending on tumor type.[18] The combination study design and the doses are based on the results of safety data from clinical trials evaluating nivolumab and ipilimumab combinations (see Section 3.2.4 and the nivolumab IB[18]) and will evaluate BMS-986288 in combination with nivolumab [redacted] mg [redacted] as outlined in the study design schematic in Figure 5.1-1.

In addition, NSCLC patients poorly tolerated certain doses and schedules of ipilimumab and nivolumab combination therapy, while alternative dosing schedules resulted in a more manageable AE profile, as demonstrated by the results in CA209012.[34] Given the CA209012 safety data and to minimize the introduction of bias in initial dose escalation, for Part 1B participants with NSCLC will not be included in a BMS-986288 + nivolumab dosing cohort during the initial DLT evaluation period. However, given the ipilimumab and nivolumab combination efficacy data in NSCLC, after a BMS-986288 + nivolumab dose level is determined to be tolerable, participants with NSCLC will then be allowed to enroll and will be evaluated to determine if NSCLC patients have a similar tolerability and efficacy profile. Data from the NSCLC participant population will therefore be available for utilization in subsequent dose selection and MTD/RP2D determination.

Modifying the ipilimumab structure into an NF Probody mAb has the potential to offer decreased systemic exposure, which may translate into better tolerability while increasing efficacy at the tumor site when administered alone or in combination, and may be a more effective CTLA-4 regimen for a larger number of patients in different tumor types. PK and pharmacodynamic data

will be evaluated to ensure there is evidence of decreased systemic absorption and activation in relation to effects in the tumor microenvironment.

The BLRM with an overdose control principle escalation was selected as an appropriate design for this study. It offers more accuracy and efficiency in determining the true MTD compared to rule based methods (such as 3 + 3 design) by incorporating external information from pre-clinical studies as well as [redacted] clinical trials. The EWOC principle limits the risk of exposing participants in the next cohort to an intolerable or toxic dose. Hence, it ensures that safety is not compromised during dose escalation. Simulation results demonstrate that BLRM allows fast escalation when the expected toxicity is very low, and limits participants treated at sub-therapeutic doses, which is attributed to the adaptive Bayesian learning from previous doses. In addition, BLRM has greater applicability to the combination therapy setting compared to other model-based methods. The drug-associated dose toxicity profiles from the BMS-986288 Monotherapy Dose Escalation (Part 1A) will be characterized and incorporated as prior knowledge into the Safety Evaluation of Combination Doses of BMS-986288 with Nivolumab (Part 1B), the [redacted] Administration of BMS-986288 as a Monotherapy and Combination with Nivolumab [redacted], the initial drug expansion phase of the study (Part 2), or used in future studies.

5.4.2 Rationale for Tumor Selection in Part 1

Specific tumor types (SCCHN, NSCLC, cutaneous melanoma, RCC, CRC, TNBC, urothelial carcinoma, gastric, esophageal, and cervical cancer) were selected in Part 1 to evaluate the safety and potential therapeutic effect of BMS-986288 monotherapy and in combination with nivolumab based on the following rationale:

- Previously assessed safety and efficacy profile of ipilimumab alone or in combination with nivolumab.
- Tumors associated with higher prevalence of [redacted] and [redacted] (internal data at BMS).[35]
- Tumors for which [redacted] has been correlated with worse prognosis.

Nonclinical data suggests that BMS-986288 [redacted] activity at the tumor site and [redacted] peripheral systemic exposure to CTLA-4 blockade compared with ipilimumab. Hence, BMS-986288 alone and in combination with nivolumab may potentially improve the [redacted] previously seen with ipilimumab treatment in the aforementioned tumor types.

5.4.3 Rationale for Tumor Selection in Part 2C

Nivolumab administered as monotherapy has demonstrated remarkable clinical benefit in several solid tumor types, including MSI-H CRC. However, MSS CRC is highly immunosuppressive, and inhibits the activation of anti-tumor immune responses that allow T-cells to engage with the tumor.[36] Single-agent immunotherapies are largely ineffective in pMMR/MSS CRC, which represents approximately 85%-96% of the CRC patient population.[37,38,39] Preclinical and clinical evidence suggests synergy between nivolumab and ipilimumab, which target distinct mechanisms that limit T-cell activation, PD-1, and CTLA-4, respectively. In vitro combinations of nivolumab

plus ipilimumab increase IFN-γ production 2- to 7-fold over either agent alone in a mixed lymphocyte reaction. The combination of nivolumab and ipilimumab has been shown to be more effective than either agent in monotherapy in the treatment of a variety of tumors including melanoma, lung, and renal cell carcinoma.[40,41,42,43] Most relevant, this combination has also demonstrated meaningful clinical efficacy (Checkmate 142) in MSI-H CRC of improved efficacy compared to immuno-oncology monotherapy. In a murine melanoma vaccine model, blockade with either CTLA-4 or PD-1 antibodies increased the proportion of CTLA-4 and PD-1-expressing CD4/CD8 tumor infiltrating T effector cells, and dual blockade increased tumor infiltration of T effector cells and decreased intratumoral T regulatory cells, as compared to either agent alone.[44]

Despite minimal activity observed in MSS CRC with the combination of nivolumab and ipilimumab, clinical activity with next generation anti-CTLA4s was seen in the form of reductions in tumor volume, including objective responses in MSS CRC.[45,46] Similar results are also observed when participants with MSS CRC are treated with BMS-986218, a Fc-enhanced ipilimumab, in combination with nivolumab.[14] BMS-986288 is an enhanced Fc ipilimumab with Probody mAb (PROBODY is a trademark of CytomX Therapeutics, Inc.) and is designed to provide a well tolerable safety profile. Modifying the ipilimumab structure with enhanced Fc engagement may result in a different dose/effect relationship; however, the addition of the protease cleavable masking peptide may minimize systemic effects (details in Section 5.4.1).[2] This combination has an added mechanism of action compared to ipilimumab in combination with nivolumab. These data collectively support the further investigation of BMS-986288 in combination with nivolumab in MSS CRC participants.

5.4.4 Rationale for Randomization in Part 2C

The overall sample size in Arm C (containing BMS-986288) is [redacted] participants to allow for sufficient sizing for safety and subgroup efficacy analyses. To maintain a suitable number of total participants, the randomization ratio is 2:1. The sample size of the comparator cohort is up to [redacted] participants; in addition, to up to [redacted] (see Section 5.4.8). The clinical data from another Fc-enhanced anti-CTLA-4 inhibitor demonstrated higher clinical benefit in MSS CRC patients without liver metastasis.[44] To minimize the potential for imbalances across treatment arms, there will be a stratification factor utilized in this trial: liver metastasis status (yes [which includes locally treated liver metastasis] or no). The prognostic implications of liver metastasis status is well established; participants in the current trial will therefore be stratified by liver metastasis as the effect on response to nivolumab and BMS-986288 combination therapies is not yet known.

5.4.5 Rationale for BMS-986288 in Participants Previously Treated with [redacted] Immunotherapy

Cancer immunotherapies that target the immunosuppressive checkpoint receptors CTLA-4 or PD-1 and its ligand, PD-L1, have changed the landscape of anti-cancer immunotherapy. In particular, checkpoint inhibitors targeting PD-1 and PD-L1 have demonstrated unprecedented

clinical efficacy in more than 15 cancer types, including melanoma, NSCLC, RCC, urothelial carcinoma, SCCHN, and Hodgkin's lymphoma.[47] Nevertheless, primary resistance to anti-PD-1 therapies is common, affecting up to 60% of patients in some cancer types. Furthermore, it is now becoming apparent that encouraging initial responses observed among some patients can be undone by their development of acquired resistance to anti-PD-1 therapies, leading to disease relapse.[48] In the current understanding of mechanisms contributing to the development of resistance to anti-PD-1 therapy, overexpression of other immune checkpoints (TIM-3, LAG-3, and CTLA-4) and influx of [redacted] (which co-express these molecules) have been demonstrated to promote either primary or acquired resistance to anti-PD-1 therapy.[49,50]

A transcriptional signature associated with resistance to PD-1 immunotherapy, termed as Innate PD-1 RESistance (IPRES) was reported. Notably, over 30% of patients whose melanomas expressed the IPRES signature responded to CTLA-4 blockade (ipilimumab), suggesting that the IPRES signature does not indicate resistance to every immunotherapy.[51]

Targeting CTLA-4 and [redacted] could present a valuable mechanism to overcome anti-PD-1 resistance, especially in tumors where a high level of [redacted] correlates with poor prognosis. Including participants with cutaneous melanoma and NSCLC will therefore enable this hypothesis to be assessed in tumor types with established responsiveness to ipilimumab, and in those where ipilimumab monotherapy did not demonstrate a sufficient level of efficacy, respectively.

5.4.6 Rationale for Two Years Fixed Duration with Checkpoint Blockade

The optimal duration of immunotherapy is an important question and continues to be investigated. Accumulating data suggest that 2 years of PD-1 checkpoint inhibitor treatment may be sufficient for long-term benefit. 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 for > 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 OSR of 25% at 2 years and 18% at 3 years.[52] 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 OSRs of 23% and 29%, and 3-year OSRs of 16% and 18% for squamous and non-squamous NSCLC, respectively).[53]

Taken together, these data suggest that 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.

In contrast, a 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. In 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-treatment allocation) not reached vs 10.3 months, respectively; HR = 0.42 (95% CI: 0.25, 0.71). With a median follow-up of 14.9 months post-treatment allocation, 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 treatment allocation (ie, 2 years after treatment initiation), suggesting that there may be minimal benefit in extending treatment beyond a total of 2 years.[54]

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 can be well tolerated, participants will be at risk for additional toxicity with longer-term treatment.

The role of immune check-point inhibitors in MSS or pMMR CRC is under investigation to validate the hypothesis of evoking immunogenic responses.[55] Although the optimal duration of checkpoint blockade in MSS or pMMR CRC is not yet defined, the data presented above indicate that the duration of 2 years in solid tumors, including MSS or dMMR CRC, would achieve an optimal risk/benefit ratio. Therefore, in this study, nivolumab and BMS-986288 treatment will be given for up to 2 years in the absence of disease progression or unacceptable toxicity. There is no maximum treatment duration for Part 2C Arm D (regorafenib). Treatment with regorafenib may continue until progression of disease or unacceptable toxicity (see Section 8.1) in accordance with locally approved prescribing information.

5.4.7 Rationale for Quality of Life Evaluation

The evaluation of patient-reported outcomes (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 (HRQoL) measures provide data needed for calculating utility values to inform health economic models.

The 5-Level EQ-5D (EQ-5D-5L) will be used to assess general health status, the Functional Assessment of Chronic Illness Therapy, General Physical item (FACIT GP5) will be used to assess the overall bother of side effects, and the Non-small Cell Lung Cancer Symptom Assessment Questionnaire (NSCLC-SAQ) will be used to assess symptoms and overall HRQoL in this patient population.

These PROs will only be administered in Part 2 of this protocol. Part 2C is excluded from PROs.

5.4.8 Rationale for Using a [redacted] Arm

In Part 2C of this study, a [redacted] arm is planned. A portion (up to [redacted] participants) of the control cohort will be [redacted].[56] The use of a [redacted] arm allows optimizing the usage of participant

data by [redacted] the number of participants in control groups. As such, more patients will have access to potentially new effective medicines during clinical development.

To establish the appropriate assessment of the treatment effect between the experimental arms and the [redacted] arm, 2 approaches will be taken:

- The baseline eligibility (inclusion/exclusion criteria) from the current study recapitulates the [redacted] randomized control trial planned to be used as the [redacted]. This ensures the consistency of the overall target population of the intended indication to enhance the confidence of any conclusions drawn (see further details in Section 10.1.6).
- During the study, it is possible that there may still be differences between the current study and the [redacted] external control due to the sampling mechanism. [redacted] using baseline prognostic information will be applied to further reduce the potential bias. Details of the [redacted] method will be described in the statistical analysis plan.

5.4.9 Rationale for Not Blinding

The study will be open label. The Site and Sponsor will be unblinded to BMS-986288 treatment assignment. This is to facilitate safety monitoring by the Sponsor and to ensure adequate ability of the clinical trial physician to monitor and discuss the management of the participants with the investigators.

5.5 Justification for Dose

5.5.1 Rationale for BMS-986288 Starting Dose in Humans

Introduction

The starting dose of BMS-986288 for this FIH study was selected to be a [redacted]-mg [redacted] initially administered [redacted].

The BMS-986288 starting dose was determined by taking into consideration:

1) The GLP toxicology studies, which utilized the HNSTD identified from a 1-month repeat-dose toxicity study in cynomolgus monkeys and demonstrated [redacted] systemic immune-activating pharmacodynamic responses and toxicities in cynomolgus monkeys compared to ipilimumab.
2) The nonclinical pharmacology-based method, which evaluated BMS-986288 in a human CTLA-4 [redacted] model, and demonstrated [redacted] in comparison with ipilimumab. In addition, human PK projection suggested that BMS-986288 will slowly convert to the fully active species in systemic circulation with the steady-state exposure [redacted] of ipilimumab, and may result in a more tolerable safety profile.
3) The known clinical safety experience data of ipilimumab. Because BMS-986288 is a Probody of the NF form of ipilimumab, it is predicted to have the same type of irAEs as ipilimumab that have been well defined and managed in clinic. BMS is also evaluating an anti-CTLA-4 NF mAb (BMS-986218) and an anti-CTLA-4 Probody mAb (BMS-986249) in separate clinical trials (clinicaltrials.gov, NCT03110107 and NCT03369223, respectively). Emerging

data from these programs may help inform BMS-986288 clinical trial design and AE management.

The BMS-986288 starting dose of [redacted] mg (approximately [redacted] mg/kg) was derived from the known ipilimumab clinical safety profile and supported by preliminary clinical data from the anti-CTLA-4 NF mAb (BMS-986218; clinical trials.gov, NCT03110107) and the anti-CTLA-4 Probody mAb (clinicaltrials.gov, NCT03369223) programs. Importantly, this dose is about [redacted] below the starting dose calculated from toxicology- and pharmacology-based methods and is also supported by the no-effect level from the in vitro cytokine release assay. Therefore, [redacted] mg/kg converted to a [redacted] mg, [redacted], is recommended as the FIH starting dose for BMS-986288.

Collectively, the proposed strategy for FIH starting dose selection represents the intent of ensuring adequate patient safety while limiting the number of cancer patients receiving sub-therapeutic doses.

Starting Dose Selection Supported by the HNSTD in Monkeys

The HNSTD of BMS-986288 from a GLP 1-month repeat-dose toxicity study in monkeys was determined to be [redacted] mg/kg.[8] Using the standard body weight (BW) conversion to the human equivalent dose and applying a safety factor of [redacted], the human starting dose was calculated to be [redacted] mg/kg (or [redacted] mg [redacted] for [redacted]). In addition, the total antibody exposure (AUC[0-168h]) observed at the HNSTD, after the 4th dose, was [redacted] µg•h/mL. Based on the monkey HNSTD exposure and the predicted human clearance of the total antibody ([redacted] mL/d/kg), the FIH starting dose, after applying a safety factor of [redacted], was estimated to be [redacted] mg/kg (or [redacted] mg [redacted] for [redacted]). However, the actual proposed FIH starting dose ([redacted] mg, or approximately [redacted] mg/kg), based on additional considerations described below, is [redacted] lower than that supported by this HNSTD-based approach, providing an additional safety factor.

Starting Dose Selection Supported by BMS-986288 Nonclinical Pharmacology

In nonclinical pharmacology and toxicology studies described in previous sections, BMS-986288 compared to ipilimumab and BMS-986218 demonstrated reduced in vitro activities, in vivo systemic active drug exposure and pharmacodynamic responses, and yet maintained comparable anti-tumor activity in the human CTLA-4 [redacted] tumor model. The key differentiation between BMS-986288, ipilimumab, and BMS-986218 is summarized below.

- BMS-986288 binds human CTLA-4 expressed on [redacted] α-β-CTLA-4/CD3 cells with approximately [redacted]-fold higher EC50 than BMS-986218 and ipilimumab [redacted] but similar to BMS-986249 [redacted] nM). These differential binding affinities translate to lower IL-2 secretion by BMS-986288 vs ipilimumab and BMS-986218 and slightly higher IL-2 secretion vs BMS-986249 in [redacted] human [redacted] functional assay.
- In the FcγR-mediated [redacted] assay, the ranking of activity by the antibodies was as follows: BMS-986218 > ipilimumab > BMS-986288 > BMS-986249. These data are consistent with the expectation that the NF version of ipilimumab is more potent, and that the addition of the Probody masking peptide reduces functional [redacted] activity.

- PK of BMS-986288 in mice and cynomolgus monkeys suggests that the intact Probody is slowly converted to [redacted] species in vivo. The projected systemic exposure of the [redacted] Probody, which is equally active as BMS-986218, is predicted to be [redacted] of BMS-986218 exposure when BMS-986288 is administered at the same dose as BMS-986218 in patients. For comparison, the conversion efficiency of BMS-986288 to its active species in monkeys was similar to BMS-986249.
- In human CTLA-4 [redacted] tumors, BMS-986288 had similar anti-tumor activity to BMS-986218 in the [redacted] model at all 3 dose levels tested, and both antibodies demonstrated greater activity than ipilimumab and BMS-986249 at the 2 lower dose levels. BMS-986288-treated mice also had similar levels of [redacted] reduction, indicating that the drug has similar pharmacodynamic activity at the tumor site. Analysis of peripheral [redacted] populations in the spleen indicated that the levels of the activation markers Ki-67 and ICOS on [redacted] and [redacted] in BMS-986288-treated animals were [redacted] compared to ipilimumab and BMS-986218-treated animals. The [redacted] in peripheral pharmacodynamic activity by the Probody is consistent with the goal of the Probody therapeutic to [redacted] CTLA-4 binding activity outside of the tumor site.
- In a non-GLP investigative 3-week monkey investigative study, BMS-986288 at [redacted] mg/kg exhibited [redacted] systemic [redacted]/pharmacodynamic responses when compared to BMS-986218 or ipilimumab at the same dose in a time-dependent manner, corresponding with a delayed conversion of BMS-986288 to its active forms. By the end of the dosing period, the magnitude of change for pharmacodynamic activity for most endpoints was generally BMS-986218 > ipilimumab ≥ BMS-986288.

Assuming the in vitro activities, in vivo systemic active drug exposure, and pharmacodynamic responses of BMS-986288 relative to ipilimumab and BMS-986218 in nonclinical studies translate to cancer patients, BMS-986288 at the starting dose of [redacted] mg may provide similar efficacy as ipilimumab, but with reduced systemic active drug exposure and pharmacodynamic responses that may be responsible for its irAEs.

Starting Dose Selection Based on Ipilimumab Clinical Exposure and Response of Safety Analysis in Melanoma Patients

BMS-986288 is the NF Probody form of ipilimumab. 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. An exposure-response of safety analysis conducted with ipilimumab data from previously treated advanced melanoma patients showed that, the probability of Grade 3+ irAEs occurred at approximately 3% in patients receiving 0.3 mg/kg.[57] The probability of Grade 3+ irAEs increased to 11% and 23% at ipilimumab doses of 3 mg/kg and 10 mg/kg, respectively. In advanced melanoma patients, the irAEs of ipilimumab at 3 mg/kg Q3W for 4 cycles occurred in approximately 60%-65% of the patients. These AEs were mostly Grade 1 or Grade 2 and affected primarily the skin (in 43%-45% of patients) and gastrointestinal tract (in 29%-32% of patients), followed by the liver and endocrine system (in 6%-8% of patients). 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.[58] In addition, a low incidence of infusion-related reaction of ipilimumab was also

reported in 2.2% and 4.3% patients treated at 3 mg/kg and 10 mg/kg infused over 90 minutes, respectively, and can be treated by premedication with diphenhydramine.[59] Management of irAEs attributed to ipilimumab treatment have been well established as the Risk Evaluation and Mitigation Strategy (REMS) Guidelines approved by FDA.[60]

The BMS-986288 FIH starting dose was selected to be [redacted] mg [redacted] (approximately [redacted] mg/kg). Considering the preclinical similarities between BMS-986288 and ipilimumab (specifically the HNTSD of BMS-986288 was [redacted] as ipilimumab, the preclinical peripheral pharmacodynamic activity for ipilimumab was [redacted] to BMS-986288, while the preclinical anti-tumor activity was [redacted] for BMS-986288 than for ipilimumab), the BMS-986288 FIH starting dose was selected to be similar to the ipilimumab dose that produced minimal Grade 3+ irAEs in the clinic. In addition, the FIH starting dose is supported by the preliminary clinical experience from the anti-CTLA-4 NF mAb (BMS-986218; clinical trials.gov, NCT03110107) and the anti-CTLA-4 Probody mAb (clinicaltrials.gov, NCT03369223) programs.

5.5.2 Rationale for BMS-986288 Maximum Dose

At the time of this Protocol Amendment 02, the preliminary clinical safety profile of BMS-986288 as a single agent ([redacted] mg to [redacted] mg [redacted]) and in combination with nivolumab (BMS-986288 [redacted] mg + nivolumab [redacted] mg [redacted]) is well tolerated and clinically manageable. The MTD for BMS-986288 has not been reached. [redacted] reported were Grade [redacted], and [redacted] were reported with monotherapy or combination therapy. Therefore, [redacted] additional dose levels ([redacted] mg [redacted] and [redacted] mg [redacted]) have been added to Part 1A to further explore the MTD for monotherapy, while maintaining the projected safety exposure margin greater than [redacted] for Cmax and [redacted] for AUC). In addition, [redacted] mg [redacted] and [redacted] mg [redacted] of BMS-986288 in combination with [redacted] mg [redacted] nivolumab have been added to Part 1 B to explore the MTD for the combination therapy. The dose of BMS-986288 to be explored in Part 1B will not exceed the safe and tolerable BMS-986288 dose identified in Part 1A.

5.5.3 Rationale for BMS-986288 Dose Selection in Part 2C

For Part 2C Arm C, a safe dose of [redacted] mg BMS-986288 in combination with [redacted] mg nivolumab [redacted] will be used. Depending on the emerging PK, PD, safety, and preliminary efficacy results from Part 1B and Part 2B, an additional dose of BMS-986288 in combination with nivolumab may be evaluated in Part 2C as Arm E. The additional dose level will not exceed the dose level that has been evaluated and determined to be safe in Part 1B.

The selection of [redacted] mg BMS-986288 in combination with [redacted] mg nivolumab [redacted] is based on the clinical safety and [redacted] from Part 1A, Part 1B, and Part 2B, as described in the investigator brochure.[2]

As expected, all AEs observed in participants receiving BMS-986288 in combination with [redacted] mg nivolumab were qualitatively similar to those seen with ipilimumab.

Aforementioned safety observations suggest that [redacted] mg BMS-986288 in combination with [redacted] mg nivolumab is safe and tolerable. The [redacted] shows [redacted] mg is the optimized dose

level. The benefit-risk balance will be continuously evaluated and compared among [redacted] mg BMS-986288 in combination with [redacted] mg nivolumab, [redacted] mg BMS-986288 in combination with [redacted] mg nivolumab, and [redacted] mg BMS-986288 in combination with [redacted] mg nivolumab with emerging data. An additional dose of BMS-986288 [redacted] mg or [redacted] mg) in combination with nivolumab may be added to Part 2C.

5.5.4 Rationale for [redacted] Selection and Dosing Schedule

5.5.4.1 BMS-986288

A [redacted] (mg) of BMS-986288 will be used in this study instead of a [redacted] dose. Therapeutic mAb doses have been routinely calculated on a body size basis. This practice assumes that [redacted] significantly reduces variability in therapeutic mAb exposure.[61] However, recent analyses of marketed and experimental mAbs have demonstrated that [redacted]-based dosing did not always offer advantages over [redacted] 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, [redacted] dosing could result in higher mAb concentrations in the heaviest participants (eg, 90th percentile), whereas [redacted] could lead to higher mAb concentrations in the lightest participants (eg, 10th percentile). Body weight distribution data from a clinical trial database of over 2500 adults with solid or hematologic cancers suggested a log-normal distribution of body weight with median, 10th percentile, and 90th percentile of 78 kg, 56 kg, and 112 kg, respectively.[62]

In addition to the above rationale, [redacted] offers practical advantages over [redacted] 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 [redacted] calculations.[61] Because the magnitude of the impact [redacted] on the human PK of BMS-986288 is not yet determined, the PK and safety data from the Phase 1/2 study will be evaluated to validate the [redacted] approach. If appropriate, based on the totality of the data, the Sponsor will consider a revision of the [redacted] strategy.

BMS-986288 will initially be administered [redacted]. This dosing frequency is supported by the projected human T-HALF for BMS-986288 of [redacted]. In addition, it complements the [redacted] dosing regimen planned in the Safety Evaluation of Combination Doses of BMS-986288 with Nivolumab (Part 1B), the [redacted] Evaluation of BMS-986288 as a Monotherapy and in Combination with Nivolumab [redacted] and the BMS-986288 in Combination with Nivolumab Cohort Expansion (Part 2B), thereby simplifying study logistics for both participants and Investigators. An alternative dosing schedule may implemented upon evaluation of available safety, PK, and pharmacodynamic data from [redacted] administration (refer to Table 2-2 and Appendix 8).

5.5.4.2 Rationale for [redacted] Administration of BMS-986288 with or without Nivolumab [redacted]

[redacted] has the potential to reduce infusion time and provide greater convenience and comfort for oncology patients. The [redacted] facilitates [redacted] as demonstrated by several [redacted] biologic therapies already approved in the US, EU, and other countries (eg, trastuzumab and rituxumab). As of 15-Nov-2018, [redacted] and other [redacted] have been administered to 1592 participants in 30 clinical studies conducted under [redacted] or in postmarketing Phase 4 studies. In these studies, individual doses have ranged from [redacted]. Across all studies, [redacted] of [redacted] were generally well-tolerated in healthy participants, dehydrated pediatric participants, hospice and palliative care participants, participants with type 1 and type 2 diabetes, and participants with rheumatoid arthritis. [redacted] alone or in combination with lactated Ringer's, normal saline, co-injected drugs (morphine, ceftriaxone, insulin, and insulin analogs), or biologic products (IgG and adalimumab) have been well-tolerated in all clinical trials. Most AEs were mild, transient [redacted] reactions, including erythema, pain, bruising, pruritus, burning, tenderness, edema, induration, irritation, paresthesia, numbness, and rash. Moderate [redacted] reactions, which have occurred less frequently, include burning, erythema, pain, and numbness. Mild-to-moderate headache was also commonly reported. AEs in these trials have otherwise generally reflected the adverse reaction profiles of the [redacted] drug or have been associated with the rapid introduction of a relatively large volume of fluid in the [redacted].

In addition, a large safety database exists for approved products coformulated with [redacted].

Studies have consistently shown that the bioavailability (BA) of monoclonal antibodies following [redacted] approximates [redacted] with lower Cmax, a delayed and decreased Tmax, a comparable trough-observed plasma concentration (Ctrough) compared to [redacted] administration, and comparable overall exposure. Comparable efficacy (ORR, complete response rate, PFS, EFS, and OS in various studies) for [redacted] routes was also demonstrated. The mAb dose ranges evaluated in these studies ranged from [redacted] mg to [redacted] mg when administered with or without [redacted] BMS-986288 will be studied in the dose range of [redacted] mg to [redacted] mg. Clinical evaluation of nivolumab [redacted] with and without [redacted] is currently ongoing (clinicaltrials.gov, [redacted]).

Overall, these data suggest that [redacted] of BMS-986288 and [redacted] of nivolumab, at a dose exposure previously shown to be safe intravenously, should be feasible and tolerable. Additionally, as part of a 1-month toxicity study in monkeys, weekly [redacted] of [redacted] mg/mL BMS-986288 and [redacted] U/mL [redacted] resulted in no significant skin irritation or local tolerance issues. In a separate nonclinical toxicity study in monkeys, nivolumab administered at [redacted] mg/kg [redacted] U/mL) was also shown to be well-tolerated with no clinical observations and no local tolerance issues at the [redacted] sites. The use and dose of [redacted] will be determined following evaluation of preliminary data from Part 1A and Part 1B. Potential risks will be further mitigated through a sentinel participant dosing strategy. The PK data from this [redacted] cohort will inform BA in comparison to [redacted] formulation and may help in

determining [redacted] for the initial expansion phase (Part 2). The participants receiving the [redacted] administration will be different from those receiving IV administration, not crossed over. It is anticipated that the cleavage of the Probody to active species will be relatively slow and, as a result, there may be accumulation after repeat dosing. In addition, there may be potential of cleavage at the [redacted] site before absorption into lymphatic system. The presence of multiple and different processes may complicate an accurate assessment of the BA. Separate [redacted] cohorts will facilitate safety assessment attributed to these different dosing routes.

5.5.4.3 Rationale for Nivolumab 30-minute Infusions

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.[68] In the substudy, 322 participants received nivolumab 3 mg/kg IV Q2W as a 30-minute infusion, and 355 participants received the same nivolumab regimen as a 60-minute infusion. As detailed in the nivolumab IB,[18] nivolumab can be safely administered as a 30-minute infusion, with a low incidence of irAEs. Given these findings, 30-minute infusions are being implemented across nivolumab development programs, including the FIH study CA043001.

5.5.4.4 Rationale for [redacted] of Nivolumab

A nivolumab [redacted] dose of [redacted] mg every 2 weeks (Q2W) was approved in the US as monotherapy for unresectable or metastatic melanoma, metastatic NSCLC, advanced RCC, locally advanced or metastatic urothelial carcinoma, MSI-H or mismatch repair deficient (dMMR) mCRC, HCC, and as maintenance therapy for unresectable or metastatic melanoma after induction therapy with nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks (Q3W) for 4 doses. In addition, nivolumab [redacted] mg [redacted] infused over 30 minutes was Food and Drug Administration (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.

The benefit-risk profiles of nivolumab [redacted] mg [redacted] and [redacted] mg [redacted] are expected to be comparable to [redacted] mg/kg [redacted]. This assessment is based on a comprehensive characterization of nivolumab PK, safety, efficacy, and E-R relationships across indications. Given that nivolumab has linear PK over a dose range of 0.1 to 10 mg/kg across multiple tumor types, the [redacted] mg [redacted] regimen was selected based on the approximate [redacted] for subjects treated in nivolumab clinical trials. The [redacted] mg [redacted] regimen was selected as it translates to a [redacted] of the [redacted] mg [redacted]. With reduced dosing frequency from [redacted], the average nivolumab exposure with [redacted] mg [redacted] is expected to be comparable to that from [redacted] mg/kg [redacted] mg [redacted]. Additional details are provided in the current version of the nivolumab IB.[18]

Given the PK, safety, and efficacy data for nivolumab monotherapy (mg/kg dosing) and the simulated [redacted] exposure data described above, a nivolumab [redacted] mg [redacted] will be examined in combination with BMS-986288 in this study.

5.5.4.5 Rationale for [redacted]

Long [redacted] times place a burden on patients and treatment centers. Establishing that nivolumab and BMS-986288 can be safely administered using shorter [redacted] times of approximately [redacted] in participants will diminish the burden provided no change in safety profile. [redacted] However, [redacted] may result in [redacted][2] Therefore, any potential safety differences between [redacted] and [redacted] regimens would be expected to be limited to infusion reactions. [redacted] versus [redacted] is not expected to impact the overall safety profile. Overall, infusion reactions including high-grade hypersensitivity reactions have been uncommon across nivolumab or BMS-986288 clinical studies [redacted].

5.5.4.6 Rationale for Choice of Standard of Care Treatment in Part 2C

Regorafenib is a standard late line therapy for patients with mCRC who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and anti-epidermal growth factor receptor (EGFR) therapy (if KRAS wild type). Regorafenib is approved by regulatory authorities in many regions of the world for patients with mCRC who have failed at least 2 prior lines of therapy (no more than 4 prior lines). Regorafenib was chosen to be the standard of care treatment in Part 2C, in accordance with practice guidelines that advise that regorafenib may provide benefit when used in the 3L+ setting.[69,30] In the 3L setting, approved therapies are used interchangeably due to their similarity in treatment benefit. A single therapy (regorafenib) was chosen as a comparator in the Part 2C cohort due to its cross-country and regional availability and because matched studies utilizing regorafenib are available to enable use of a [redacted] in this cohort. Participants in Arm D (regorafenib) can transition to BMS-986288 and nivolumab after disease progression (Arm Z).

5.5.4.7 Rationale for KRAS Testing

Activating mutations of the KRAS gene have been reported to occur in 35% to 40% of colorectal cancers.[70]

Although the prognostic value of KRAS mutations in CRC (independent of anti-EGFR therapy) is unclear due to conflicting data, KRAS mutations are predictive for a lack of response and clinical benefit from anti-EGFR mAbs in patients with mCRC based on several large clinical trials.[71]

All participants with metastatic colorectal cancer should have tumor genotyped for RAS (KRAS and NRAS), and after lines of treatment to address RAS status changes and to collect real-time data on RAF/RAS genetics. Participants with any known KRAS or NRAS mutation should not be treated with EGFR-targeting monoclonal antibodies.[72]

5.5.4.8 Rationale for [redacted] Testing

[redacted] are observed in 5% to 10% of CRC, with 80% to 90% of [redacted] being [redacted] Given the poor prognosis associated with [redacted] mutations, these patients will be excluded.

5.5.4.9 Rationale for Dose Selection of Regorafenib and Line of Therapy (in 3rd/4th Line MSS CRC)

Recommended starting dose for regorafenib ([redacted] mg) is selected based on approved product labels across various regions. Local product label and institutional guidelines for regorafenib starting dose can be considered in consultation with BMS Medical Monitor/designee.

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.

6.1 Inclusion Criteria

1) Signed Written Informed Consent

a) The participant or their legally acceptable representative (see Appendix 2) 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 or their legally acceptable representative (see Appendix 2) must sign the consent for pretreatment, on treatment, and upon progression [redacted].

2) Type of Participant 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) and have at least 1 soft-tissue tumor lesion accessible for biopsy.

b) Eastern Cooperative Oncology Group Performance Status of 0 or 1 (Appendix 9).

c) The BMS-986288 Dose Escalation Phase (Part 1)

i) Participants with [redacted] proven NSCLC, SCCHN, CRC, RCC, TNBC, urothelial cancer, gastric cancer (including gastro-esophageal junction), esophageal cancer, cervical cancer, and cutaneous melanoma will be permitted during dose escalation, except for participants with tumors with CNS metastases as the only site of active disease.

(1) Part 1B participants with NSCLC will not be permitted as part of the initial DLT assessment; instead, Part 1B NSCLC participants will be evaluated only as part of additional participant enrollment to a previously tested tolerable cohort.

ii) All Part 1 participants must be anti-CTLA-4 naive. Prior anti-PD-1 or anti-PD-L1 exposure is allowed.

iii) Participants with Gastric or Esophageal Cancer:

(1) Must have received, and then progressed, relapsed, or been intolerant to, at least 1 standard treatment regimen in the advanced or metastatic setting (or have progressed within 6 months of adjuvant therapy).

(2) Participants with human epidermal growth factor receptor 2 (HER2)-positive gastric cancer must have received prior treatment with a HER2 inhibitor (eg, trastuzumab).

iv) Participants with Urothelial Carcinoma:

(1) Must have received, and then progressed, relapsed, been intolerant to, or ineligible for, at least 1 platinum-containing chemotherapy regimen

OR

Within 12 months of peri-operative (neo-adjuvant or adjuvant) treatment with a platinum agent in the setting of cystectomy for localized muscle-invasive urothelial cancer.

v) Participants with NSCLC:

(1) Must have received, and then progressed, relapsed, or been intolerant to, at least 1 standard treatment regimen in the advanced or metastatic setting

OR

Must have recurrent or progressive disease within 6 months after completing platinum based chemotherapy for local disease.

(2) **Not Applicable as of Amendment 02. See 2.c.v.3 below:** Participants with adenocarcinoma must have known epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK) status, and ROS1 mutational status.

(a) Must have been offered mutation-directed therapy, if indicated, that has proven survival benefit. This must be documented in the medical record.

(3) All participants with adenocarcinoma must have known EGFR, ALK, KRAS, and ROS1 status (when testing is available as per country/region standard of care practices); participants with an activating EGFR mutation, ALK translocation, or ROS1 mutation must have received appropriate inhibitor therapy (as available per country/region standard of care). Note: If KRAS results are not known, then a sample [redacted] should be sent for testing locally. [redacted] may be used if [redacted] results are not feasible, with prior Sponsor approval.

(a) Must have been offered mutation-directed therapy, if indicated, that has proven survival benefit. This must be documented in the medical record.

vi) 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).

(a) Prior treatment with fluoropyrimidine, oxaliplatin, and irinotecan given as a single regimen or over multiple regimens is required.

(b) Prior treatment with an anti-angiogenic therapy (eg, bevacizumab) is required.

(2) Participants must have known MSI or mismatch repair status. [redacted] status, if known, should be documented.

(a) If [redacted], prior treatment with an anti-EGFR therapy (eg, cetuximab or panitumumab) is required.

vii) 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-γ), vaccine therapy, or treatment with cytotoxics is allowed.

(2) **Not Applicable as of Amendment 02:** 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.

viii) Participants with SCCHN:

(1) Histologically confirmed, recurrent, or metastatic SCCHN (oral cavity, pharynx, larynx), and not amenable to local therapy with curative intent.

(a) Any other cancers of the head and neck, including salivary gland and neuroendocrine tumors, are excluded.

(2) Participants who progressed on or after, or were intolerant to, a platinum-containing regimen.

(3) Prior curative radiation therapy must have been completed at least 4 weeks prior to first study drug administration. Prior local palliative radiotherapy must have been completed at least 2 weeks before study drug administration.

(4) Documentation of p16 is sufficient to determine HPV status of tumor for SCCHN of the oropharynx. If results are not available, then a sample [redacted] should be sent to the central laboratory for analysis.

ix) Participants with TNBC:

(1) Males and females with histologically confirmed TNBC as defined by American Society of Clinical Oncology/College of American Pathologists guidelines.

(2) Participants must have had at least 1 chemotherapeutic regimens for the treatment of metastatic or locally advanced and unresectable disease.

(3) Participants must have been considered for all other potentially efficacious therapies.

x) Participants with Cervical Cancer:

(1) 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.

xi) Participants with cutaneous melanoma:

(1) Participants must have received, and then progressed, relapsed, or been intolerant to, at least 1 standard treatment regimen in the advanced or metastatic setting.

(a) If anti-PD-(L)1 therapy is approved then participants are eligible to receive this treatment as part of the Part 1B combination regimen in this study prior to having completed the 1 prior systemic therapy regimen, after discussion and agreement with the Medical Monitor (or designee).

(2) Participants must have known BRAF status.

d) The Expansion Phase of BMS-986288 [redacted] (Part 2A):

i) Participants with cutaneous melanoma:

(1) Histologically confirmed cutaneous melanoma that is unresectable or metastatic.
(a) Participants with ocular or mucosal melanoma are excluded.

(2) Must have radiologically or clinically documented progressive or recurrent disease occurring either during treatment with or within 3 months of discontinuing anti-PD-(L)1 therapy when administered as either monotherapy or as part of a combination.
(a) No more than 1 intervening therapy is allowed but not required between prior anti-PD-(L)1 containing regimen and enrollment.
(b) No more than 70% of participants should have had progression of disease within a period of 6 months of start of therapy with [redacted] agent.

(3) Must not have received prior anti-CTLA-4 therapy in the advanced or metastatic setting.

(4) Participants must have known BRAF status.
(a) Must have been offered mutation-directed therapy, if indicated, that has proven survival benefit. This must be documented in the medical record.

ii) Participants with histologically or cytologically documented metastatic or recurrent NSCLC:

(1) Must have received, and then progressed, relapsed, or been intolerant to, at least 1 standard treatment regimen in the advanced or metastatic setting

OR

Must have recurrent or progressive disease within 6 months after completing platinum based chemotherapy for local disease.

(2) All participants with adenocarcinoma must have known EGFR, ALK, KRAS, and ROS1 status (when testing is available as per country/region standard of care practices); participants with an activating EGFR mutation, ALK translocation, or ROS1 mutation must have received appropriate inhibitor therapy (as available per country/region standard of care). Note: If KRAS results are not known, then a sample [redacted] should be sent for testing locally. [redacted] may be used if [redacted] results are not feasible, with prior Sponsor approval.
(a) Must have been offered mutation-directed therapy, if indicated, that has proven survival benefit. This must be documented in the medical record.

(3) Must have radiologically or clinically documented progressive or recurrent disease occurring either during treatment with or within 3 months of discontinuing anti-PD-(L)1 therapy when administered as either monotherapy or as part of a combination.
(a) No more than 1 intervening systemic anti-cancer regimen is allowed but not required between prior anti-PD-(L)1 containing regimen and enrollment.

(b) Prior anti-CTLA-4 therapy is not allowed.

(4) [redacted] available from screening [redacted] will be sent for analysis for [redacted]. If adequate [redacted] is unavailable, then prior outside genomic or other testing result from [redacted] from within 3 months and no intervening therapy prior to enrollment on this study may be used for this purpose only.

(5) The Sponsor may elect to prioritize enrollment of participants with BOR of SD, PR, or CR > than 6 months' duration in response to prior anti-PD-1/anti-PD-L1 treatment.

e) <u>The Expansion Phase of BMS-986288 in Combination with Nivolumab (Part 2B)</u>

i) Participants with histologically or cytologically documented metastatic or recurrent NSCLC:

(1) Must have received, and then progressed, relapsed, or been intolerant to, at least 1 standard treatment regimen in the advanced or metastatic setting

OR

Must have recurrent or progressive disease within 6 months after completing platinum based chemotherapy for local disease.

(2) All participants with adenocarcinoma must have known EGFR, ALK, KRAS, and ROS1 status (when testing is available as per country/region standard of care practices); participants with an activating EGFR mutation, ALK translocation, or ROS1 mutation must have received appropriate inhibitor therapy (as available per country/region standard of care). Note: If KRAS results are not known, then a sample [redacted] should be sent for testing locally. [redacted] may be used if [redacted] results are not feasible, with prior Sponsor approval.

(a) Must have been offered mutation-directed therapy, if indicated, that has proven survival benefit. This must be documented in the medical record.

(3) Must have radiologically or clinically documented progressive or recurrent disease occurring either during treatment with or within 3 months of discontinuing anti-PD-(L)1 therapy when administered as either monotherapy or as part of a combination.

(a) No more than 1 intervening systemic anti-cancer regimen is allowed but not required between prior anti-PD-(L)1 containing regimen and enrollment.

(b) Prior anti-CTLA-4 therapy is not allowed.

(4) [redacted] available from screening [redacted] will be sent for analysis for [redacted]. If adequate [redacted] is unavailable, then prior outside genomic or other testing result from [redacted] from within 3 months and no intervening therapy prior to enrollment on this study may be used for this purpose only.

(5) The Sponsor may elect to prioritize enrollment of participants with BOR of SD, PR, or CR > than 6 months' duration in response to prior anti-PD-1/anti-PD-L1 treatment.

f) <u>The Randomized cohort of BMS-986288 in Combination with Nivolumab versus Regorafenib (Part 2C)</u>

i) Histologically or cytologically confirmed previously treated patients with mCRC with adenocarcinoma histology, pMMR/MSS and in Stage IV per American Joint Committee on Cancer (Edition 7.0) at study entry.

(1) Microsatellite status should be performed per local standard of practice, IHC and/or PCR. If the MSI molecular test and MMR IHC test results are both available, then both MSS and MMR proficiency will be required for study entry. Patients with MSI-high or MSI-low or MMR deficiency will not be eligible.

(2) KRAS and NRAS (extended RAS) and [redacted] status should be verified based on available local testing results as part of medical history. Regardless of whether or not RAS mutation status is known, all participants will be tested during screening for extended RAS (NRAS and KRAS) and BRAF mutation status. Results from this testing at screening is not required prior to receiving treatment on study (except [redacted]). Note: If results are not known, then a sample [redacted] should be sent for testing locally. [redacted] may be used if [redacted] results are not feasible, with prior Sponsor approval. The proportion of participants with [redacted] will be monitored on an ongoing basis. The sponsor may limit the number of [redacted] participants after discussion with the investigators. Patients with [redacted] are not eligible for the study.

(3) Participants with 3L/4L mCRC must have progressed or been intolerant to 2 prior lines of chemotherapy in the metastatic disease setting, which must include at least oxaliplatin- and irinotecan-containing regimens.

(a) Participants who received FOLFOXIRI (or equivalent) in the 1L setting may be considered for enrollment in the second line setting.

(b) Prior therapies containing anti-VEGF agents and/or anti-EGFR agents are permitted.

(c) Disease recurrence within 6 months after the last dose of the adjuvant/neoadjuvant therapy is permitted and will be considered as 1 line of prior therapy for study entry. Disease recurrence beyond 6 months after the last dose of the adjuvant/neoadjuvant therapy is also permitted but will NOT be considered as 1 line of prior therapy for study entry.

(d) Disease progression must have occurred during or within 3 months following the last dose of approved standard therapies

(4) Participants must have measurable disease per RECIST 1.1 (Appendix 5). Participants with lesions in a previously irradiated field as the sole site of measurable disease will be permitted to enroll provided the lesion(s) have demonstrated clear progression and can be measured accurately.

(5) Participants with or without liver metastasis. Participants post local liver metastasis therapy (surgery, selective internal radiation therapy, etc) will be categorized as participants with liver metastasis. Side of primary tumor needs to be documented if known. Participants with or without active carcinoembryonic antigen tumor marker are eligible. If feasible, the Sponsor aims to prioritize participants without liver metastasis, including [redacted] and at study entry, in each arm to achieve 50% treated participants without liver metastasis through enrollment.

(6) Be able to swallow and absorb oral tablets.

(7) Anticipated life expectancy greater than 3 months.

3) Physical and Laboratory Test Findings

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

i) Neutrophils ≥ 1,500/μL.

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

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

iv) WBC ≥ 2000/μL.

b) Adequate hepatic function for participants as defined by the following:

i) Alanine aminotransferase (ALT) and aspartate aminotransferase (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).

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 pharmacodynamic 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 hCG) within 24 hours prior to the start of study treatment.

c) Women must not be breastfeeding.

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

e) WOCBP must agree to follow instructions for method(s) of contraception (Appendix 4) for the duration of BMS-986288 combination therapy treatment, plus 5 months post treatment completion. WOCBP receiving monotherapy treatment with BMS-986288 must agree to follow instructions for method(s) of contraception for the duration of monotherapy treatment with BMS-986288, plus 3 months post treatment completion. Local laws and regulations may require use of alternative and/or additional contraception methods. See Appendix 4.

f) **Not Applicable as of Amendment 02:** Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception and fetal protection (Appendix 4) for the duration of BMS-986288 combination treatment, plus 5 half-lives of nivolumab, 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-986288, plus 5 half-lives of BMS-986288, plus 90 days (duration of sperm turnover), for a total of 165 days post treatment completion. In addition, male participants must be willing to refrain from sperm donation during this time. See Appendix 4.

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

h) WOCBP must agree to follow instructions for method(s) of contraception (Appendix 4) for the duration of treatment, plus 2 months after last dose of regorafenib (or local guidelines). Local laws and regulations may require use of alternative and/or additional contraception methods. See Appendix 4.

Investigators shall counsel WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise on the use of highly effective methods of contraception (Appendix 4), which have a failure rate of < 1% when used consistently and correctly.

6.2 Exclusion Criteria

1) Target Disease Exclusions

a) Participants with primary CNS malignancies, tumors with CNS metastases as the only site of disease, [redacted] brain metastases, or leptomeningeal metastasis will be excluded. However, participants with [redacted] metastases are eligible. [redacted] 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.

b) For Part 2C:

i) Participants with [redacted] mutant [redacted].

(1) Verify [redacted] status based on available local testing results as part of medical history prior to study treatment. [redacted]

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.

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 4 weeks prior to treatment. If less than 4 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 who have received live/attenuated vaccine within 30 days of first treatment.

   i) The use of inactivated seasonal influenza vaccines (eg, Fluzone®) will be permitted on study without restriction.

f) Previous SARS-CoV-2 vaccine within 7 days of Cycle 1 Day 1 (C1D1). For vaccines requiring more than 1 dose, the full series (eg, both doses of a 2-dose series) should be completed prior to enrollment when feasible and when a delay in enrollment would not put the study participant at risk.

g) Treatment with complementary medications (eg, herbal supplements or traditional Chinese medicines) to treat the disease under study within 2 weeks prior to first study treatment. Such medications are permitted if they are used as supportive care. Refer to Section 7.7.1 for prohibited therapies.

h) Concomitant participation in treatment period of any clinical vaccine studies.

i) Prior radiotherapy must be completed at least 2 weeks prior to treatment allocation. Participants must have recovered from all radiation-related toxicities.

j) For Part 2C:

   i) Prior treatment with an [redacted] antibody.

3) Medical History and Concurrent Disease

a) Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured, [redacted].

   i) In Part 2, the BMS-986288 Cohort Initial Expansion 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] v5.0).

e) Participants with the following:
   i) Active, known, or suspected autoimmune disease, including history of uveitis or autoimmune ocular 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-(L)1 treatment or any other antibody or drug specifically targeting [redacted] 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 corticosteroids > 10 mg daily prednisone equivalent within 14 days or other immunosuppressive medications within 30 days of study treatment administration. Inhaled or topical steroids and adrenal replacement steroid doses of ≥10 mg daily prednisone equivalent are permitted 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) **Not Applicable as of Amendment 03. See 3.e.iv.9 below:** History of other clinically significant heart disease (eg, cardiomyopathy, congestive heart failure with New York Heart Association functional classification III to IV [Appendix 10], 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.

(8) History of other clinically significant heart disease (eg, cardiomyopathy, congestive heart failure with New York Heart Association functional classification II, III, or IV [Appendix 10], pericarditis, or significant pericardial effusion).

v) **Not Applicable as of Amendment 02. See 3.e.xiii and xiv below:** History of chronic hepatitis as evidenced by the following:

(1) Positive test for hepatitis B surface antigen (HBsAg).

(2) Positive test for qualitative hepatitis C viral load by polymerase chain reaction (PCR).

(a) Participants with positive hepatitis C antibody 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) 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.

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

ix) 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.

x) **Not Applicable as of Amendment 02. See 3.e.xv below:** Positive test for human immunodeficiency virus (HIV).

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

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

xii) WOCBP who are pregnant or breastfeeding.

xiii) Any positive test result for hepatitis B virus (HBV) indicating presence of virus, eg, HBsAg, Australia antigen positive.

xiv) Any positive test result for hepatitis C virus (HCV) indicating presence of active viral replication (detectable HCV-RNA). Note: Participants with positive HCV antibody and an undetectable HCV RNA are eligible to enroll.

xv) Known human immunodeficiency virus (HIV) positive with an AIDS-defining opportunistic infection within the last year, or a current CD4 count < 350 cells/uL.

Participants with HIV are eligible if:

a) they have received antiretroviral therapy (ART) for at least 4 weeks prior to treatment assignment, as clinically indicated, while enrolled on study

b) they continue on ART as clinically indicated while enrolled on study

c) CD4 counts and viral load are monitored per standard of care by a local health care provider.

NOTE: Testing for HIV must be performed at sites where mandated locally. HIV-positive participants must be excluded where mandated locally.

xvi) Participants with serious or uncontrolled medical disorders.

xvii) Participant has any condition, including active or uncontrolled infection, or the presence of laboratory abnormalities, which places the participant at unacceptable risk if he/she were to participate in the study.

xviii) Previous SARS-CoV-2 infection within 10 days for mild or asymptomatic infections or 20 days for severe/critical illness prior to screening or predose C1D1.

(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 study treatment.

xix) <u>For MSS CRC Part 2C</u>

(1) Any evidence of active bleeding, or hemorrhage or bleeding event ≥ NCI-CTCAE version 5.0 Grade 3 within 4 weeks prior to the start of study medication.

(2) Arterial or venous thrombotic or embolic events such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis, or pulmonary embolism within 6 months before the start of study medication (except for adequately treated catheter-related venous thrombosis occurring more than 1 month before the start of study medication).

(3) Prior or current gastrointestinal perforation or fistula.

(4) Non-healing wound, non-healing ulcer, or non-healing bone fracture.

4) Allergies and Adverse Drug Reactions

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

Not applicable. No restrictions are required.

6.4 Screen Failures

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

6.4.1 Retesting During Screening or Lead-In Period

This study permits the re-enrollment of a participant who has discontinued the study as a pretreatment failure (ie, participant has not been treated).

Retesting of laboratory parameters and/or other assessments during the extended screening period will be allowed. The most current result prior to treatment allocation 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 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 by reverse transcription 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 SARS-CoV-2 infection sequelae that may place the participant at a higher risk of receiving investigational treatment
- In the instance of a SARS-CoV-2 infection during screening, the screening period may be extended beyond the protocol-specified timeframe with medical monitor approval. Any screening tests already performed which could potentially be affected by the SARS-CoV-2

infection or its complications on an individual basis and agreed upon with the Medical Monitor (eg, safety labs, oxygen saturation, chest CT scan) should be repeated.

7 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 treatment allocation.

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

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

In this protocol, IPs are the following:

- BMS-986288
- Nivolumab
- [redacted]
- Regorafenib

All 4 drugs used in this open-label study qualify as IPs, as per previous text, and their description and storage information are shown in Table 7-1.

Table 7-1: Investigational Product Description for CA043001

Product Description / Class and Dosage Form	Potency	IP/Non-IP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
Nivolumab (BMS-936558) Solution for Injection	[redacted] mg (10 mg/mL)	IP	Open label	Vial	Refer to the label on container and/or Pharmacy Manual
BMS-986288 Powder for Solution for Injection	[redacted] mg per vial	IP	Open label	Vial	Refer to the label on container and/or Pharmacy Manual
[redacted]	[redacted] mg (1 mg/mL)	IP	Open label	Vial	Refer to the label on container and/or Pharmacy Manual
Regorafenib Tablet[b]	40 mg[c]	IP	Open Label	Bottle	Refer to the label on container and/or Pharmacy Manual

Abbreviations: IP = investigational product; [redacted]

[redacted]

[b] These products may be obtained by investigational sites as local commercial product in certain countries if allowed by local regulations. In these cases, products may be a different pack size/potency than listed in the table. These products should be prepared/stored/administered in accordance with the package insert or SmPC.

[c] May include other commercially available strengths.

7.1 Schedule of Dose for Each Investigational Product

The dosing schedule for each IP is detailed below in Table 7.1-1 for all study parts. Planned dose levels may be modified (eg, change in administration schedule) or intermediate dose levels may be added, based upon the BLRM analysis and clinical evaluation of available safety, PK, and pharmacodynamic 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 7.4.

Table 7.1-1: Selection and Timing of Dose[a]

Study Treatment	Planned Unit Dose Strength(s)/ Dosage Level(s)	Planned Dosage Formulation Frequency of Administration	Route of Administration
BMS-986288	[redacted], and [redacted] mg	[redacted]	IV
Nivolumab	[redacted] mg		IV
BMS-986288/ Nivolumab	[redacted] mg[a]/ [redacted] mg		[redacted]
BMS-986288 + [redacted]	See note[b]		
Nivolumab + [redacted]	See note[b]		
Regorafenib Tablet	[redacted] mg[c]		Oral

Abbreviations: IV = intravenous; [redacted]

Note: Additional dose levels and/or administration schedules may be explored. BMS-986288 doses from [redacted] mg to [redacted] mg should be administered [redacted], BMS-986288 doses of [redacted] mg to [redacted] mg should be administered [redacted], and BMS-986288 doses of [redacted] mg to [redacted] mg should be administered [redacted]. The [redacted] of [redacted] mg of BMS-986288 in combination with [redacted] mg of nivolumab should be administered [redacted]. For participants weighing < 40 kg, [redacted] will be limited to 80 mL.

[a] Potential additional dose levels of BMS-986288 ([redacted] mg and [redacted] mg) could be [redacted] with [redacted] mg of nivolumab

[b] Dose(s) for BMS-986288 alone (Arm A) or in combination with nivolumab (Arm B) for [redacted] will be selected based on preliminary data from Part 1A and Part 1B. [redacted]

[c] See dose modification of regorafenib (Section 7.4.6).

For Part 2C Arm D dosing, please refer to local product label and institutional guidelines for further details.

The recommended dose of regorafenib is [redacted] mg (four 40-mg tablets) taken orally once daily for the first 21 days of each 28-day cycle. Continue treatment until disease progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first. The participant should take regorafenib at the same time each day. Swallow tablet as a whole with water after a low-fat meal that contains less than 600 calories and less than 30% fat. The participant should not take 2 doses of regorafenib on the same day to make up for a missed dose from the previous day. Any missed doses reported by the participant should be recorded in the participant's source documents and in the participant's diary.

Initiation of the next treatment cycle:

1. The next cycle will be initiated [redacted] with regorafenib dosing.
2. If regorafenib dosing is delayed, the next cycle will start if at least 4 weeks have passed from the first dose in the current cycle to dosing re-initiation.
3. The next treatment cycle may be initiated within a ± 3-day window of scheduled dose due to scheduling conflict.

See Table 2-2 for treatment related Schedule of Activities. Refer to the Pharmacy Manual for additional dose preparation details for BMS-986288, nivolumab, and [redacted] (if applicable).

7.2 Method of Treatment Assignment

During the screening visit for all study parts, the investigative site will call into 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 dosed, will be assigned sequential participant numbers starting with [redacted]. The participant identification number (PID) will ultimately be comprised of the site number and participant number. For example, the first participant screened (ie, enrolled) at site number 1, will have a PID of [redacted]. Specific instructions for using the IRT system will be provided to the investigational sites in a separate document.

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.

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. [redacted] will be initiated once an appropriate BMS-986288 monotherapy or combination dose is identified, will be incorporated through a protocol amendment, and may run in parallel with Part 1A and Part 1B. Treatment assignments for participants eligible for Part 1A, Part 1B, or [redacted] will alternate between the 3 parts (if open), with consecutively treated participants assigned to different parts through IRT whenever possible according to the corresponding inclusion criteria. If there are no openings available in the part to which the participant would be assigned by this algorithm, 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 BMS-986288 in the Safety Evaluation of BMS-986288 in Combination with Nivolumab (Part 1B) does not exceed the highest dose evaluated in the BMS-986288 Monotherapy Dose Escalation (Part 1A).

In Part 2A and Part 2B Combination Expansion, multiple doses may be open concurrently. In that case, treatment assignments will alternate between the dose levels, with consecutively treated participants assigned to different parts through IRT whenever possible. If there are no openings available in the dose level to which the participant would be assigned by this algorithm, then the subject will be assigned to the next open dose. Study treatment will be dispensed at the study visits as listed in the Schedule of Activities (Section 2) or Appendix 8 (if applicable).

Part 2C

Part 2C is a randomized, open-label study with 2 treatment arms, nivolumab in combination with BMS-986288 (Arm C) versus regorafenib (Arm D). Once enrolled in IRT, participants who have met all eligibility criteria for Part 2C will be randomized in a 2:1 ratio to nivolumab in combination with BMS-986288 (Arm C) or regorafenib (Arm D) and stratified by liver metastases status. Participants in Part 2C Arm D receiving regorafenib will have the option to transition to BMS-986288 in combination with nivolumab (Part 2C Arm Z) after BICR-assessed progression.

An additional dose of BMS-986288 [redacted] mg or [redacted] mg) in combination with nivolumab may be opened in Part 2C (as Arm E). This additional dose level will not be randomized with Arm C and Arm D.

7.3 Blinding

This is an open-label study (open to sponsor and site/participant; not treated as sponsor-blind); however, the specific treatment to be taken by a participant will be assigned using an IRT. The site will contact the IRT prior to the start of study treatment administration for each participant. The site will record the treatment assignment on the applicable case report form, if required. Designated staff of BMS can have access to treatment assignments prior to database lock to facilitate data analysis, as well as the bioanalytical analysis of PK and immunogenicity samples. See Section 10.3.8 for details of interim analysis. A bioanalytical scientist in the Bioanalytical Sciences department of BMS Research & Development (or a designee in the external central bioanalytical laboratory) and/or Clinical Pharmacology groups may obtain the treatment assignments in order to minimize unnecessary bioanalytical analysis of samples. This access to the treatment codes will not impact the data integrity of the study.

7.4 Dosage Modification

Intra-participant dose escalation/reduction of BMS-986288 or nivolumab is not permitted in this study in order to allow better evaluation of the safety and efficacy at individual dose levels and schedules. Regorafenib starting dose modification can be considered in consultation with BMS Medical Monitor/designee. For AEs that are deemed to be related to regorafenib by the investigator, refer to local product label and institution guidelines for further detail in addition to the recommendation provided in Section 7.4.6.

7.4.1 Dose-limiting Toxicities

For the purpose of guiding dose escalation, all AEs will be assessed and DLTs will be defined based on the incidence, intensity, and duration of the AEs for which no clear alternative cause is identified. The DLT period will be 5 weeks (35 days) in both BMS-986288 monotherapy and combination dose escalation (Part 1A and Part 1B). Any toxicities that occur beyond the DLT period will be accounted for in making final dose level decisions. Participants who have discontinued due to a DLT or who have received 2 doses of BMS-986288 monotherapy or in combination with nivolumab and have completed the 5-week DLT period will be considered as DLT-evaluable participants. Participants who withdraw from the study during the DLT evaluation period or have received less than 2 doses 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 within 8 weeks.

For the purpose of participant management, any drug related AE that meets DLT criteria, regardless of the cycle or cohort in which it occurs, will lead to discontinuation of study treatment.

AEs will be graded according to the NCI CTCAE v5.0.

[redacted]

Continuous evaluation of toxicity events in the [redacted] Evaluation of BMS-986288 [redacted] and BMS-986288 Cohort Expansion Combination Therapy (Part 2) will be performed. If at any time, the aggregate rate of treatment-related toxicities meeting DLT criteria in a BMS-986288 containing cohort exceeds 33% across patients treated in a cohort, the findings will be discussed with the Investigators and further enrollment may be interrupted. If a cohort is discontinued due to toxicity, a new cohort at a previously tested alternative dose level which was found to be safe in Part 1A or Part 1B may be considered based on the aggregate safety experience and in consultation and agreement between Investigators and Sponsor. An alternative dose or administration schedule may also be initiated in a specific [redacted] or Part 2 cohort upon

assessment of available safety, PK, pharmacodynamics, and efficacy data from that cohort. A protocol amendment reflecting any such new cohort will be submitted prior to enrollment to the cohort.

7.4.2 Management Algorithms for Immuno-oncology Agents

I-O agents are associated with imAEs that can differ in severity and duration from AEs caused by other therapeutic classes. BMS-986288 and nivolumab are considered I-O agents in this protocol. Early recognition and management of imAEs 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 imAEs:

- GI
- Renal
- Pulmonary
- Hepatic
- Endocrinopathies
- Skin
- Neurological (including encephalitis)
- Cardiac

The clinical nature of AEs noted with BMS-986288 will determine the role of the algorithms for use in toxicities related to its use in this study. The algorithms recommended for the management of imAEs in this protocol are in Appendix 6.

7.4.3 Dose Delays Due to Toxicity

If an event is attributed to BMS-986288 or nivolumab, alone or in combination, then all study drugs must be delayed until treatment can resume (see Section 7.4.3.1). Delay administration of both nivolumab and BMS-986288 if any of the delay criteria in Table 7.4.3.1-1 are met. 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:

- Potential DLTs, until DLT relatedness is defined.
- Drug-related select AEs and laboratory abnormalities in Table 7.4.3.1-1.
- AE, laboratory abnormality, or concurrent illness that, in the judgment of the Investigator, warrants delaying study treatment administration.
- Confirmed SARS-CoV-2 infection.

Participants who require a delay of study drug should be re-evaluated weekly or more frequently if clinically indicated. For participants receiving a combination (eg, Part 1B, [redacted], Part 2B), if dosing is delayed, then study drugs must be delayed together. If dosing with both study drugs 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 AEs should be evaluated and managed per the toxicity management algorithms in Appendix 6. Participants not meeting guidelines for permanent discontinuation will be permitted to resume therapy based on the criteria specified below in Section 7.4.3.1. Participants eligible to resume study therapy will resume study therapy at the nominal treatment visit after their last received study medication dose.

7.4.3.1 Criteria to Resume Treatment

Subsequent dosing with study therapy may resume once drug-related non-DLT AEs resolve to Grade 1 or baseline. When criteria to resume treatment are met, resume both nivolumab and BMS-986288 on the same day.

- Participants experiencing AEs not meeting criteria for permanent discontinuation may resume treatment with study intervention(s) if they have completed AE management (eg, corticosteroid taper) or are on ≤ 10 mg prednisone or equivalent and meet the requirements per Table 7.4.3.1-1.
- Prior to re-initiating treatment in a participant with a dosing delay lasting > 8 weeks (unless the exceptions in Table 7.4.3.1-1 are met), the Medical Monitor (or designee) must be consulted. Continue tumor assessments per protocol even if dosing is delayed. Continue periodic study visits to assess safety and laboratory studies [redacted] or more frequently if clinically indicated during such dosing delays.
- Participants with confirmed SARS-CoV-2 infection may resume treatment after 1) at least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared, positive RT-PCR test result, or positive viral antigen test result, 2) resolution of acute symptoms (including at least 24 hours has passed since last fever without fever reducing medications), 3) 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 4) 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.
  - Prior to re-initiating on-study treatment in a participant with a dosing delay lasting > 8 weeks due to SARS-CoV-2 infection, the medical monitor/designee must be consulted.

Table 7.4.3.1-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Nivolumab and/or BMS-986288

Drug-Related Adverse Event (AE) per CTCAE v5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Gastrointestinal			
Colitis or Diarrhea	Grade 2	Delay dose	Dosing may resume when AE resolves to baseline. Grade 2 colitis > 5 days is a DLT.
	Grade 3	Permanently discontinue	
	Grade 4	Permanently discontinue	
Hematologic			
Anemia	Grade 4	Delay or permanently discontinue	For first occurrence: Delay dose until recovery. If event recurs, permanently discontinue. Dose delay during Cycle 1 is considered a DLT.
Hemolysis	Grade ≥ 3	Permanently discontinue	
Neutropenia	Grade 3	Delay dose	Delay dose until recovery; resume treatment when AE resolves to Grade ≤ 1 or baseline. Grade 3 with duration ≥ 7 days during Cycle 1 is considered a DLT; resume treatment once AE resolves, as described above.
	Grade 4 or febrile neutropenia	Delay or permanently discontinue	If duration < 7 days, delay until recovery. If duration ≥ 7 days or for neutropenic fever of any duration, permanently discontinue. Dose delay during Cycle 1 is considered a DLT.
Thrombocytopenia	Grade 3 thrombocytopenia > 7 days or associated with Grade ≥ 2 hemorrhage	Delay or permanently discontinue	If duration ≤ 7 days, delay until recovery. If duration > 7 days or associated with clinically significant bleeding, permanently discontinue.
	Grade 4	Permanently discontinue	
Renal			
Serum Creatinine Increased	Grade 2 or 3	Delay dose	Dosing may resume when AE resolves to Grade ≤ 1 or baseline value.
	Grade 4	Permanently discontinue	
Pulmonary			
Pneumonitis	Grade 2	Delay dose	Dosing may resume after pneumonitis has resolved to ≤ Grade 1.

Table 7.4.3.1-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Nivolumab and/or BMS-986288

Drug-Related Adverse Event (AE) per CTCAE v5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
			Grade 2 pneumonitis that does not respond to dose delay and systemic steroids within 14 days is a DLT.
	Grade 3 or 4	Permanently discontinue	
Hepatic			
Aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin (T.bili) increased	AST or ALT > 3x and ≤5x upper limit of normal (ULN) or T.Bili > 1.5x and ≤3x ULN, regardless of baseline value	Delay dose	Dosing may resume when laboratory values return to baseline.
	AST or ALT > 5 x ULN or T. bili > 3 x ULN, regardless of baseline value	Delay dose or Permanently discontinue	In most cases of AST or ALT > 5 x ULN, study treatment will be permanently discontinued. 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 and approval from Medical Monitor prior to resuming therapy.
	Concurrent AST or ALT > 3 x ULN and T.bili > 2 x ULN, regardless of baseline value	Permanently discontinue	
Endocrinopathy			
Adrenal Insufficiency	Grade 2 adrenal insufficiency	Delay dose	Dosing may resume after adequately controlled with hormone replacement.
	Grade 3 or 4 adrenal insufficiency or adrenal crisis	Delay dose or permanently discontinue	Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If adrenal insufficiency resolves or is adequately controlled with physiologic hormone replacement, participant may not require discontinuation of study drug.
Hyperglycemia	Hyperglycemia requiring initiation or change in daily management (Grade 2 or 3)	Delay dose	Dosing may resume if hyperglycemia resolves to Grade ≤1 or baseline value, or is adequately controlled with glucose-controlling agents.
	Grade 4	Delay dose or permanently discontinue	Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If hyperglycemia resolves, or is adequately controlled with glucose-

Table 7.4.3.1-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Nivolumab and/or BMS-986288

Drug-Related Adverse Event (AE) per CTCAE v5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
			controlling agents, participant may not require discontinuation of study drug.
Hypophysitis/Hypopituitarism	Symptomatic Grade 1-3 that is also associated with corresponding abnormal lab and/or pituitary scan	Delay dose	Dosing may resume if endocrinopathy resolves to be asymptomatic, or is adequately controlled with only physiologic hormone replacement.
	Grade 4	Delay dose or permanently discontinue	Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If endocrinopathy resolves or is adequately controlled with physiologic hormone replacement, participant may not require discontinuation of study drug.
Hyperthyroidism or Hypothyroidism	Grade 2 or 3	Delay dose	Dosing may resume if endocrinopathy resolves to be asymptomatic, or is adequately controlled with only physiologic hormone replacement or other medical management.
	Grade 4	Delay dose or permanently discontinue	Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If endocrinopathy resolves or is adequately controlled with physiologic hormone replacement or other medical management, participant may not require discontinuation of study drug.
Skin			
Rash	Grade 2 rash covering > 30% body surface area or Grade 3 rash	Delay dose	Dosing may resume when rash reduces to ≤10% body surface area.

Table 7.4.3.1-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Nivolumab and/or BMS-986288

Drug-Related Adverse Event (AE) per CTCAE v5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
	Suspected Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), or drug reaction with eosinophilia and systemic symptoms (DRESS)	Discontinue or delay dose	Dosing may resume if SJS, TEN, or DRESS is ruled out and rash reduces to ≤10% body surface area.
	Grade 4 rash or confirmed SJS,TEN, or DRESS	Permanently discontinue	
Neurological			
Guillain-Barre Syndrome (GBS)	Any Grade	Permanently discontinue	
Myasthenia Gravis (MG)	Any Grade	Permanently discontinue	
Encephalitis	Any Grade encephalitis	Delay dose	After workup for differential diagnosis, (ie, infection, tumor-related), if encephalitis is not drug related, then dosing may resume when AE resolves.
	Any Grade drug-related encephalitis	Permanently discontinue	
Myelitis	Any Grade myelitis	Delay dose	After workup for differential diagnosis, (ie, infection, tumor-related), if myelitis is not drug related, then dosing may resume when AE resolves.
	Any Grade drug-related myelitis	Permanently discontinue	
Neurological (other than GBS, MG, encephalitis, or myelitis)	Grade 2	Delay dose	Dosing may resume when AE resolves to baseline.
	Grade 3 or 4	Permanently discontinue	
Myocarditis			
Myocarditis	Symptoms induced from mild to moderate activity or exertion	Delay dose	Dosing may resume after myocarditis has resolved.
	Severe or life threatening, with symptoms at rest or with minimal activity or exertion, and/or where intervention indicated.	Permanently discontinue	

Table 7.4.3.1-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Nivolumab and/or BMS-986288

Drug-Related Adverse Event (AE) per CTCAE v5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Other Clinical AE			
Pancreatitis: Amylase or Lipase increased	Grade 3 with symptoms	Delay dose	Note: Grade 3 increased amylase or lipase without signs or symptoms or radiographic evidence of pancreatitis does not require dose delay. Dosing may resume when patient becomes asymptomatic.
	Grade 4	Permanently discontinue	Grade 4 increased amylase or lipase without signs or symptoms or radiographic evidence of pancreatitis does not require permanent discontinue.
Uveitis, episcleritis, iritis, eye pain, or blurred vision	Grade 2	Delay dose	Dosing may resume with response to topical therapy (eye drops) and after resolution to Grade ≤ 1 or baseline. If patient requires oral steroids, then permanently discontinue study drug.
	Grade 3 or 4	Permanently discontinue	
Other Drug-related AE **(not listed above)**	Grade 2 non-skin AE, except fatigue	Delay dose	Dosing may resume when AE resolves to Grade ≤ 1 or baseline value.
	Grade 3 AE - First occurrence lasting ≤ 7 days	Delay dose	Dosing may resume when AE resolves to Grade ≤ 1 or baseline value.
	Grade 3 AE- First occurrence lasting > 7 days	Permanently discontinue	
	Recurrence of Grade 3 AE of any duration	Permanently discontinue	Exception to permanent discontinuation: Grade 3 fatigue < 7 days in any cycle does not require permanent discontinuation. Grade 3 tumor flare (defined as pain, irritation, or rash that localizes to sites of known or suspected tumor). Grade 3 fever not associated with hemodynamic compromise (eg, hypotension, clinical, or laboratory evidence of impaired end-organ perfusion). Grade 3 nausea, vomiting, or abdominal pain that returns to Grade 1 or baseline within 48 hours, either spontaneously or with medical intervention.
	Grade 4 or Life-threatening adverse reaction	Permanently discontinue	

Table 7.4.3.1-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Nivolumab and/or BMS-986288

Drug-Related Adverse Event (AE) per CTCAE v5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Other Lab abnormalities			
Other Drug-Related lab abnormality **(not listed above)**	Grade 3	Delay dose	Exception: No delay required for Grade 3 lymphopenia.
	Grade 4	Permanently discontinue	Exceptions: The following events do not require discontinuation of study drug: • Grade 4 lymphopenia or leukopenia. Grade 4 lymphopenia or leukopenia that lasts > 7 day is a DLT. • Grade 3 or 4 isolated electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are responding to supplementation/appropriate management within 72 hours of their onset.
Infusion Reactions (manifested by fever, chills, rigors, headache, rash, pruritus, arthralgia, hypotension, hypertension, bronchospasm, or other allergic-like reactions.)			
Hypersensitivity reaction or infusion reaction	Grade 3 or 4	Permanently discontinue	Refer to Section 7.4.5 on Treatment of Related Infusion Reactions

7.4.4 Exceptions to Permanent Discontinuation Criteria

Any drug-related AE occurring at any time that meets DLT criteria as outlined in Section 7.4.1 will require permanent discontinuation, with the **exceptions detailed in Table 7.4.3.1-1 and the following:**

- 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 BMS Medical Monitor (or designee) must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue [redacted], 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 BMS Medical Monitor (or designee). Prior to re-initiating treatment in a participant with a dosing delay lasting > 8 weeks, the BMS Medical Monitor (or designee) must be consulted.

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 BMS Medical Monitor (or designee) to determine the risks and benefits of continuing on therapy following resolution vs discontinuing therapy permanently.

7.4.5 Management of Drug-related Infusion Reactions

Because BMS-986288 and nivolumab contain only human Ig protein sequences, they are unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, based on the non-clinical toxicology evaluation of BMS-986288, infusion reactions due to [redacted] 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. Report all Grade 3 or 4 infusion reactions within 24 hours as an SAE if it meets the criteria.

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-986288 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.

Grade 3 or 4 infusion reactions require permanent discontinuation of both study treatments.

For Grade 3 or 4 symptoms (severe reaction, Grade 3: prolonged [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms 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 [redacted] 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 SC 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. 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).

7.4.6 Dose Modification for Regorafenib

If dose modifications are required, reduce the dose in 40 mg (one tablet) increments; the lowest recommended daily dose of regorafenib is 80 mg daily. The following dose modification is provided as a recommendation. Local product labels and/or institutional guidelines should be followed if they are more conservative than the recommendations below.

Interrupt regorafenib for the following:

- Grade 2 hand-foot skin reaction (HFSR) (palmar-plantar erythrodysesthesia syndrome) that is recurrent or does not improve within 7 days despite dose reduction; interrupt therapy for a minimum of 7 days for Grade 3 HFSR. If restarting treatment, decrease dose by 40 mg.
- Symptomatic Grade 2 hypertension.
- Any Grade 3 or 4 adverse reaction.
- Worsening infection of any grade.

Reduce the dose of regorafenib to [redacted] mg:

- For the first occurrence of Grade 2 HFSR of any duration.
- After recovery of any Grade 3 or 4 adverse reaction except infection.
- For Grade 3 AST/ALT elevation, only resume if the potential benefit outweighs the risk of hepatotoxicity.

Reduce the dose of regorafenib to 80 mg:

- For re-occurrence of Grade 2 HFSR at the 120-mg dose.
- After recovery of any Grade 3 or 4 adverse reaction at the 120-mg dose (except hepatotoxicity or infection).

Discontinue regorafenib permanently for the following:

- Failure to tolerate 80-mg dose.
- Any occurrence of AST or ALT more than 20 × ULN.
- Any occurrence of AST or ALT more than 3 × ULN with concurrent bilirubin more than 2 × ULN.
- Re-occurrence of AST or ALT more than 5 × ULN despite dose reduction to 120 mg.
- Gastrointestinal perforation or fistula.
- Severe or life-threatening hemorrhage.
- Reversible posterior leukoencephalopathy syndrome.
- Wound dehiscence.
- Any event that leads to delay in dosing for > 8 weeks from the previous dose requires discontinuation with the following exception: dosing delays > 8 weeks that occur for non-drug-related reasons may be allowed if approved by the BMS Medical Monitor. Prior to re-initiating treatment in a participant with a dosing delay lasting > 8 weeks, the BMS Medical Monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed.
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the participant with continued treatment.

- For any Grade 4 adverse reaction, only resume if the potential benefit outweighs the risks.

7.5 Preparation/Handling/Storage/Accountability

The IP should be stored in a secure area according to local regulations. It is the responsibility of the Investigator 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).

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

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

Please refer to the current version of the IBs[2,18] and/or Pharmacy Manual for complete preparation, storage, and handling information.

When study treatments nivolumab and BMS-986288 are to be administered on the same day, nivolumab is to be administered first. Nivolumab infusion must be promptly followed by a flush of diluent to clear the line of nivolumab before starting the BMS-986288 infusion. The second infusion will always be the BMS-986288 study treatment and will start after the infusion line has been flushed, filters changed, and the participant has been observed to ensure no infusion reaction has occurred.

7.5.1 Retained Samples for Bioavailability/Bioequivalence

Not applicable.

7.6 Treatment Compliance

Not applicable.

7.7 Concomitant Therapy

7.7.1 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).
- Any concurrent approved or investigational anti-neoplastic therapy (eg, chemotherapy, immunotherapy, extensive, non-palliative radiation therapy). Palliative hormonal therapy will be permitted when indicated.
- Any botanical preparation (eg, herbal supplements or traditional Chinese medicines) intended to treat the disease under study. 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.
- Any live/attenuated vaccine (eg, varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella [MMR]) during treatment and until 100 days post last dose.
- Administration of investigational SARS-CoV-2 vaccines is not allowed during the study.
- Treatment of active SARS-CoV-2 infections or high-risk exposures, including use of investigational therapies, is allowed and should be discussed with the medical monitor.
- Participants may receive authorized or approved SARS-CoV-2 vaccines while continuing on study treatment at the discretion of the Investigator.

7.7.1.1 Imaging Restriction and Precautions

It is the local imaging facility's responsibility to determine, based on participant attributes (eg, allergy history, diabetic history, renal status), the appropriate imaging modality and contrast regimen per imaging study. Imaging contraindications and contrast risks are to be considered in this assessment. Participants with renal insufficiency are to be assessed as to whether or not they should receive contrast, and if so, which contrast agent and dose is appropriate. Specific to MRI, participants with severe renal insufficiency (ie, estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2) are at increased risk of nephrogenic systemic fibrosis; therefore, MRI contrast is contraindicated. In addition, participants may be excluded from MRI if they have tattoos, metallic implants, pacemakers, etc. This will be outlined in the Image Acquisition Manual.

Gentle hydration before and after IV contrast should follow local standard of care. The ultimate decision to perform MRI in an individual participant in this study rests with the site radiologist, the Investigator, and standards set by the local Ethics Committee.

7.7.2 Permitted Therapy

Participants are permitted the use of the following treatments:

- Topical, ocular, intra-articular, intra-nasal, and inhalational corticosteroids (with minimal systemic absorption).
- Adrenal replacement steroid doses ≥ 10 mg daily prednisone equivalent.
- 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).
- Supportive care: For participants receiving regorafenib, follow local product label, institutional guidelines, or relevant regional guidelines (eg, American Society of Clinical Oncology or European Society for Medical Oncology) to manage expected toxicities. Supportive care includes, but is not limited to, hematologic support and management of diarrhea,

nausea/vomiting, skin toxicities, as well as prophylactic or therapeutic administration of appropriate therapies.

7.7.3 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 BMS 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 BMS Medical Monitor (or designee) in discussion with the investigator. The BMS 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 electronic case report form (eCRF). Details in the source records should include dates of treatment, anatomic site, dose administered and fractionation schedule, and AEs. Symptoms requiring palliative radiotherapy should be evaluated for objective evidence of disease progression. If a participant is considered to have progressed at the time of palliative therapy, then they must meet the treatment beyond progression criteria (Section 5.1.4) 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. Participants undergoing major surgery for any reason while on study should have study treatment(s) held for at least 4 weeks after surgery. Prior to resuming study treatment wound healing must be evaluated by the surgeon, surgically related AEs should resolve to Grade 1 or baseline, and participants must meet relevant eligibility criteria as determined by the BMS Medical Monitor (or designee) in discussion with the investigator. The BMS 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 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 duration of 2 years. 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-986288 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) unless participants meet criteria for treatment beyond progression (Section 5.1.4).
- 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 7.4.1 will require permanent discontinuation. Exceptions to permanent discontinuation are listed in Section 7.4.4.
- 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 BMS.
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness. (Note: Under specific circumstances, 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 BMS 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 BMS Medical Monitor (or designee).
- If a participant in any of the BMS-986288 in combination with nivolumab arms meets criteria for discontinuation, the participant should discontinue both nivolumab and BMS-986288, as it may not be possible to determine whether the event is related to one or both study treatments.

Refer to the Schedule of Activities (Section 2) for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that can be completed.

In the case of pregnancy, the Investigator must immediately, within 24 hours of awareness of the pregnancy, notify the BMS Medical Monitor/designee of this event. In most cases, the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). Refer to Section 9.2.5 Pregnancy.

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

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

Regorafenib Dose Discontinuation

Discontinue regorafenib permanently for any of the following (local product label and institutional guidelines should be followed if they are more conservative):

- Failure to tolerate 80-mg dose
- Any occurrence of AST or ALT > 20× ULN
- Any occurrence of AST or ALT > 3× ULN with concurrent bilirubin > 2× ULN, except in participants with Gilbert's syndrome
- Re-occurrence of AST or ALT > 5× ULN despite dose reduction to 120 mg
- Gastrointestinal perforation or fistula
- Severe or life-threatening hemorrhage
- Reversible posterior leukoencephalopathy syndrome
- Wound dehiscence
- For any Grade 4 adverse reaction; only resume if the potential benefit outweighs the risks
- Any event that leads to delay in dosing for > 8 weeks from the previous dose requires discontinuation with the following exception:

  - Dosing delays > 8 weeks that occur for non-drug-related reasons may be allowed if approved by the BMS Medical Monitor. Prior to re-initiating treatment in a participant with a dosing delay lasting > 8 weeks, the BMS Medical Monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed.
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the participant with continued treatment.

8.1.1 Post-Study 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 must 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 5.3 until death or the conclusion of the study.

8.2 Discontinuation from the Study

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

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

8.3 Lost to Follow-Up

- All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant.
- Lost to follow-up is defined by the inability to reach the participant after a minimum of **three** documented phone calls, faxes, or emails as well as lack of response by participant to one registered mail letter. All attempts should be documented in the participant's medical records.
- If it is determined that the participant has died, the site will use permissible local methods to obtain date and cause of death.
- If Investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the participant's informed consent, then the Investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining participant's

contact information or other public vital status data necessary to complete the follow-up portion of the study.

- The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information.
- If after all attempts, the participant remains lost to follow-up, then the last known alive date as determined by the Investigator should be reported and documented in the participant's medical records.

9 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and timing are summarized in the Schedule of Activities (Section 2). Protocol waivers or exemptions are not allowed.

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

Adherence to the study design requirements, including those specified in the Schedule of Activities (Section 2), 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 treatment allocation. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Schedule of Activities (Section 2).

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

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

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

9.1 Efficacy Assessments

Efficacy assessments for the anti-tumor activity of BMS-986288 alone, BMS-986288 in combination with nivolumab, and [redacted] will be based on tumor measurements, using

RECIST v1.1. Efficacy evaluation of BMS-986288 alone and in combination with nivolumab per modified RECIST in cancer immunotherapy trials (iRECIST) using BICR is an exploratory objective.

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 for all study participants will be submitted to a central imaging vendor and collected images from Part 2C participants will undergo BICR review. All other images may undergo BICR review at any time during the study. Prior to scanning first participant, sites should be qualified and understand the image acquisition guidelines and submission process as outlined in the CA043001 Imaging Manual provided by the central imaging vendor.

Refer to Schedule of Activities (Section 2) for timing of tumor assessments.

Any additional CT/MRI images performed either at unscheduled time points and/or at an outside institution, which may demonstrate tumor response or progression per RECIST v1.1 should be submitted to the central imaging vendor. X-rays, bone scans, and FDG PET scans which clearly demonstrate interval progression of disease, for example most commonly as unequivocal lesions, that are unmistakably new since the prior CT/MRI, should also be submitted to central imaging vendor.

9.1.1.1 Methods of Measurement

Contrast-enhanced CT of the chest, abdomen, pelvis, and all other known and/or suspected sites of disease should be performed for tumor assessments. 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. Change in tumor measurements and tumor response to guide ongoing study treatment decisions will be assessed by the Investigator using the RECIST v1.1 criteria.

For participants with cancer of the head and neck, a CT or MRI scan of the neck is required.

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

In case of a contraindication for either contrast agent or MRI (eg, incompatible pacemaker) it is recommended to use the following guidance:

If a participant has a contraindication for CT IV contrast, then 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 a participant has a contraindication for both MRI and CT IV contrasts, then 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 a participant has a contraindication for MRI in addition to contraindication to CT IV contrast, then 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, and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast-enhanced CT scans for anatomically-based RECIST v1.1 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 which may bias an Investigator if it is not routinely or serially performed.

Bone scan or PET scan are 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.

Bone scans may be collected per local standards, as clinically indicated.

MRI of the brain should be acquired as outlined in the Schedule of Activities (Section 2). CT of the brain (without and with contrast) can be performed if MRI is contraindicated.

9.1.1.2 Imaging and Clinical Assessment

Tumor assessments should continue on the protocol defined imaging schedule regardless if dosing is delayed or discontinued. Changes in tumor measurements and tumor responses should be assessed by the same Investigator using RECIST v1.1 criteria. Investigators will report the number and size of new lesions that appear while on study. The time point of tumor assessments will be reported on the eCRF based on the Investigator's assessment using RECIST v1.1 criteria (see Appendix 5 for specifics of RECIST v1.1 criteria to be used in this study). 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).

9.1.2 Clinical Outcomes Assessments

The evaluation of the participant's experience in the evaluation of biopharmaceutical treatments is important to fully understand the impact of such products on how participants feel and function. PROs have been incorporated in oncology trials in order to more fully understand the participant's

experience. In addition, there is an increased focus from the clinical community on the specific concepts that are influenced by therapeutic products, including disease-related symptoms, symptomatic AEs, and physical functioning. When used in tandem with traditional clinical measures, the Non-small Cell Lung Cancer Symptom Assessment Questionnaire (NSCLC-SAQ) can provide additional context for safety and efficacy results. In the current trial, the participant's experience will be directly measured through the NSCLC-SAQ, the FACIT GP5, and the EQ-5D-5L. The Center for Drug Evaluation and Research has determined that the NSCLC-SAQ demonstrated adequate evidence of content validity and cross-sectional measurement properties (ie, internal consistency reliability, test-retest reliability, convergent validity, and known-groups validity) to measure symptoms of NSCLC in the context of the participant population being studied in this trial. Other indication-specific PROs will be included through a protocol amendment if other indications are included in the study.

The NSCLC-SAQ, FACIT GP5, and EQ-5D-5L will be collected during Part 2A and Part 2B only using electronic devices. The EQ-5D-5L may be collected using a validated telephone script in Survival Follow-up Period. However, if exceptional circumstances preclude the continued administration of measures using planned modalities, then alternate administration methods may be required, after consultation with Sponsor or the Sponsor's representative.

9.1.2.1 NSCLC-SAQ

The NSCLC-SAQ is a 7-item PRO measure intended for use in advanced NSCLC clinical trials to support medical product labeling.[75] The NSCLC-SAQ uses a 7-day recall period and verbal rating scale. It was developed in accordance with the US FDA's PRO Guidance and scientific best practices, and the resulting qualitative interview data provide evidence of content validity. The NSCLC-SAQ total score measures overall severity of the following NSCLC symptoms: cough, pain, dyspnea, fatigue, and appetite. The NSCLC-SAQ has been qualified for exploratory use to measure symptoms of NSCLC in drug development programs. Further evaluation is needed on the instrument's longitudinal measurement properties and the interpretation of clinically meaningful within-patient change in score. After the NSCLC-SAQ's longitudinal measurement properties and the interpretation of clinically meaningful within-patient change have been evaluated, the NSCLC-SAQ total score is intended to support labeling claims related to change in overall symptoms of NSCLC. The NSCLC-SAQ will be administered electronically to NSCLC participants only in Part 2 (see Section 2 Schedule of Activities).

9.1.2.2 EQ-5D-5L

The EQ-5D-5L was introduced by the EuroQoL Group to improve the instrument's sensitivity and to reduce ceiling effects, as compared to the 3-Level EQ-5D (EQ-5D-3L). Participants' reports of general health status will be assessed using the EQ-5D-5L, which has 2 components, the EQ-5D-5L descriptive system and the EQ-5D Visual Analog Scale (EQ-5D-VAS).[76] The EQ-5D-5L has been shown to be reliable in cancer patient populations.[77]

The EQ-5D-5L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The

participant is asked to indicate his or her health state by ticking the box next to the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number that expresses the level selected for that dimension. A total of 3125 possible health states are defined in this way. Each state is referred to in terms of a 5-digit code. For example, state 11111 indicates no problems on any of the 5 dimensions, while state 12345 indicates no problems with mobility, slight problems with washing or dressing, moderate problems with doing usual activities, severe pain or discomfort, and extreme anxiety or depression. EQ‗5D‗5L health states, defined by the EQ‗5D‗5L descriptive system, may be converted into a single summary index by applying a formula that attaches values (also called weights) to each of the levels in each dimension. The index can be calculated by deducting the appropriate weights from 1, the value for full health (ie, state 11111). This is referred to as the EQ‗5D-5L utility index. Currently, there are no published minimally important differences for change in scores for the EQ-5D-5L utility index score in a cancer population.

The EQ‗5D‗5L VAS records the respondent's self-rated health on a scale from 0 (Worst imaginable health state) to 100 (Best imaginable health state); higher scores represent better self-rated health. A change of 7 points is considered a clinically meaningful change and will be used to aid interpretation of change from baseline scores.

The EQ-5D-5L will be administered electronically to all participants in Part 2, except Part 2C (see Section 2 Schedule of Activities).

9.1.2.3 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 AEs. Evidence exists for the validity of this single item and its usefulness as an overall measure of burden due to symptomatic treatment toxicities.[78]

The FACIT GP5 will be administered electronically to all participants in Part 2 (see Section 2 Schedule of Activities).

9.2 Adverse Events

The definitions of an AE or SAE can be found in Appendix 3. Use CTCAE v5 definitions and grading for safety reporting of all AE and SAEs on the case report form.

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.

For regorafenib, refer to local product labels for safety profile, including Warnings and Precautions.

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

The continuous collection of nonserious AE information (with the exception of nonserious AEs related to SARS-CoV-2 infection [see below]) should begin at initiation of study treatment until 100 days after last dose of study treatment administration, at the time points specified in the Schedule of Activities (see Section 2).

- All SAEs must be collected continuously from the time of signing the consent, including those thought to be associated with protocol-specified procedures and within 100 days of last dose of study treatment must be collected, except in cases where a study participant has started a new anti-neoplastic treatment. However, any SAE occurring after the start of a new anti-neoplastic treatment 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 drug or protocol-specified procedure, (eg, a follow-up [redacted]).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the appropriate section of the eCRF module.
- 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 or designee within 24 hours of updated information being available.

All SAEs and all AEs (SAEs and nonserious AEs) associated with confirmed or suspected SARS-CoV-2 infection must be collected from the date of the participant's written consent until 100 days following discontinuation of study treatment. 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. Care should be taken not to introduce bias when collecting AE and/or SAEs. Inquiry about specific AEs should be guided by clinical judgement in the context of known adverse events, when appropriate for the program or protocol.

Every 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

- Nonserious 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 nonserious AEs that cause interruption or discontinuation of study treatment and for those present at the end of study treatment as appropriate.
- All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic). Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

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

- After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AEs associated with confirmed or suspected SARS-CoV-2 infection will be followed 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.

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 (IRB)/Independent Ethics Committee (IEC), if appropriate according to local requirements.

Sponsor or designee will be reporting AEs to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/EC and FDA Code of Federal Regulations 21 CFR Parts 312 and 320. A suspected, unexpected serious adverse reaction (SUSAR) 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 [redacted] months after BMS-986288 combination therapy, [redacted] months after BMS-986288 monotherapy administration, and 2 months after the last dose of regorafenib, the Investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Appendix 3.

In most cases, the study treatment will be permanently discontinued in an appropriate manner. Please call the BMS 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.

If, for whatever reason, the pregnancy has ended, confirmed by negative serum pregnancy test, treatment may be resumed (at least 3 weeks after the pregnancy has ended), following approvals of participant/sponsor/IRB/EC, as applicable.

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.

9.2.6 Laboratory Test Result Abnormalities

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

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

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

9.2.7 Immune-Mediated Adverse Events

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

9.2.8 Potential Drug-induced Liver Injury (DILI)

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

Potential DILI is defined as:

1) Aminotransaminases (ATs; ALT or AST elevation > 3 times upper limit of normal [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.

The key responsibilities for Investigators during p-DILI assessment include: (i) Early detection, medical evaluation (including the exclusion of other potential causes) and rapid laboratory confirmation of liver-related abnormalities; and (ii) BMS notification of p-DILI cases via SAE forms. Following the gathering and assessment of relevant clinical information, BMS is responsible for: (i) Timely evaluation and triaging of p-DILI cases; (ii) Expedited reporting of p-DILI cases; and (iii) 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, 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 physical examinations, ECG, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

9.3 Overdose

For this study, any dose of BMS-986288 or nivolumab greater than the assigned dose and considered excessive and medically important by the Investigator will be considered an overdose (see Appendix 3).

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

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

2) Closely monitor the participant for AEs/SAEs and laboratory abnormalities until BMS-986288 or nivolumab can no longer be detected systemically (at least 125 days).
3) Obtain a serum sample for PK if requested by the Medical Monitor/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.

For regorafenib overdose, please refer to local product label.

9.4 Safety

Safety assessments will be based on reported AEs 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 (MedDRA), and the incidence of observed AEs will be tabulated and reviewed for potential significance and clinical importance. AEs will be assessed continuously during the study and for 100 days after last dose of study treatment. 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 v5.0. Collection of AEs and severity will also include local [redacted] reactions after [redacted] administration and IV-related infusion reactions.

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

9.4.1 Physical Examinations

Refer to Schedule of Activities (Section 2).

9.4.2 Vital signs

Refer to Schedule of Activities (Section 2).

[redacted]

9.4.4 Electrocardiograms

Refer to Schedule of Activities (Section 2) for timing of assessments.

The effect of BMS-986288 on the QTc interval will be evaluated by a central reader using ECG data collected in triplicate along with time-matched PK during the BMS-986288 Monotherapy Dose Escalation (Part 1A) only (eg, 1 ECG test equals 3 consecutive individual 12-lead ECGs performed approximately 5 minutes apart). For the purposes of monitoring participant safety (all other ECG assessments), 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.

9.4.5 Clinical Safety Laboratory Assessments

- Investigators must document their review of each laboratory safety report.

- A local laboratory 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 9.4.5-1.
- 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 9.4.5-1: Clinical Laboratory Assessments

Hematology	
Hemoglobin	
Hematocrit	
Total leukocyte count, including differential	
Platelet count	
Prothrombin time, activated partial thromboplastin time, and international normalized ratio (at screening only)	
Coagulation (screening only. Monitor INR levels more frequently in participants on regorafenib and participants receiving warfarin according to institutional guidelines)	
Chemistry	
Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Total bilirubin Direct bilirubin (reflex[a]) Alkaline phosphatase Lactate dehydrogenase (LDH) Creatinine Creatine kinase/Creatine phosphokinase C-reactive protein Blood Urea Nitrogen (BUN) Uric acid Glucose Lipase Amylase Gamma glutamyl transferase (reflex only[b]) Thyroid stimulating hormone (TSH) Free T3 and T4 (screening and reflex only[c])	Total Protein Albumin Sodium Potassium Chloride Calcium Phosphorus Magnesium Creatinine clearance (Cockcroft-Gault method; screening only) Troponin
Urinalysis	
Protein	
Glucose	
Blood	
Leukocyte esterase and/or white blood cell (WBC)	

Table 9.4.5-1: Clinical Laboratory Assessments

Specific gravity
pH
Microscopic examination of the sediment if blood, protein or leukocytes esterase are positive on the dipstick
Serology
Serum for hepatitis C antibody, hepatitis B surface antigen, HIV-1 and HIV-2 antibody (at screening, and as mandated by local requirement)
Other Analyses
Pregnancy test (WOCBP only: screening, predose, discharge)
Follicle stimulating hormone (FSH) (screening only for women only)

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

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

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

9.4.6 Imaging Safety Assessment

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

9.5 Pharmacokinetics and Immunogenicity Assessment

The PK of BMS-986288 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 nivolumab serum samples will be collected and may be used in an integrated PPK or ER analysis along with data from other nivolumab studies, which would be the subject of a separate report. Separate samples will be collected for PK and ADA assessments using validated methods.

Plasma samples for BMS-986288 ADA and serum samples for nivolumab ADA and cytokines will be collected from all participants at specified time points (see Table 9.5-2, Table 9.5-3, and Table 9.5-4). PK samples may be analyzed by validated and exploratory methods that measure different forms of the Probody mAb for exploratory purposes; exploratory results may be reported. Immunogenicity samples will be analyzed by validated methods and may also be analyzed for neutralizing antibodies. 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.

Additionally, residual bioanalytical samples will be archived and may be used for potential exploratory bioanalysis (including, but not limited to, analysis of drug-ADA immune complexes, metabolite analyses, etc) and/or for additional method purposes (including, but not limited to, cross-validation, ADA/PK selectivity, cut point, etc).

Table 9.5-1: BMS-986288 Pharmacokinetic Analyses

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 one 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
Cavgss	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 maximum observed concentration [Cmax])
T-HALF	Terminal half-life if data permit (Cycle 4)

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. For participants enrolled in [redacted] receiving [redacted] administration, a non-compartmental or PPK approach will be used to assess the PK data, and parameters such as Cmax, AUC(0-T), and bioavailability (F) will be assessed as feasible and applicable.

Table 9.5-2, Table 9.5-3, and Table 9.5-4 list the sampling schedule to be followed for the assessment of PK. [redacted] PK and ADA sample collection schedules [redacted]. Further details of blood collection and processing will be provided to the site in the Laboratory Manual.

On-treatment PK samples are intended to be drawn relative to actual dosing days. If a dose occurs on a different day within the cycle due to delays or minor schedule adjustments, PK samples should be adjusted accordingly. 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. However, if a predose sample is collected but the dose is subsequently delayed, then an additional predose sample should not be collected. 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.

Table 9.5-2: PK and ADA Sampling Schedule for BMS-986288 IV [redacted] Monotherapy in Dose Escalation (Part 1A) and BMS-986288 IV [redacted] Cohort Expansion (Part 2A)

Study Day of Sample Collection (1 Cycle = [redacted])	Event	Time (Relative to Start of BMS-986288 Infusion) Hr:Min[a]	BMS-986288 PK [redacted] Sample	BMS-986288 ADA [redacted] Sample
C1D1	Predose[b]	00:00	X	X
	EOI	See note[c]	X	
		[redacted]	X	
C1D[redacted]			X	
C1D[redacted] (± 1 day)			X	
C1D[redacted] (± 2 days)			X	
C1D[redacted] (± 2 days)			X	
C1D[redacted] (± 2 days)			X	
C2D1	Predose[b]	00:00	X	X
	EOI	See note[c]	X	
C2D[redacted][d] (± 3 days)		168:00	X	
C3D1	Predose[b]	00:00	X	X
	EOI	See note[c]	X	
C4D1	Predose[b]	00:00	X	X
	EOI	See note[c]	X	
		[redacted]	X	
C4D[redacted]			X	
C4D[redacted]			X	
C4D[redacted]			X	
C4D[redacted]			X	
C4D[redacted]			X	
C5D1	Predose[b]	00:00	X	X
C6D1	Predose[b]	00:00	X	X
Every fourth cycle after C6 until EOT (C10D1, C14D1, C18D1, etc until EOT)	Predose[b]	00:00	X	X

Table 9.5-2: PK and ADA Sampling Schedule for BMS-986288 IV [redacted] Monotherapy in Dose Escalation (Part 1A) and BMS-986288 IV [redacted] Cohort Expansion (Part 2A)

Study Day of Sample Collection (1 Cycle = [redacted])	Event	Time (Relative to Start of BMS-986288 Infusion) Hr:Min[a]	BMS-986288 PK [redacted] Sample	BMS-986288 ADA [redacted] Sample
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: ADA = anti-drug antibody; C = cycle; D = day; EOI = end of infusion; EOT = end of treatment; Hr = hour; Min = minute; [redacted]; PK = pharmacokinetics; [redacted].

[a] Every effort should be taken to collect the sample as close to the designated time as possible. The actual time of collection should be recorded.

[b] All predose samples should be taken within 30 minutes prior to the start of the infusion.

[c] EOI PK samples should be collected when all study drug has been infused. If a flush is administered to clear the IV lines of the drug and to ensure delivery of the entire drug dose, then draw the EOI PK sample within approximately 15 minutes after end of the flush. Do not draw EOI samples from the same IV access through which the drug was administered. Refer to the Pharmacy Manual for infusion duration. If the EOI is delayed beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.

[d] Sample should be collected with [redacted] (see Table 9.8.3-1).

Table 9.5-3: PK and ADA Sampling Schedule for BMS-986288 IV [redacted] in Combination with Nivolumab IV [redacted] in Dose Escalation (Part 1B) and BMS-986288 IV [redacted] in Combination with Nivolumab IV [redacted] Cohort Expansion (Part 2B)

Study Day of Sample Collection (1 Cycle = [redacted])	Event	Time (Relative to Start of Nivolumab Infusion) Hr:Min[a]	BMS-986288 PK [redacted] Sample	Nivolumab PK [redacted] Sample	BMS-986288 ADA [redacted] Sample	Nivolumab ADA [redacted] Sample
C1D[redacted]	Predose[b]	00:00	X	X	X	X
	EOI	See note[c]	X	X		
		[redacted]	X			
C1D[redacted]			X			
C1D[redacted]			X			
C1D[redacted]			X			
C1D[redacted]			X			
C1D[redacted]			X			
C2D1	Predose[b]	00:00	X	X	X	X
	EOI	See note[c]	X	X		
C2D8[d] (± 3 days)		168:00	X	X		
C3D1	Predose[b]	00:00	X	X	X	X
	EOI	See note[c]	X	X		
C4D1	Predose[b]	00:00	X	X	X	X
	EOI	See note[c]	X	X		
		04:00	X			
C4D2		24:00	X			
C4D4 (± 1 day)		72:00	X			

Table 9.5-3: PK and ADA Sampling Schedule for BMS-986288 IV [redacted] in Combination with Nivolumab IV [redacted] in Dose Escalation (Part 1B) and BMS-986288 IV [redacted] in Combination with Nivolumab IV [redacted] Cohort Expansion (Part 2B)

Study Day of Sample Collection (1 Cycle = [redacted])	Event	Time (Relative to Start of Nivolumab Infusion) Hr:Min[a]	BMS-986288 PK [redacted] Sample	Nivolumab PK [redacted] Sample	BMS-986288 ADA [redacted] Sample	Nivolumab ADA [redacted] Sample
C4D8 (± 2 days)		168:00	X			
C4D15 (± 2 days)		336:00	X			
C4D22 (± 2 days)		504:00	X			
C5D1	Predose[b]	00:00	X	X	X	X
C6D1	Predose[b]	00:00	X	X	X	X
Every fourth cycle after C6 until EOT (C10D1, C14D1, C18D1, etc until EOT)	Predose[b]	00:00	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: ADA = anti-drug antibody; C = cycle; D = day; EOI = end of infusion; EOT = end of treatment; Hr = hour; Min = minute; IV = intravenous; PK = pharmacokinetics; [redacted].

[a] Every effort should be taken to collect the sample as close to the designated time as possible. The actual time of collection should be recorded.

[b] All predose samples should be taken within 30 minutes prior to the start of the first drug (eg, nivolumab) infusion.

[c] EOI PK samples should be collected when all study drug has been infused. If a flush is administered to clear the IV lines of the drug and to ensure delivery of the entire drug dose, then draw the EOI PK sample within approximately 15 minutes after end of the flush. Do not draw EOI samples from the same IV access

through which the drug was administered. Refer to the Pharmacy Manual for infusion duration. If the EOI is delayed beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.

[d] Sample should be collected with [redacted] (see Table 9.8.3-1).

Table 9.5-4: PK and ADA Sampling Schedule for BMS-986288 IV [redacted] in Combination with Nivolumab IV [redacted] Cohort Expansion (Part 2C Arm C, Arm E, and Arm Z)

Study Day of Sample Collection (1 Cycle = [redacted])	Event	Time (Relative to Start of Nivolumab Infusion) Hr:Min[a]	BMS-986288 PK [redacted] Sample	Nivolumab PK [redacted] Sample	BMS-986288 ADA [redacted] Sample	Nivolumab ADA [redacted] Sample
C1D1	Predose[b]	0:00	X	X	X	X
	EOI	See note[c]	X	X		
C1D2		24:00:00	X	X		
C2D1	Predose[b]	0:00	X	X	X	X
	EOI	See note[c]	X	X		
C3D1	Predose[b]	0:00	X	X		
C4D1	Predose[b]	0:00	X	X	X	X
C6D1	Predose[b]	0:00	X	X	X	X
Every fourth cycle after C6 until EOT (C10D1, C14D1, C18D1, etc until EOT)	Predose[b]	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

Table 9.5-4: PK and ADA Sampling Schedule for BMS-986288 IV [redacted] in Combination with Nivolumab IV [redacted] Cohort Expansion (Part 2C Arm C, Arm E, and Arm Z)

Study Day of Sample Collection (1 Cycle = [redacted])	Event	Time (Relative to Start of Nivolumab Infusion) Hr:Min[a]	BMS-986288 PK [redacted] Sample	Nivolumab PK [redacted] Sample	BMS-986288 ADA [redacted] Sample	Nivolumab ADA [redacted] Sample
Grade 3+ infusion reaction			X	X	X	X

Abbreviations: ADA = anti-drug antibody; C = cycle; D = day; EOI = end of infusion; EOT = end of treatment; Hr = hour; IV = intravenous; Min = minute; PK = pharmacokinetics; [redacted].

[a] Every effort should be taken to collect the sample as close to the designated time as possible. The actual time of collection should be recorded.

[b] All predose samples should be taken within 30 minutes prior to the start of the first drug (eg, nivolumab) infusion.

[c] EOI PK samples should be collected when all study drug has been infused. If a flush is administered to clear the IV lines of the drug and to ensure delivery of the entire drug dose, then draw the EOI PK sample within approximately 15 minutes after end of the flush. Do not draw EOI samples from the same IV access

9.6 Pharmacodynamics

Details on pharmacodynamic biomarker assessments are included in Section 9.8.

9.7 Pharmacogenomics

Not applicable.

9.7.1 ADME Sampling

Not applicable.

9.8 Biomarkers

For all participants, biomarker measures of baseline, on-treatment, and upon disease progression [redacted], serum, and tumor samples will be used, if sufficient material collected, to identify pharmacodynamic markers associated with treatment. Additional biomarkers related to mechanisms of action, such as, but not limited to, safety biomarkers, and associations with response to BMS-986288 alone and in combination with nivolumab will be explored.

[redacted] will be collected prior to therapy, on treatment, and upon disease progression ([redacted] are not required for participants enrolled in the regorafenib arm [Part 2C Arm D], but [redacted] are required for participants that elect to join the cross-over arm [Part 2C Arm Z] in order to provide pre-treatment information). 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 and Table 9.8.3-2. Further details of [redacted] collection and processing will be provided to the site in the Procedure Manual.

9.8.1 [redacted] Biomarkers

A variety of factors that may impact the immunomodulatory properties and efficacy of BMS-986288 will be investigated in [redacted] specimens taken from all participants prior to or during treatment at the time points indicated in Table 9.8.3-1 and Table 9.8.3-2. 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

[redacted] samples as well as [redacted] samples used for PK analysis may also be used to evaluate [redacted], over the course of the treatment. [redacted] and quantified by immunoassays in serum. Analyses may include, but not necessarily be limited to, soluble [redacted].

9.8.1.2 Immunophenotyping

The proportion of specific lymphocyte subsets [redacted] preparations will be quantified by flow

cytometry. Analyses may include, but not necessarily be limited to, the proportion of [redacted]; as well as expression levels of [redacted].

9.8.1.3 [redacted] Analysis

The [redacted] of the peripheral [redacted] compartment and changes over the course of treatment with immunotherapeutic agents may be related to the mechanism of action of BMS-986288. In order to explore whether a [redacted] is associated with response to therapy, next generation, high-throughput, deoxyribonucleic acid (DNA) sequencing will be performed on DNA or RNA isolated from [redacted] and [redacted] to quantitate the composition of the [redacted] prior to and during therapy.

9.8.1.4 [redacted] Variants

Whole blood will be collected from all participants prior to treatment to generate genomic DNA for single nucleotide polymorphism (SNP) analyses [redacted]. These genomic analyses will include assessment of [redacted][79] to determine if natural variation within those genes is associated with response to BMS-986288 and/or with AEs during treatment.

[redacted]

[redacted]

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 [redacted]. These

IHC analyses may include, but will not necessarily be limited to, the following markers: [redacted].

9.8.2.2 Characterization of [redacted]

As described above, [redacted] may be performed on pre- and post-treatment [redacted] to assess the composition of the [redacted]. DNA will be isolated from the [redacted] and/or [redacted].

[redacted] that are collected at screening and on treatment will be examined for messenger RNA gene expression by RNA sequencing, quantitative real-time PCR, or other technologies to characterize gene expression profiles associated with immune modulation, [redacted], or outcome following treatment with BMS-986288.

9.8.2.4 Mutational and DNA Methylation Analyses

DNA from [redacted] will be collected and analyzed using whole-exome sequencing to determine the number and identity of mutations found [redacted].

[redacted]

DNA may also be analyzed to assess methylation status of genes of interest, including, but not limited to, [redacted].

9.8.3 Biomarker Sampling Schedule

The biomarker sampling schedule is outlined in Table 9.8.3-1 and Table 9.8.3-2.

Table 9.8.3-1: Biomarker Sampling Schedule for [redacted] Dosing Schedule for Part 1, Part 2A, Part 2B, and Part 2C Arm C, Arm E, and Arm Z

Study Day of Sample Collection [redacted]	Time (Relative to BMS-986288 Dose) Hr:Min	[redacted]						
Screening			X[c]					X[d]
C1D1	00:00[e]	X	X	X	X	X	X	
C1D2	24:00	X				X		
C1D8 (± 2 days)	168:00	X				X	X	
C1D15 (± 2 days)	336:00	X				X	X	
C2D1	00:00[e]	X				X	X	
C2D8[b,] (± 3 days)	168:00	X	X	X	X	X		X[f]
C2D15 (± 2 days)	336:00	X						
C3D1	00:00[e]	X	X					
C4D1		X	X					
EOT or at progression		X	X					X

Abbreviations: C = cycle; [redacted] D = day; EOT = end of treatment; KRAS = Kirsten rat sarcoma virus; [redacted]

[a] Instructions for the collection and processing [redacted] will be provided in the Laboratory Manual.

[b] Pre-treatment (screening) [redacted] can be performed on C1D1. Mandatory on-treatment [redacted] to be performed at C2D8; specimens may be collected within 3 days of the time point and must be obtained prior to administration of study treatments. C2D8 biomarker collections should occur at the same time as [redacted]. Adjust the biomarker collection in accordance with the [redacted] collection. An optional additional [redacted] can be collected on treatment if the Investigator and the Medical Monitor (or designee) find it indicated. A [redacted] is required, if medically feasible, upon confirmation of PD (within 7 days) except for: 1) participants who have an [redacted] within 4 cycles; 2) participants who will be imminently (within 4 weeks) enrolling in a subsequent clinical research study that requires a screening [redacted]; 3) participants who consent to be treated beyond progression will require the [redacted] only at the subsequent confirmation of progression; and 4) participants in Part 2C, unless the participant elects to crossover to Arm Z. [redacted] are unacceptable for submission.

[c] For Part 2C. Sample only needed if other available options for assessing KRAS are not viable, and KRAS testing must be recent (following prior lines of therapy) and not from diagnosis as KRAS testing can change with treatment.

[d] For the cross-over arm, a [redacted] is required [redacted] in order to provide pre-treatment information. This [redacted] can be from EOT [redacted] in Table 9.8.3-2

[e] All predose samples should be taken prior to the start of the infusion/administration.

[f] Optional collection for cross-over participants.

Table 9.8.3-2: Biomarker Sampling Schedule for [redacted] Dosing Schedule for Part 2C Arm D

Study Day of Sample Collection [redacted]	**Time (Relative to BMS-986288 Dose) Hr:Min**	[redacted]					
Screening			X[c]				X
C1D1	00:00[d]	X	X	X	X	X	
C1D15 (± 2 days)	336:00	X				X	
C2D1	00:00[d]	X				X	
C3D1	00:00[d]	X	X		X	X	
C4D1	00:00[d]	X	X				

Table 9.8.3-2: Biomarker Sampling Schedule for [redacted] Dosing Schedule for Part 2C Arm D

Study Day of Sample Collection [redacted]	**Time (Relative to BMS-986288 Dose) Hr:Min**	[redacted]					
EOT or at progression		X	X			X	X[b]

Abbreviations: C = cycle; [redacted] D = day; EOT = end of treatment; KRAS = Kirsten rat sarcoma virus; Q4W = every 4 weeks; TCR = T-cell receptor.

[a] Instructions for the collection and processing [redacted] will be provided in the Laboratory Manual.

[b] [redacted] can be performed on C1D1. A new [redacted] is required for participants that elect to cross-over to study treatment in order to provide pre-treatment information. For participants that do not cross-over to Arm Z, an EOT [redacted] is optional. [redacted]

[c] For Part 2C. Sample only needed if other available options for assessing KRAS are not viable.

[d] All predose samples should be taken prior to the start of the infusion/administration.

9.8.4 Additional Research Collection

This protocol will include residual sample storage for additional research (AR). All PK, biomarker, cytokine, and residual samples will be stored for AR.

For All US Sites:

AR participation is required for all investigational sites in the US.

AR is required for all study participants, except where prohibited by IRBs/ethics committees, or academic/institutional requirements. Where 1 or more of these exceptions occurs, participation in the AR should be encouraged but will not be a condition of overall study participation.

- If the IRB/ethics committees and site agree to the mandatory AR retention and/or collection, then the study participant must agree to the mandatory AR as a requirement for inclusion in the study.
- If optional participation is permitted and approved, then the study participants may opt out of the AR retention and/or collection.

For Non-US Sites:

AR is optional for all study participants, except where retention and/or collection is prohibited by local laws or regulations, ethics committees, or institutional requirements.

Sample retention for AR is intended to expand the translational Research & Development capability at BMS, and will support as yet undefined research aims that will advance our understanding of disease and options for treatment. It may also be used to support health authority requests for analysis, and advancement of pharmacodiagnostic development to better target drugs to the right patients. This may also include genetic/genomic exploration aimed at exploring disease pathways, progression and response to treatment etc.

Sample Collection and Storage

All requests for access to samples or data for AR will be vetted through a diverse committee of the study sponsor's senior leaders in Research & Development (or designee) to ensure the research supports appropriate and well-defined scientific research activities.

Samples kept for future research will be stored at the BMS Biorepository in [redacted] or an independent, BMS-approved storage vendor.

The manager of these samples will ensure they are properly used throughout their usable life and will destroy the samples at the end of the scheduled storage period, no longer than [redacted] years after the end of the study or the maximum allowed by applicable law.

Transfers of samples by research sponsor to third parties will be subject to the recipient's agreement to establish similar storage procedures.

Samples will be stored in a coded fashion, and no researcher will have access to the key. The key is securely held by the Investigator at the clinical site, so there is no direct ability for a researcher to connect a sample to a specific individual.

No additional sampling is required for supplementary testing. Further details of sample collection and processing will be provided to the site in the Procedure 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
[redacted]	
[redacted] biomarker samples	All
[redacted]	All

9.9 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 Monotherapy Dose Escalation (Part 1A)

Dose escalation during BMS-986288 Monotherapy Escalation (Part 1A) 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 and nivolumab (for Part 1B). The targeted toxicity rate in this study is in the range of (16%, 33%). The boundary is similar to the toxicity boundary used by a rule-based design (ie, 3 + 3 design) in that a minimum is set at 16% (~ 1 in 6) DLT rate and a maximum at 33% (~ 2 in 6) DLT rate. The use of the EWOC principle limits the risk of exposing patients in the next cohort to an intolerable dose by ensuring the posterior probability of the DLT rate at or exceeding 33% at any dose is capped at 35%.

In order to understand operational characteristics of the BLRM, the total maximum number of participants for the simulation will be set to [redacted]. Simulation studies with various scenarios show that the expected number of DLT-evaluable participants needed for BLRM is no more than approximately [redacted].

For the trial, approximately 4 participants (3+1) will be treated at the starting dose levels of BMS-986288. While the BLRM will use DLT information from the DLT period, clinical assessment will take into consideration of the totality of available data including PK/pharmacodynamic from all treated participants in assigning a dose level for the next cohort. 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 [redacted] DLT-evaluable participants will be treated at the BLRM-recommended MTD (BLRM-MTD). A maximum of [redacted] 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 pharmacodynamic parameters as required without exceeding a total of [redacted] evaluable participants.

The BLRM-MTD is the dose that satisfies the following 3 conditions:

1) The empirical posterior probability that the "DLT rate of 16% to < 33%" is greater than a pre-specified value (ie, 50%);
2) This probability needs to be the largest among the dose levels that satisfy the EWOC condition (ie, the probability that the "DLT rate ≥ 33%" must be no greater than 35%);
3) A minimum number of participants (ie, 6) were treated at this dose level.

The final recommended MTD/RP2D will be based on the recommendation from the BLRM and overall clinical assessment of available safety, PK, pharmacodynamic, and efficacy data. Lower doses or alternative administration schedules of BMS-986288 may be tested if none of the planned doses are found to be tolerable as monotherapy. Such decisions will be made after discussion and agreement between the Investigators and the BMS Medical Monitor (or designee).

10.1.2 The Safety Evaluation of Combination Doses of BMS-986288 with Nivolumab (Part 1B)

In the Safety Evaluation Combination Doses of BMS-986288 with Nivolumab (Part 1B), the starting dose of BMS-986288 will be at least 1 dose level lower than the current monotherapy dose level of BMS-986288 demonstrating an acceptable safety profile, and will be administered in combination with nivolumab at the planned [redacted] mg [redacted]. Dose escalation and determination of MTD for the Safety Evaluation of Combination Doses of BMS-986288 with Nivolumab (Part 1B) will be guided by BLRM-copula with EWOC principle. Subsequent dose selection of the combination will be based on evaluating the recommendation from BLRM-copula and an overall assessment of available safety and PK/pharmacodynamic data. BLRM-copula will incorporate historical information from ipilimumab and nivolumab studies and the DLT information from the DLT period from both ipilimumab arms and nivolumab arms to estimate dose-toxicity surface, and will provide guidance for dose adjustment of either drug as needed.

While guided by the BLRM-copula, clinical assessment will take into consideration the totality of available data including PK/pharmacodynamics from all treated participants in assigning a dose level for the next cohort. 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-copula recommendation. At least [redacted] DLT-evaluable participants will be treated at the BLRM-copula recommended MTD (BLRMc-MTD). A maximum of [redacted] DLT-evaluable participants will be treated at each dose level. Once the BLRMc-MTD is identified, then additional participants may be treated at the BLRMc-MTD or any dose level below the BLRMc-MTD for further evaluation of safety, PK, or pharmacodynamic parameters as required without exceeding a

total of [redacted] evaluable participants. A combination with a higher dose level of either drug may be considered if recommended per BLRM-copula, after consideration of available safety, and PK/pharmacodynamic data. At no time will the dose of BMS-986288 in the Safety Evaluation of Combination Doses of BMS-986288 with Nivolumab (Part 1B) exceed the highest tolerated dose equivalent in the BMS-986288 Monotherapy Escalation (Part 1A).

The BLRMc-MTD is the dose that satisfies the following 3 conditions:

1) The empirical posterior probability that the "DLT rate of 16% to < 33%" is greater than a pre-specified value (ie, 50%);
2) This probability needs to be the largest among the dose levels that satisfy the EWOC condition (ie, the probability that the "DLT rate ≥ 33%" must be no greater than 35%);
3) A minimum number of participants (ie, 6) were treated at this dose level.

The final recommended MTD/RP2D will be based on the recommendation from the BLRM-copula and overall clinical assessment of available safety, PK, pharmacodynamic, and efficacy data. Lower doses or alternative administration schedules of BMS-986288 + nivolumab may be tested if none of the planned doses are found to be tolerable as a combination. Such decisions will be made after discussion and agreement between the Investigators and the BMS Medical Monitor (or designee).

10.1.3 The [redacted] Evaluation of BMS-986288 as a Monotherapy and in Combination with Nivolumab [redacted]

Sample size calculations for the [redacted] of BMS-986288 as a Monotherapy and in Combination with Nivolumab [redacted] are based on width of the confidence interval (CI) for the geometric mean ratio (GMR) of exposure measures for [redacted] dosing. For each dose to be tested in [redacted], the PK parameters are assumed to be distributed log-normally, with an inter-participant coefficient of variation of [redacted], and an intra-participant correlation of the log transformed values of 0.6. With [redacted] participants, the lower bound for the 90% CI is [redacted] of the point estimate for the GMR and the upper bound for the 90% CI is [redacted] of the point estimate. Up to [redacted] evaluable participants will be treated in [redacted] (eg, [redacted] evaluable participants for BMS-986288 monotherapy [Arm A]; [redacted] evaluable participants for BMS-986288 in combination with nivolumab [Arm B]).

10.1.4 The BMS-986288 [redacted] Cohort Expansion (Part 2A)

The primary purpose of the BMS-986288 [redacted] Cohort Expansion (Part 2A) is to evaluate preliminary efficacy of BMS-986288. The sample size calculation will be based on the ORR.

The preliminary efficacy of BMS-986288 as a monotherapy will be evaluated in participants with advanced cutaneous melanoma and NSCLC with disease relapse/recurrence or progression after prior immunotherapy treatment with an anti-PD-1 or anti-PD-L1 containing regimen. Up to [redacted] cutaneous melanoma participants will be treated. For NSCLC, initial evaluation of efficacy signal (ORR) will be based on approximately the first [redacted] treated participants at a dose level. Based on the results of this initial evaluation, additional participants for a total of up to [redacted] participants may

be treated at a dose level. If more than 1 dose level is evaluated, up to [redacted] participants (eg, [redacted] participants × 2 arms) may be enrolled. Other tumor types may be explored in the future.

With [redacted] treated participants in each BMS-986288 arm, the lower limit of the 2-sided 80% Clopper Pearson CI for ORR estimate will be [redacted] assuming ORR estimate size of [redacted] respectively. With [redacted] treated participants in each BMS-986288 arm, the lower limit of the 2-sided 80% Clopper Pearson CI for ORR estimate will be [redacted] assuming ORR estimate size of [redacted] respectively.

10.1.5 The BMS-986288 in Combination with Nivolumab Cohort Expansion (Part 2B)

The purpose of the BMS-986288 Expansion Combination Therapy (Part 2B) is to gather additional data including safety, tolerability, and preliminary efficacy for combination therapy of BMS-986288 with nivolumab in NSCLC. The sample size calculation will be based on the ORR.

Approximately [redacted] participants will be treated. Initial evaluation of efficacy signal (ORR) will be based on approximately the first [redacted] treated participants at a dose level and will be descriptive based on a point estimate and an 80% Clopper Pearson CI for ORR. In order for an 80% CI to exclude a [redacted] ORR (as reported for ipilimumab with nivolumab in similar population), at least [redacted] responders ([redacted] ORR) will need to be observed in the first [redacted] participants evaluated at this dose. If [redacted] responders are observed [redacted], the 80% CI will equal [redacted]. Based on the results of this initial evaluation, additional participants for a total of up to [redacted] participants may be treated at a dose level. If more than 1 dose level is evaluated, up to [redacted] participants (eg, [redacted] participants × [redacted] arms) may be enrolled.

In addition, if [redacted] participants are evaluated at a dose level, there will be approximately 80% power to detect a difference between the null hypothesis assuming ORR of [redacted] and the alternative assuming ORR of [redacted], based on a one group $\chi 2$ test with a 0.10 one-sided significance alpha level.

10.1.6 The BMS-986288 in Combination with Nivolumab Cohort Expansion in MSS CRC Participants (Part 2C)

Part 2C of the study uses a [redacted] arm. A portion of the [redacted] cohort will be [redacted] These [redacted] studies will have a similar design and population to Part 2C (ie, similar enrolment methods, randomized population, similar inclusion and exclusion criteria, and baseline characteristics). Approximately [redacted] participants will be randomized in Part 2C. These [redacted] participants will be randomized in a 2:1 ratio for the experimental arm (Arm C) and control arm (Arm D) ([redacted] participants for the experimental arm and [redacted] participants for the control arm). An additional dose may be open in Part 2C as Arm E (see Section 7.2). If multiple doses are open, no multiple comparison adjustments will be performed.

For each interim analysis of efficacy signal (ORR), no formal statistical comparison will be performed with a small administrative alpha of 0.0001. Interim analyses may be performed when at least [redacted] participants in the experimental arm have at least 1 post-treatment tumor assessment

(after 49 days). This will be a descriptive evaluation based on a point estimate. The study may be stopped early if the number of responders in the treatment arm is less than the number of responders in the control arm at interim analysis. For example, using this futility criteria, Bayesian predictive probability of success (with delta ORR of [redacted]) is [redacted], with [redacted] responders out of [redacted] participants in the experimental arm and [redacted] responder out of [redacted] participants in the control arm. Based on the results of this initial evaluation, additional participants for a total of up to [redacted] participants may be randomized to each existing experimental arm. See Section 10.3.8 for further information regarding interim analyses.

At the final analysis, there will be approximately [redacted] randomized participants in each experimental arm and [redacted] participants in the [redacted] arm ([redacted] participants from the randomized control arm and [redacted] participants from the [redacted] control data). This will provide approximately 80% power to detect the delta ORR of [redacted] with a two-sided alpha of 0.1. The trial can reach statistical significance when the delta ORR is [redacted] or larger. If it is not possible to borrow information from [redacted] data or studies, approximately [redacted] randomized participants in the experimental arm and [redacted] participants from the randomized control arm will be evaluated. This will provide approximately 73% power to detect the delta ORR of [redacted] with a two-sided alpha of 0.1 and unpooled variance assumption.

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 and are registered into the Interactive Response Technology (IRT)
Treated	All participants who take at least 1 dose of study treatment
Response-evaluable	All treated participants with measurable disease at baseline and 1 of the following: (a) at least 1 post baseline tumor assessment; (b) clinical progression; and (c) death
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
Biomarker	All treated participants with available biomarker data
Clinical outcomes population (Part 2A and Part 2B only)	All treated participants who have a valid clinical outcomes assessment at baseline and at least 1 matched on-treatment post-baseline assessment

10.3 Statistical Analyses

The Statistical Analysis Plan will be developed and finalized before database lock, and below is a summary of planned statistical analyses of the primary and secondary endpoints.

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

10.3.1 Efficacy Analyses

The primary efficacy analyses (Table 10.3.1-1) will be performed on the treated population for the final analysis. Efficacy analyses based on the treated population may be performed for interim analyses when the minimum follow-up period is less than sufficient to warrant adequate interpretation of the result. Details of the censoring scheme on time-to-event endpoints such as DOR, PFS, TTR, and OSR will be described in the Statistical Analysis Plan.

Analysis of exploratory endpoints using iRECIST by BICR (ORR, DOR, and PFS) will also be performed.

Table 10.3.1-1: Efficacy - Statistical Analyses

Endpoint	Statistical Analysis Methods
ORR is defined as the proportion of all treated participants whose BOR is either CR or PR by Investigator (Part 2A/Part 2B) and BICR (Part 2C) per RECIST v1.1. BOR for a participant will be assessed per RECIST v1.1 by Investigator (Part 2A/Part 2B) and BICR (Part 2C), unless otherwise specified.	Estimate of ORR and corresponding 2-sided exact 95% CI using the Clopper-Pearson method by treatment for each tumor type.
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 death, whichever occurs first.	Estimate by the Kaplan-Meier method and corresponding 2-sided 95% CI using Brookmeyer and Crowley methodology (using log-log transformation) by treatment for each tumor type.
PFS PFS for a participant is defined as the time from the first dosing date to the date of first objectively documented disease progression or death due to any cause, whichever occurs first.	Estimate by the Kaplan-Meier method and corresponding 2-sided 95% CI using Brookmeyer and Crowley methodology (using log-log transformation) by treatment for each tumor type.
TTR TTR for a participant is defined as the time from the first dosing date to the date of the first confirmed response (CR or PR) per RECIST v1.1.	Listing of TTR will be provided.
OSR OSR at a certain time point is defined as the proportion of subjects alive at that time point since the first dosing date.	Estimate by the Kaplan-Meier method and corresponding 2-sided 95% CI using Brookmeyer and Crowley methodology (using log-log transformation) by treatment for each tumor type.

Abbreviations: BICR = blinded independent central review; BOR = best overall response; CI = confidence interval; CR = complete response; DOR = duration of response; ORR = objective response rate; OSR = overall survival rate; PFS = progression-free survival; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; TTR = time to response.

10.3.2 Safety Analyses

All safety analyses (see Table 10.3.2-1) will be performed on the treated population.

Table 10.3.2-1: Safety - Statistical Analyses

Endpoint	Statistical Analysis Methods
Incidence of DLTs, AEs, SAEs, AEs leading to discontinuation, and death. AEs will be graded according to CTCAE v5.0.	DLT rate by dose level, frequency distribution of treated participants with AE using the worst CTC grade. Participants will only be counted (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
Laboratory abnormalities. Laboratory values will be graded according to CTCAE v5.0.	Laboratory shift table using the worst CTC grade on-treatment per participant

Abbreviations: AE = adverse event; DLT = dose-limiting toxicity; CTC = common terminology criteria; CTCAE = common terminology criteria for adverse events; PT = preferred term; SAE = serious adverse event.

10.3.3 Pharmacokinetic Analysis for BMS-986288

See Table 10.3.3-1 for PK statistical analyses.

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), AUC(TAU)	Scatter plots vs 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 vs 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 plasma serum 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 serum concentration-time curve in 1 dosing interval; CLT = total body clearance; Cmax = maximum observed concentration; Css-avg = average serum concentration over a dosing interval (AUC[TAU]/tau) at steady state; Ctau = observed serum concentration at the end of a dosing interval; Ctrough = trough observed serum concentrations (this includes predose concentrations [C0] and Ctau); T-HALF = terminal serum half-life; Tmax = time of maximum observed plasma serum concentration.

A non-compartmental or PPK approach will be used to assess the PK data and parameters such as Cmax, AUC(0-T), and bioavailability (F) will be assessed as feasible and applicable. PK concentration-time data for BMS-986288, and sparse plasma concentration-time for nivolumab

may be pooled with data from other studies for integrated PPK and ER analyses, which will be presented in a separate report.

10.3.4 Immunogenicity

Endpoint	Statistical Analysis Methods
Incidence of anti-drug antibodies (ADAs) 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

[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

Endpoint	Statistical Analysis Methods
Summary measures of change (or % change) from baseline in various biomarkers in the [redacted]	Summary statistics/plots by planned study day and dose in each arm Plots of the time course of biomarkers

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. The details of ECG data analysis will be provided in the Statistical Analysis Plan.

10.3.7 Other Analyses

Pharmacodynamic biomarker exploratory analyses and exploratory analyses of clinical outcomes assessments will be described in detail in the Statistical Analysis Plan finalized before database lock. OSR at 1 year and 2 years will be analyzed similarly to PFS. The population PK/ER and pharmacodynamic analyses may be presented separately from the main Clinical Study Report.

10.3.8 Interim Analyses

Interim analyses will be performed for administrative purposes or publication. No formal inferences requiring any adjustment to statistical significance level will be performed.

Preliminary efficacy may be assessed for Part 2 to determine an initial signal, and enrollment may be paused, prior to enrolling additional participants. If an inadequate signal is detected from a preliminary analysis, then enrollment may be closed for that cohort.

10.3.8.1 Bayesian Continuous Monitoring for Treatment-related Toxicities Meeting DLT Criteria in Part 2

A Bayesian continuous monitoring framework[80] will be used to ascertain safety signals that occur during Part 2 that may lead to suspension or evaluation of toxicity by the Sponsor/Medical Monitor in BMS-986288 as a monotherapy and/or in combination with nivolumab participants. Incidence rates of treatment-related toxicities meeting DLT criteria (defined in Section 7.4.1) are compared to 33%.

The Bayesian safety monitoring boundaries are established using a noninformative prior, Beta (0.5, 0.5). The posterior distribution is Beta (0.5+n, 0.5+[m-n]), where m is number of treated Part 2 participants per dose level and n is the subset of these m participants who experience treatment-related toxicities meeting DLT criteria. All treated Part 2 participants are considered evaluable. The criterion for not continuing for future participants is based on the posterior probability of (treated Part 2 participants who experience treatment-related toxicities meeting DLT criteria > 33% | cumulative data) > 0.80. This criterion implies that continuation of BMS-986288 as a monotherapy and/or in combination with nivolumab at that dose level in Part 2 will be re-evaluated if there is greater than 80% probability that the number of participants with treatment-related toxicities meeting DLT criteria is larger than 33%, corresponding to a final boundary of 16 out of 40 total participants. When the stopping boundaries shown in Table 10.3.8.1-1 are met, further enrollment at that expansion dose level will be temporarily halted. Recommendations from interim calculations, and the totality of the data will be reviewed by the independent SMT. Based on the SMT's review, the current dose level may be permanently discontinued, and a lower dose level will be evaluated in the remaining study part. Similar continuous safety monitoring will be applied to the new dose level being evaluated.

Table 10.3.8.1-1: Monitoring Boundaries for Treatment-related Toxicities Meeting DLT Criteria in Part 2

Number of Evaluable Participants: Treated Part 2 Participants (Cumulative)	Critical Region: At or Above Number of Part 2 Participants Who Experience Treatment-related Toxicities Meeting the DLT Criteria (Defined in Section 7.4.1)
[redacted]	

Table 10.3.8.1-1: Monitoring Boundaries for Treatment-related Toxicities Meeting DLT Criteria in Part 2

Number of Evaluable Participants: Treated Part 2 Participants (Cumulative)	Critical Region: At or Above Number of Part 2 Participants Who Experience Treatment-related Toxicities Meeting the DLT Criteria (Defined in Section 7.4.1)
[redacted]	

Abbreviation: DLT = dose-limiting toxicity.

These boundaries can be applied on a continuous basis and are intended to assist the clinical interpretation. Other parameters may be considered and other posterior probabilities and boundaries may be calculated. Recommendations from interim monitoring calculations are not binding, and the totality of the data will be considered for decisions by SMT.

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12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
3L/4L	3rd/4th line
ADA	anti-drug antibody
[redacted]	
ADME	absorption, distribution, metabolism, and excretion
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
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AR	additional research
ART	antiretroviral therapy
AST	aspartate aminotransferase
AT	aminotransaminase
AUC	area under the concentration-time curve
AUC(INF)	area under the concentration-time curve from time zero extrapolated to infinite time
AUC(0-T)	area under the concentration-time curve from time zero to the time of the last quantifiable concentration
AUC(TAU)	area under the concentration-time curve in one dosing interval
BA	bioavailability
BICR	blinded independent central review
BLRM	Bayesian Logistic Regression Model
BLRMc-MTD	Bayesian Logistic Regression Model-copula recommended maximum tolerated dose
BLRM-MTD	Bayesian Logistic Regression Model-recommended maximum tolerated dose
BMS	Bristol-Myers Squibb
BOR	best overall response

Term	Definition
BUN	blood urea nitrogen
BW	body weight
C	Cycle
Cavg	average concentration
Cavgss	average steady-state concentration
CBC	complete blood count
CD	cluster of differentiation
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL	clearance
CLT	total body clearance
Cmax	maximum observed concentration
Cmin	minimum observed concentration
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CR	complete response
CRC	colorectal cancer
CrCl	creatinine clearance
CRF	case report form
CT	computed tomography
CTAg	Clinical Trial Agreement
Ctau	concentration in a dosing interval (eg, concentration at 24 hours, concentration at 12 hours, etc.)
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
Ctrough	trough-observed plasma concentration
[redacted]	
D	Day

Term	Definition
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
dMMR	mismatch repair deficient
DNA	deoxyribonucleic acid
DOR	duration of response
DRESS	drug reaction with eosinophilia and systemic symptoms
EC50	half-maximal effective concentration
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
eg	exempli gratia (for example)
eGFR	estimated glomerular filtration rate
EGFR	epidermal growth factor receptor
ELISA	enzyme-linked immunosorbent assay
EOI	end of infusion
EOT	end of treatment
EQ-5D-VAS	EQ-5D Visual Analog Scale
EQ-5D-3L	3-Level EQ-5D
EQ-5D-5L	5-Level EQ-5D
ER	exposure-response
EU	European Union
EWOC	escalation with overdose control
FACIT GP5	Functional Assessment of Chronic Illness Therapy, General Physical item
FcγR	Fc gamma receptor
FDA	Food and Drug Administration
[redacted]	
FIH	first in human

Term	Definition
FSH	follicle stimulating hormone
[redacted]	
GBS	Guillain-Barre Syndrome
GCP	Good Clinical Practice
GI	gastrointestinal
GLP	good laboratory practice
GMR	geometric mean ratio
h	hour
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
hCG	human chorionic gonadotrophin
HCV	hepatitis C virus
HER2	human epidermal growth factor receptor 2
HFSR	hand-foot skin reaction
HIV	human immunodeficiency virus
HNSTD	highest non-severely toxic dose
HPV	human papilloma virus
HR	hazard ratio
HRQoL	health-related quality of life
IB	Investigator Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
ie	id est (that is)
IEC	Independent Ethics Committee
IFN	interferon
Ig	immunoglobulin
IgG	immunoglobulin G
IL	interleukin
imAE	immune-mediated adverse event

Term	Definition
IMP	investigational medicinal product
INR	international normalized ratio
I-O	immuno-oncology
IP	investigational product
IPRES	Innate PD-1 RESistance
IQR	interquartile range
irAE	immune-related adverse event
IRB	Institutional Review Board
iRECIST	modified Response Evaluation Criteria in Solid Tumors in cancer immunotherapy trials
IRT	Interactive Response Technology
IU	International Unit
IUS	intrauterine hormone-releasing system
IV	intravenous
kg	kilogram
[redacted]	
KLH	keyhole limpet hemocyanin
KRAS	Kirsten rat sarcoma virus
L	liter
LAM	lactation amenorrhea method
LDH	lactate dehydrogenase
mAb	monoclonal antibody
[redacted]	
mCRC	metastatic colorectal cancer
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MG	Myasthenia Gravis
[redacted]	
min	minute
mL	milliliter

Term	Definition
MMR	measles, mumps, rubella
MRI	magnetic resonance imaging
[redacted]	
MSI-H	microsatellite instability high
MSS	microsatellite stable
MTD	maximum tolerated dose
µg	microgram
N	number of participants or observations
[redacted]	
NCI	National Cancer Institute
[redacted]	
NF	non-fucosylated
ng	nanogram
[redacted]	
NSCLC	non-small cell lung cancer
NSCLC-SAQ	Non-small Cell Lung Cancer Symptom Assessment Questionnaire
ORR	objective response rate
OS	overall survival
OSR	overall survival rate
PBMC	peripheral blood mononuclear cell
PBS	phosphate buffered saline
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed cell death 1
p-DILI	potential drug-induced liver injury
PD-L1	programmed death ligand 1
PD-L2	programmed death ligand 2
PE	physical examination
PET	positron emission tomography

Term	Definition
PFS	progression-free survival
PFSR	progression-free survival rate
PI	prediction interval
PID	participant identification number
PK	pharmacokinetics
pMMR	proficient mismatch repair
PPK	population pharmacokinetics
PR	partial response
PRO	patient-reported outcome
Q2W	every 2 weeks
Q3W	every 3 weeks
[redacted]	
Q6W	every 6 weeks
[redacted]	
Q12W	every 12 weeks
[redacted]	
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
[redacted]	
RNA	ribonucleic acid
[redacted]	
RP2D	recommended Phase 2 dose
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
[redacted]	
SCCHN	squamous cell carcinoma of the head and neck

Term	Definition
[redacted]	
SD	stable disease
SJS	Stevens-Johnson syndrome
SmPC	summary of product characteristics
SMT	Safety Management Team
SNP	single nucleotide polymorphism
[redacted]	
SUSAR	suspected, unexpected serious adverse reaction
T.bili	total bilirubin
TEN	toxic epidermal necrolysis
T-HALF	half-life
[redacted]	
Tmax	time of maximum observed concentration
[redacted]	
TNBC	triple-negative breast cancer
TNF-α	tumor necrosis factor alpha
TRAE	treatment-related adverse event
Treg	T-regulatory cell
TSH	thyroid stimulating hormone
TTR	time to response
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information
Vss	apparent volume of distribution at steady state
Vz	volume of distribution of terminal phase (if IV and if multi-exponential decline)
WBC	white blood cell
WOCBP	women of childbearing potential
WWPS	Worldwide Patient Safety

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

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

REGULATORY AND ETHICAL CONSIDERATIONS

GOOD CLINICAL PRACTICE

This study will be conducted in accordance with:

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

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

All potential serious breaches must be reported to the Sponsor or designee immediately. A potential serious breach is defined as a Quality Issue (eg, protocol deviation, etc) that is likely to affect, to a significant degree, 1 or more of the following: (1) the physical, safety, or mental integrity of 1 or more subjects/particpants; (2) the scientific value of the 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, consent form, participant recruitment materials (eg, advertisements), and any other written information to be provided to subjects/participants. The investigator or BMS should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to subjects/participants and any updates.

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

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 by 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

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

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

STUDY TREATMENT RECORDS

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

If	Then
Supplied by BMS (or its vendors):	Records or logs must comply with applicable regulations and guidelines and should include: • amount received and placed in storage area • amount currently in storage area • label identification number or batch number • amount dispensed to and returned by each participant, including unique participant identifiers • amount transferred to another area/site for dispensing or storage • nonstudy disposition (e.g., lost, wasted) • amount destroyed at study site, if applicable • amount returned to BMS • retain samples for bioavailability/bioequivalence/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 sites stock or commercial supply, or a specialty pharmacy)	The investigator or designee accepts responsibility for documenting traceability and study treatment integrity in accordance with requirements applicable under law and the SOPs/standards of the sourcing pharmacy.

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

CASE REPORT FORMS

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

For sites using the Sponsor or designee electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will

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

The confidentiality of records that could identify subjects/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 subinvestigator and who is delegated this task on the Delegation of Authority Form. Subinvestigators in Japan may not be delegated the CRF approval task. For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet Sponsor or designee training requirements and must only access the BMS electronic data capture tool using the unique user account provided by Sponsor or designee. User accounts are not to be shared or reassigned to other individuals

MONITORING

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). If study treatments will be returned, the return will be arranged by the responsible Study Monitor.
Study treatments sourced by site, not supplied by BMS (or its vendors) (examples include study treatments sourced from the sites stock or commercial supply, or a specialty pharmacy)	It is the investigator's or designee's responsibility to dispose of all containers according to the institutional guidelines and procedures.

It is the investigator's or designee's responsibility to arrange for disposal, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The following minimal standards must be met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The

method of disposal, 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.

CLINICAL STUDY REPORT

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

For each CSR related to 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 [Study site or Investigator] participation in the study. These requirements include, but are not limited to, submitting proposed publications to Sponsor or designee at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTAg.

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.

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.

In the European Union (EU), the summary of results and summary for laypersons will be submitted within 1 year (6 months for studies including pediatric populations) of the end of trial in EU/European Economic Area and third countries.

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).

EVALUATING AES AND SAES

Assessment of Causality

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

Follow-up of AEs and SAEs

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

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

All SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

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

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

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

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

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

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

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

Note: Females treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgement in checking serum FSH levels.

- 1-week minimum for vaginal hormonal products (rings, creams, gels)
- 4-week minimum for transdermal products
- 8-week minimum for oral products

Other parenteral products may require washout periods as long as 6 months. If the serum FSH level is > 40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal.

End of Relevant Systemic Exposure

End of relevant systemic exposure is the timepoint where the Investigational Medicinal Product (IMP) or any active major metabolites have decreased to a concentration that is no longer

considered to be relevant for human teratogenicity or fetotoxicity. This should be evaluated in context of safety margins from the no-observed-adverse-effect level or the time required for 5 half-lives of the IMP to pass.

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-986288 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-986288, 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.

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
• Combined (estrogen- and progestogen-containing) hormonal contraception must begin at least 30 days prior to initiation of study therapy.
• Progestogen-only hormonal contraception associated with inhibition of ovulation[b] – oral – injectable • Progestogen-only hormonal contraception must begin at least 30 days prior to initiation of study therapy.
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation and/or implantation (This method of contraception 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.

- Continuous abstinence must begin at least 30 days prior to initiation of study therapy.
- It is not necessary to use any other method of contraception when complete abstinence is elected.
- WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2.
- Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence.
- Periodic abstinence (including, but not limited to, calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception for this study.
-

NOTES:

[a] Typical use failure rates may differ from failure rates when contraceptive methods are used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

[b] Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized. For information specific to this study regarding permissibility of hormonal contraception, refer to Sections 6.1 (Inclusion Criteria) and 7.7.1 (Prohibited and/or Restricted Treatments) of the protocol.

[c] IUSs are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness. For information specific to this study regarding permissibility of hormonal contraception, refer to Sections 6.1 (Inclusion Criteria) and 7.7.1 (Prohibited and/or Restricted Treatments) of the protocol.

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)

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 Appendix 3 Adverse Events and Serious Adverse Events: Definitions and Procedures for Evaluating, Follow-up and Reporting.

APPENDIX 5 RESPONSE EVALUATION CRITERIA IN SOLID TUMORS GUIDELINES (VERSION 1.1) WITH BMS MODIFICATIONS

1 EVALUATION OF LESIONS

Solid tumors will be evaluated using Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST v1.1) guideline with BMS modifications.[1]

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

1.1 Measurable

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

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

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

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

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

1.2 Non-Measurable

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

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

1.3 Special considerations regarding lesion measurability

1.3.1 Bone lesions

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

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

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

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

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

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

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

2 RESPONSE CRITERIA

2.1 Evaluation of Target Lesions

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

2.1.1 Special Notes on the Assessment of Target Lesions

2.1.1.1 Lymph nodes

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

2.1.1.2 Target lesions that become 'too small to measure'

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

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

2.1.1.3 Lesions that split or coalesce on treatment

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

2.2 Evaluation of Non-Target Lesions

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

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

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

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

2.2.1.1 When the patient also has measurable disease

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

2.2.1.2 When the patient has only non-measurable disease

This circumstance arises in some trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable

disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include, an increase in lymphangitic disease from localized to widespread, or may be described as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore the increase must be substantial.

2.2.2 New Lesions

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

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

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

1) Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

2) No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

2.3 Response Assessment

2.3.1 Evaluation of Best Overall Response

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

2.3.2 Time Point Response

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

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

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

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

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

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

2.3.3 Best Overall Response

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

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

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

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

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

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

2.3.4 Confirmation Scans

Verification of Response: To be assigned a status of CR or PR, changes in tumor measurements must be confirmed by consecutive or subsequent repeat assessments that should be performed no less than 28 days after the criteria for response are first met. Subsequent documentation of a CR may provide confirmation of a previously identified CR even with an intervening NE or PR (eg, 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 (eg, 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.

REFERENCES

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

APPENDIX 6 MANAGEMENT ALGORITHMS FOR IO AGENTS

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.

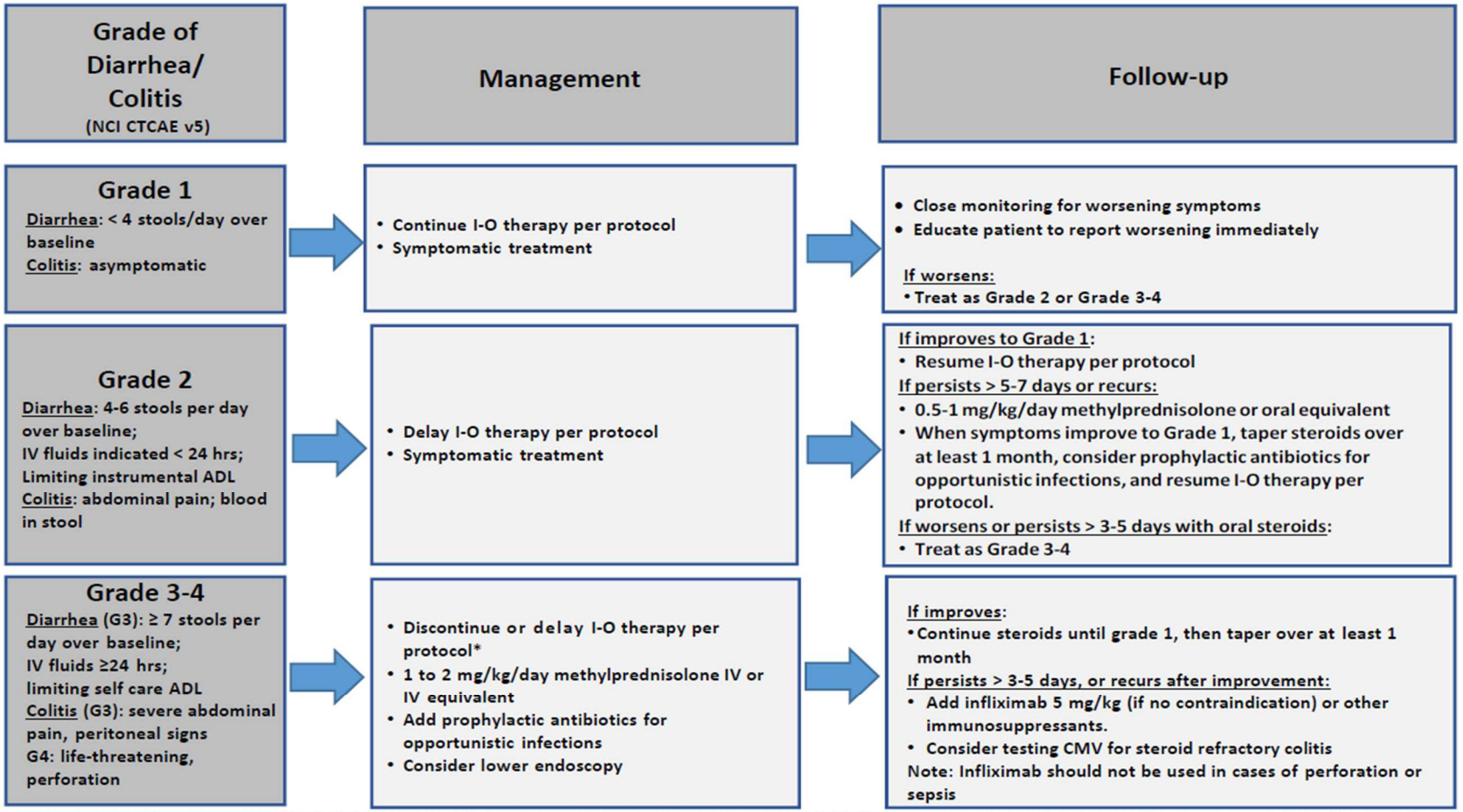
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or 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.



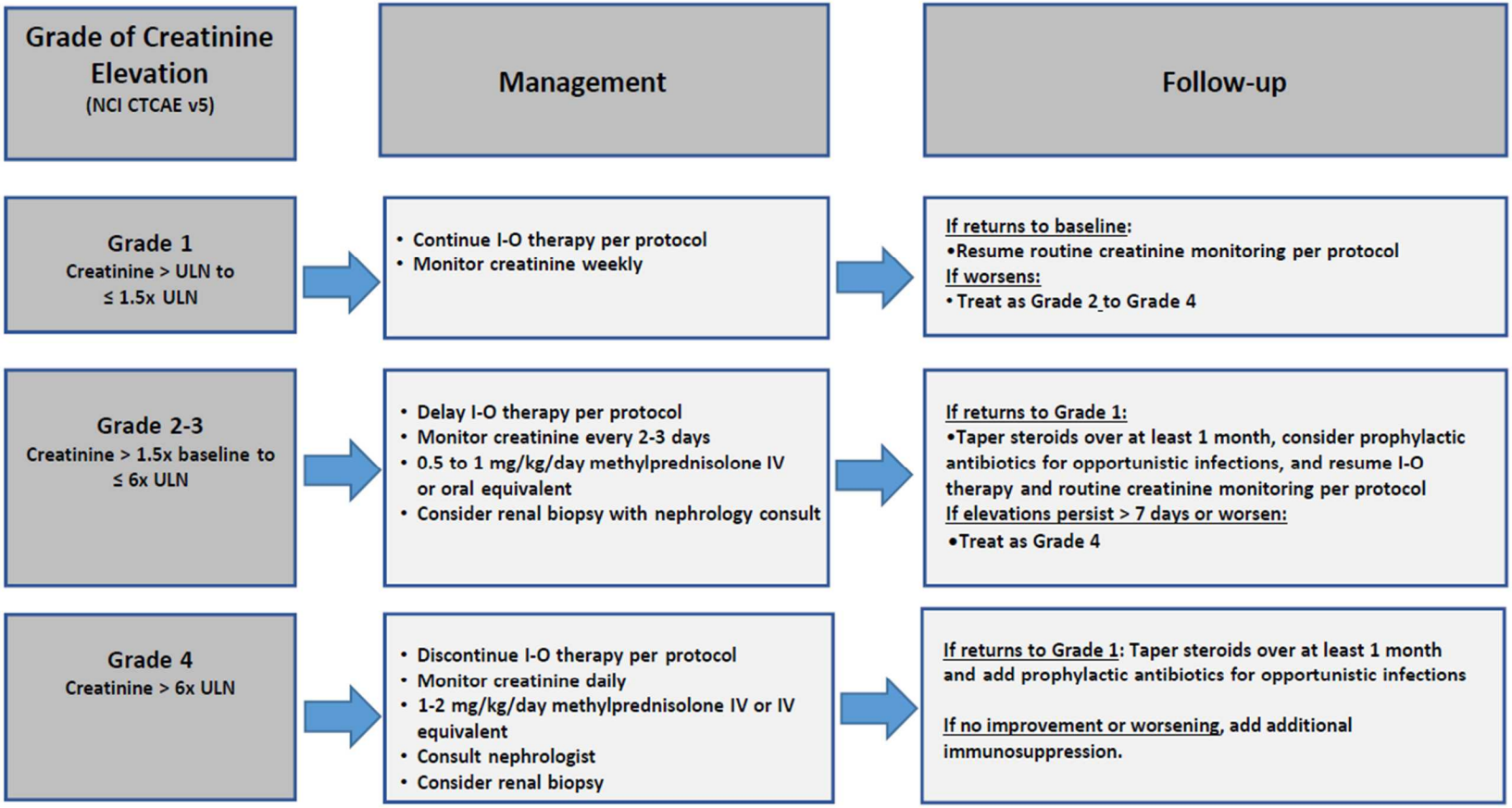
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

* Discontinue for Grade 4 diarrhea or colitis. For Grade 3 diarrhea or colitis, 1) Nivolumab monotherapy: Nivolumab can be delayed. 2) Nivolumab+ Ipilimumab combination: Ipilimumab should be discontinued while nivolumab can be delayed. Nivolumab monotherapy can be resumed when symptoms improve to Grade 1. Please refer to protocol for dose delay and discontinue criteria for other combinations.

[redacted]

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 (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

[redacted]

Pulmonary Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.
Evaluate with imaging and pulmonary consultation.

Grade of Pneumonitis (NCI CTCAE v5)	Management	Follow-up
Grade 1 Radiographic changes only	• Consider delay of I-O therapy • Monitor for symptoms every 2-3 days • Consider Pulmonary and ID consults	• Re-image at least every 3 weeks If worsens: • Treat as Grade 2 or 3-4
Grade 2 Mild to moderate new symptoms	• Delay I-O therapy per protocol • Pulmonary and ID consults • Monitor symptoms daily, consider hospitalization • 1 mg/kg/day methyl prednisolone IV or oral equivalent • Consider bronchoscopy, lung biopsy	If improves to Grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recur: • 0.5-1 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to Grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as Grade 3-4
Grade 3-4 Severe new symptoms; New/worsening hypoxia; Life-threatening	• Discontinue I-O therapy per protocol • Hospitalize • Pulmonary and ID consults • 2-4 mg/kg/day methyl prednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider bronchoscopy, lung biopsy	If improves to baseline: • Taper steroids over at least 6 weeks If not improving after 48 hours or worsening: • Add additional immunosuppression

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

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.

Liver Function Test	Management	Follow-up
AST or ALT > ULN to 3.0 x ULN and/or T. bili > ULN to 1.5 x ULN	• Continue I-O therapy per protocol • Consider increasing frequency of monitoring	• Continue LFT monitoring per protocol If worsens: • Treat as below
AST or ALT > 3.0 to ≤ 5 x ULN and/or T. bili > 1.5 to ≤ 3 x ULN	• Delay I-O therapy per protocol • Increase frequency of monitoring to every 3 days	If returns to baseline: •Resume routine monitoring, resume I-O therapy per protocol If elevations persist > 5-7 days or worsen: • 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when and AST ALT returns to <3X ULN and bili <1.5X ULN, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol
AST or ALT > 5 x ULN or T.bili >3 x ULN	• Delay or Discontinue I-O therapy per protocol^ • Increase frequency of monitoring to every 1-2 days • 1 to 2 mg/kg/day methylprednisolone IV or IV equivalent* • Add prophylactic antibiotics for opportunistic infections • Consult gastroenterologist or hepatologist	If AST and ALT returns to <5X ULN and bili <3X ULN, • Taper steroids over at least 1 month If does not improve in >3-5 days, worsens, or rebounds: • Add mycophenolate mofetil 1 g BID • If no response within an additional 3-5 days, consider tacrolimus or other immunosuppressants per local guidelines Note: Avoid infliximab due to potential risk of liver failure

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
^ Please refer to protocol dose delay and discontinue criteria for specific details.
*The recommended starting dose for AST or ALT > 20 x ULN or bilirubin >10 x ULN is 2 mg/kg/day methylprednisolone IV.

[redacted]

Endocrinopathy Adverse Event Management Algorithm

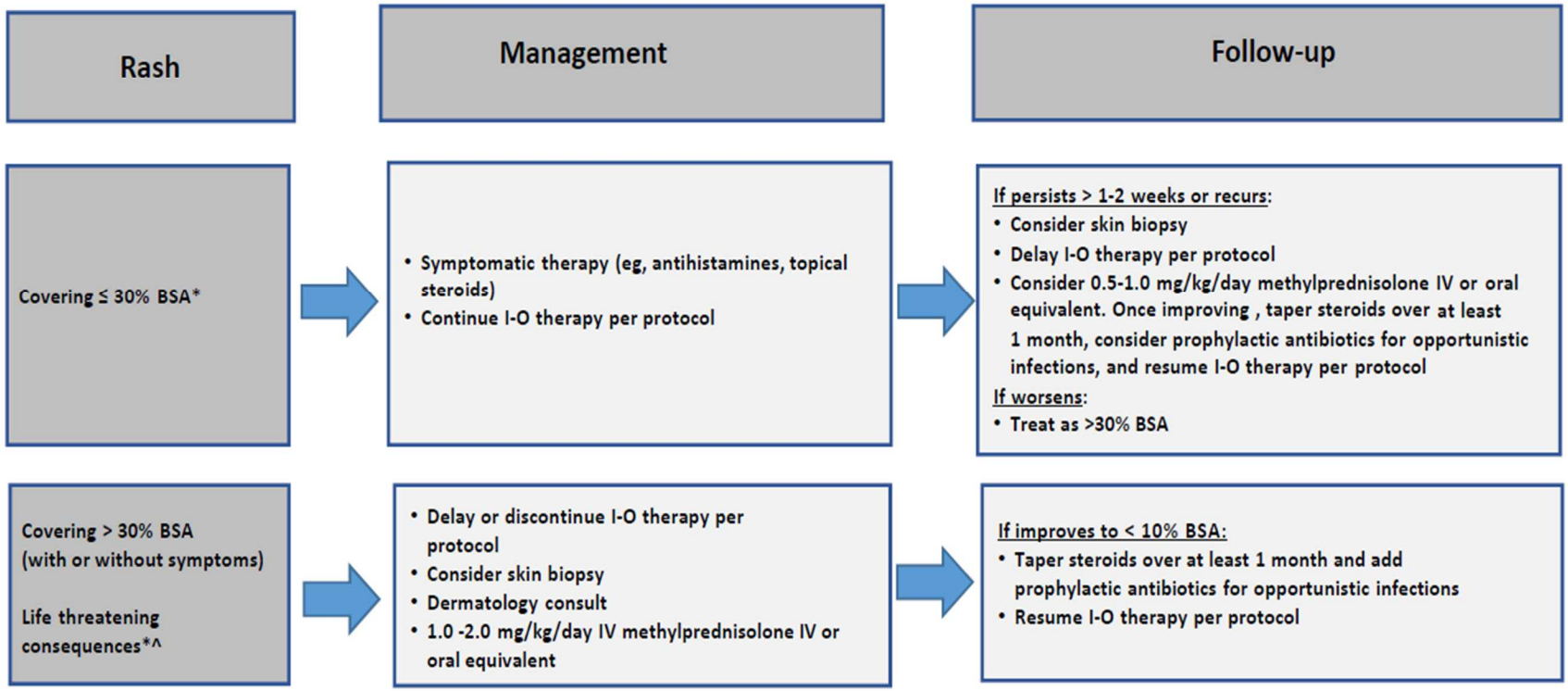
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.
Consider visual field testing, endocrinology consultation, and imaging.

Endocrinopathy	Management	Follow-up
Asymptomatic TSH abnormality or Hyperglycemia requiring no medical intervention	• Continue I-O therapy per protocol • If TSH < 0.5 x LLN, or TSH > 2 x ULN, or consistently out of range in 2 subsequent measurements: o include fT4 at subsequent cycles as clinically indicated; o consider endocrinology consult	• Monitor TSH as per protocol • Monitor blood sugar • If symptomatic or blood sugar requiring initiation of treatment or change in management, manage as below
Symptomatic endocrinopathy or hyperglycemia requiring initiation of treatment or change in daily management or work up	• Evaluate endocrine function; consider endocrinology consult • Consider pituitary scan Symptomatic with abnormal lab/pituitary scan: • Delay I-O therapy per protocol • 1-2 mg/kg/day methylprednisolone IV or PO equivalent for hypophysitis • Initiate appropriate hormone/medical therapy No abnormal lab/pituitary MRI scan but symptoms persist: • Continue IO therapy. Repeat labs in 1-3 weeks /MRI in 1 month Hyperglycemia: Screen for Diabetic Ketoacidosis (DKA). If negative, continue IO and treat diabetes. If DKA hold IO, admit, manage DKA. Steroids not recommended for DKA/hyperglycemia	If improves (with or without hormone replacement): • Taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections • Resume I-O therapy per protocol • Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component
Suspicion of adrenal crisis (eg, severe dehydration, hypotension, shock out of proportion to current illness)	• Delay or discontinue I-O therapy per protocol • Rule out sepsis • Stress dose of IV steroids with mineralocorticoid activity • IV fluids • Consult endocrinologist	• Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component • If adrenal crisis resolves and patient is adequately controlled with physiologic hormone replacement, patient can resume IO therapy per protocol.

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

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, after 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 v5 for term-specific grading criteria.

^If Steven-Johnson Syndrome (SJS),toxic epidermal necrosis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS, TEN, or DRESS is diagnosed, permanently discontinue I-O therapy.

Neurological Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

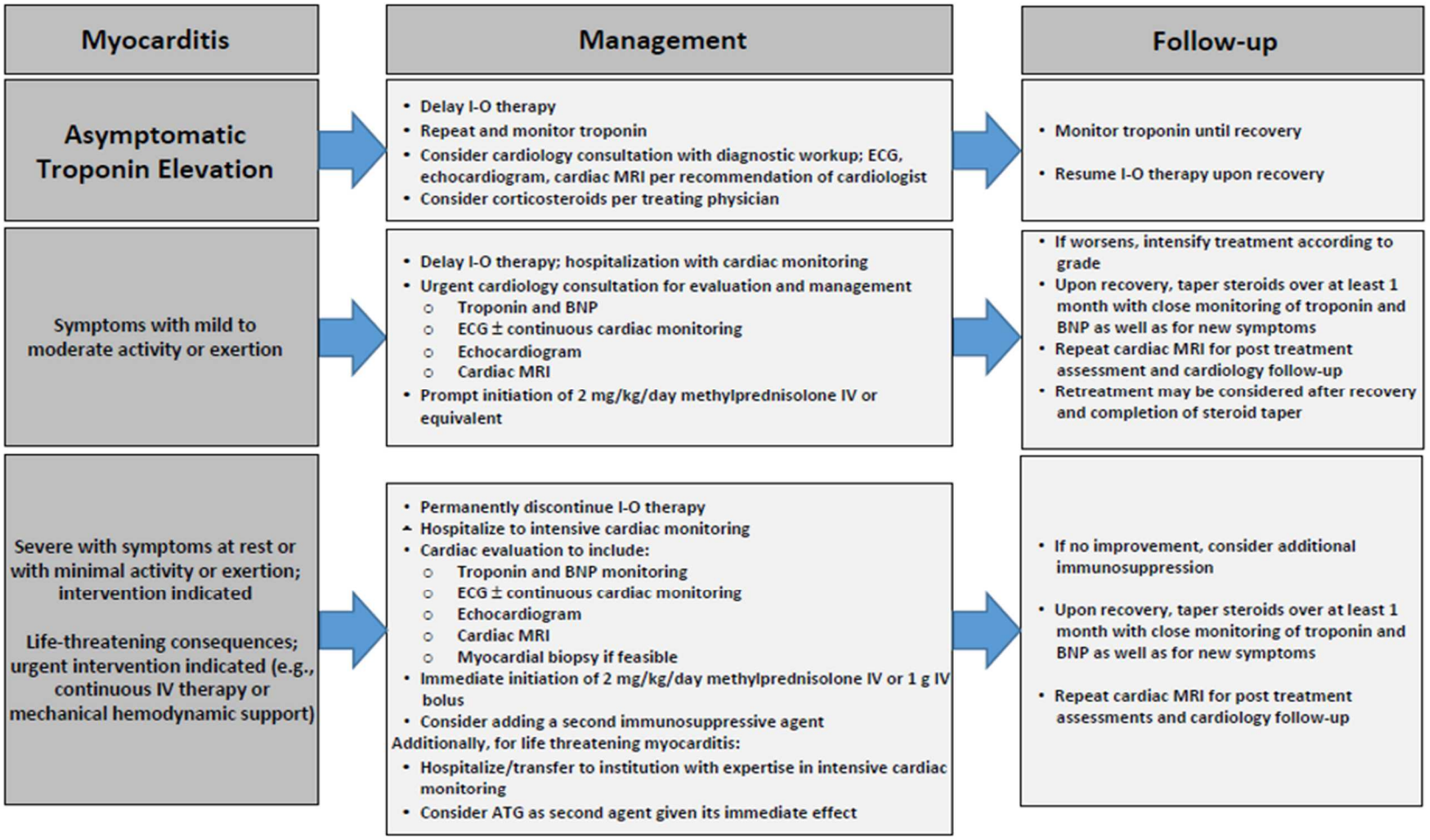
Grade of Neurological Toxicity (NCI CTCAE v5)	Management	Follow-up
Grade 1 Asymptomatic or mild symptoms; Intervention not indicated	• Continue I-O therapy per protocol • Discontinue I-O for select AEs^	• Continue to monitor per protocol. If worsens: • Treat as Grade 2 or Grade 3-4
Grade 2 Moderate symptoms; Limiting instrumental ADL	• Delay I-O therapy per protocol • Discontinue I-O for select AEs^ • Consider neurology consult • Treat symptoms per local guidelines • Consider 0.5 to 1 mg/kg/day methylprednisolone IV or PO equivalent	If returns to baseline: • Resume I-O therapy per protocol when improved to baseline If worsens: • Treat as Grade 3-4
Grade 3-4 Severe symptoms; Limiting self-care ADL; Life-threatening	• Discontinue I-O therapy per protocol • Obtain neurology consult • Treat symptoms per local guidelines • 1-2 mg/kg/day IV methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections	If improves to Grade 2: • Taper steroids over at least 1 month If worsens or atypical presentation: • Consider IVIG or other immunosuppressive therapies per local guidelines

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

^Discontinue for any grade myasthenia gravis, Guillain-Barre syndrome, treatment-related myelitis, or encephalitis.

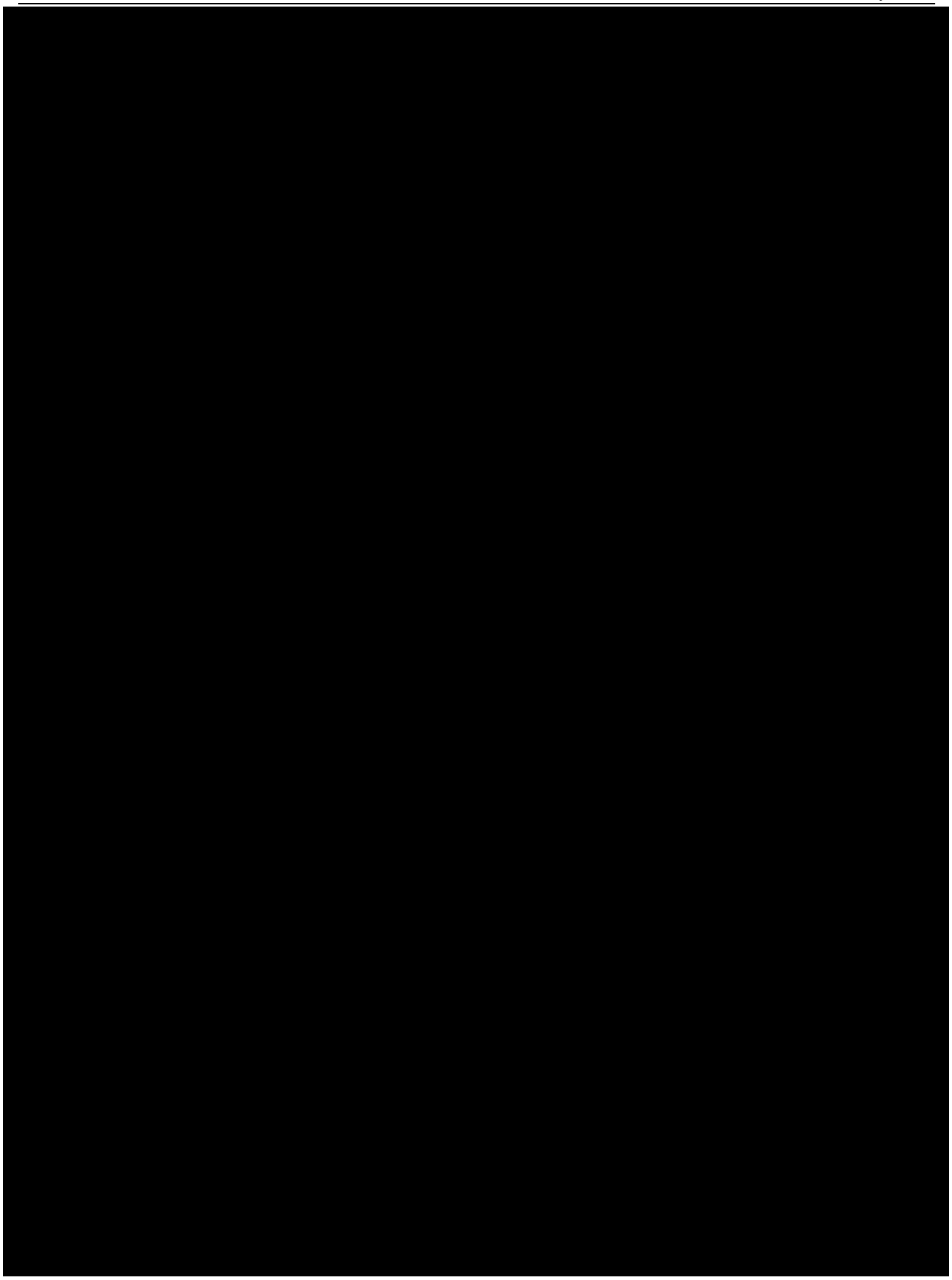
Myocarditis Adverse Event Management Algorithm

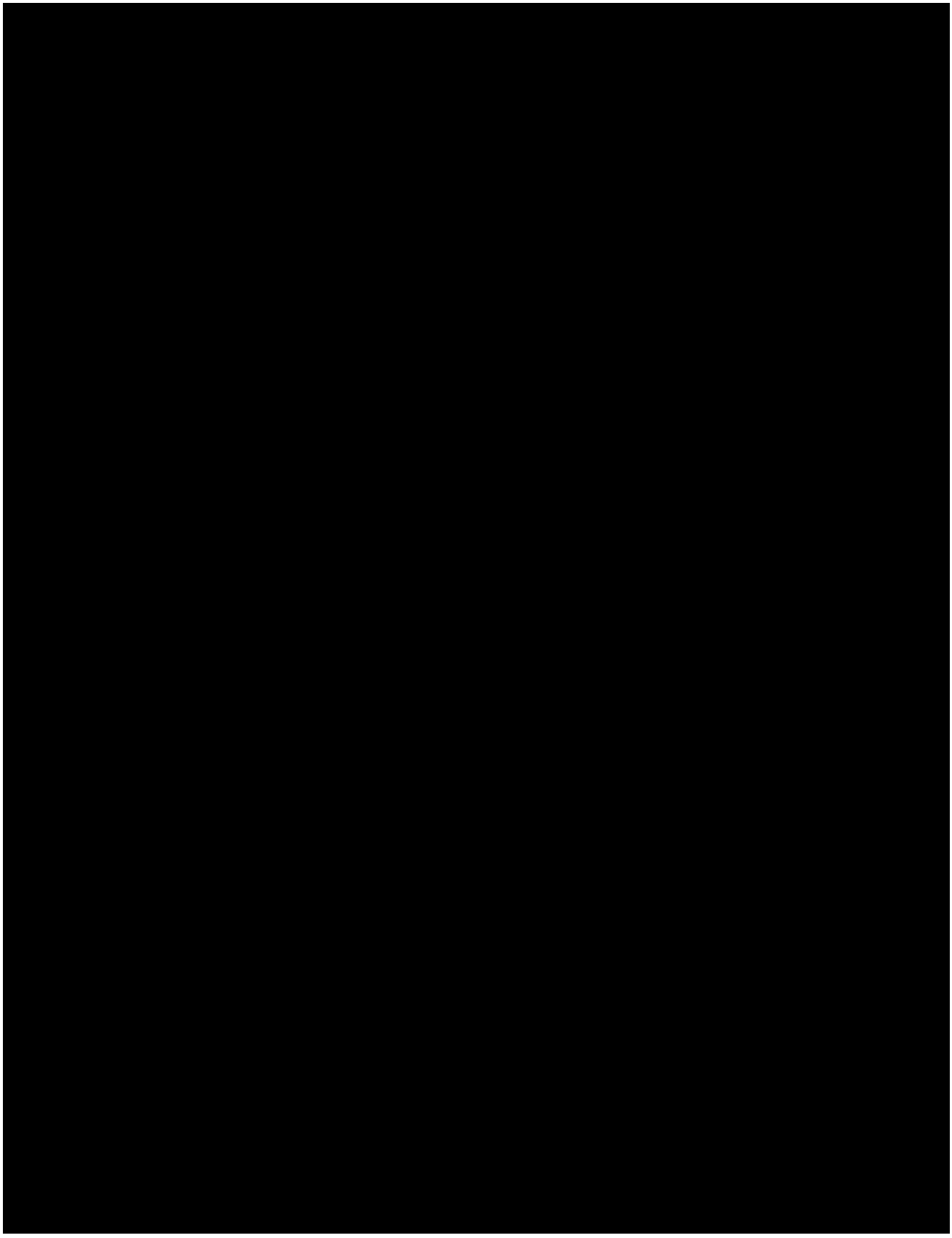
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



For the protocols under CTCAE version 5.0. 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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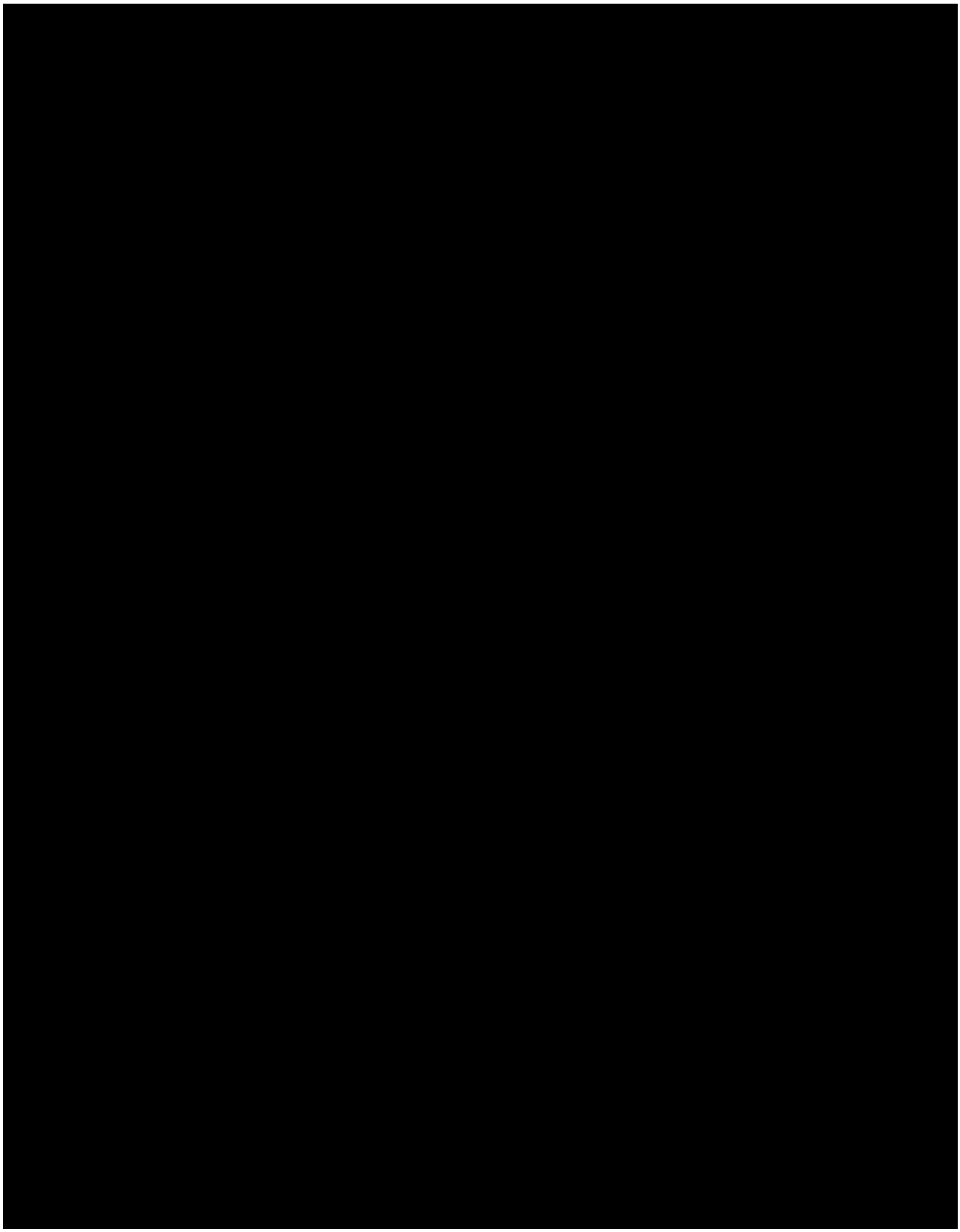

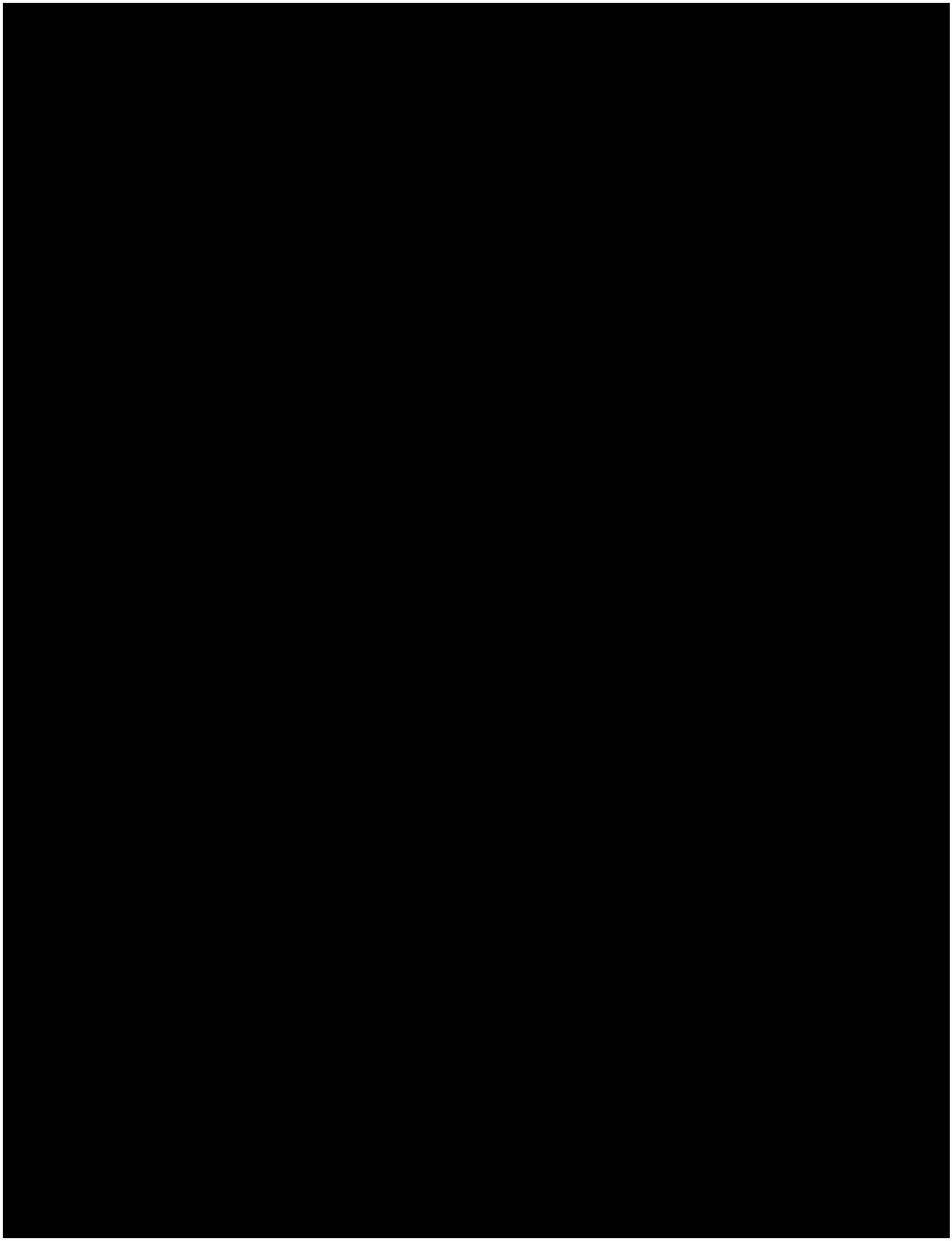

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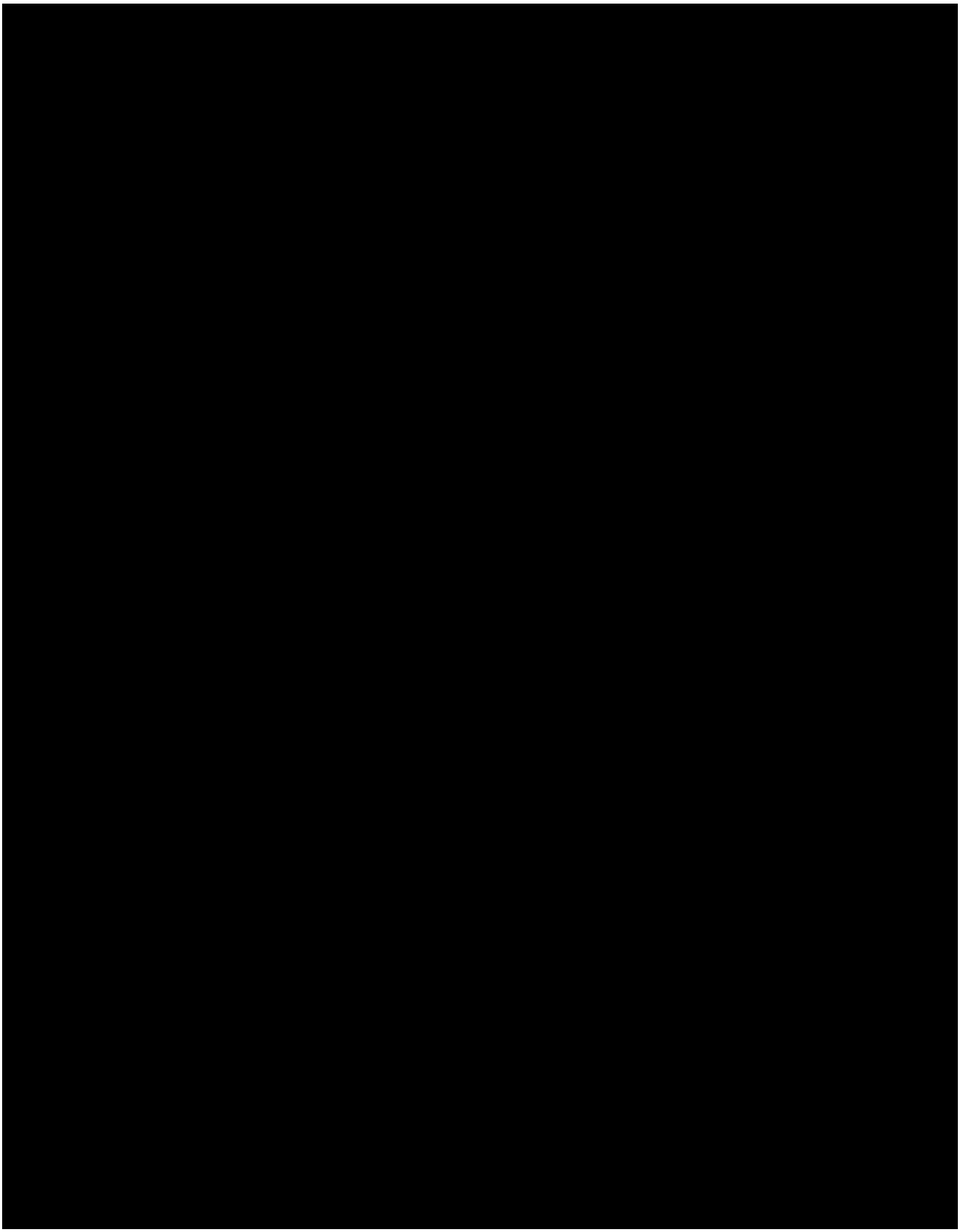
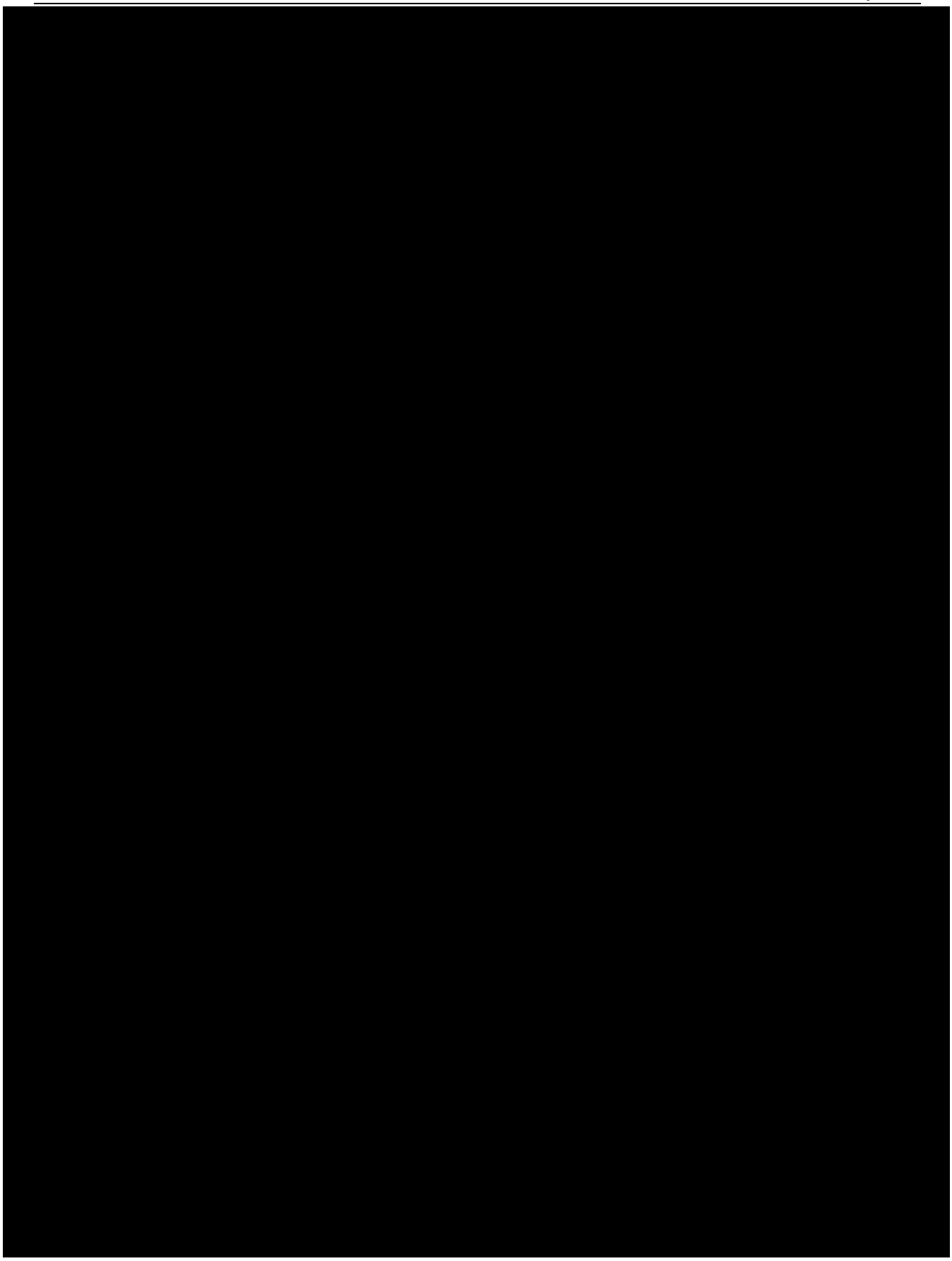
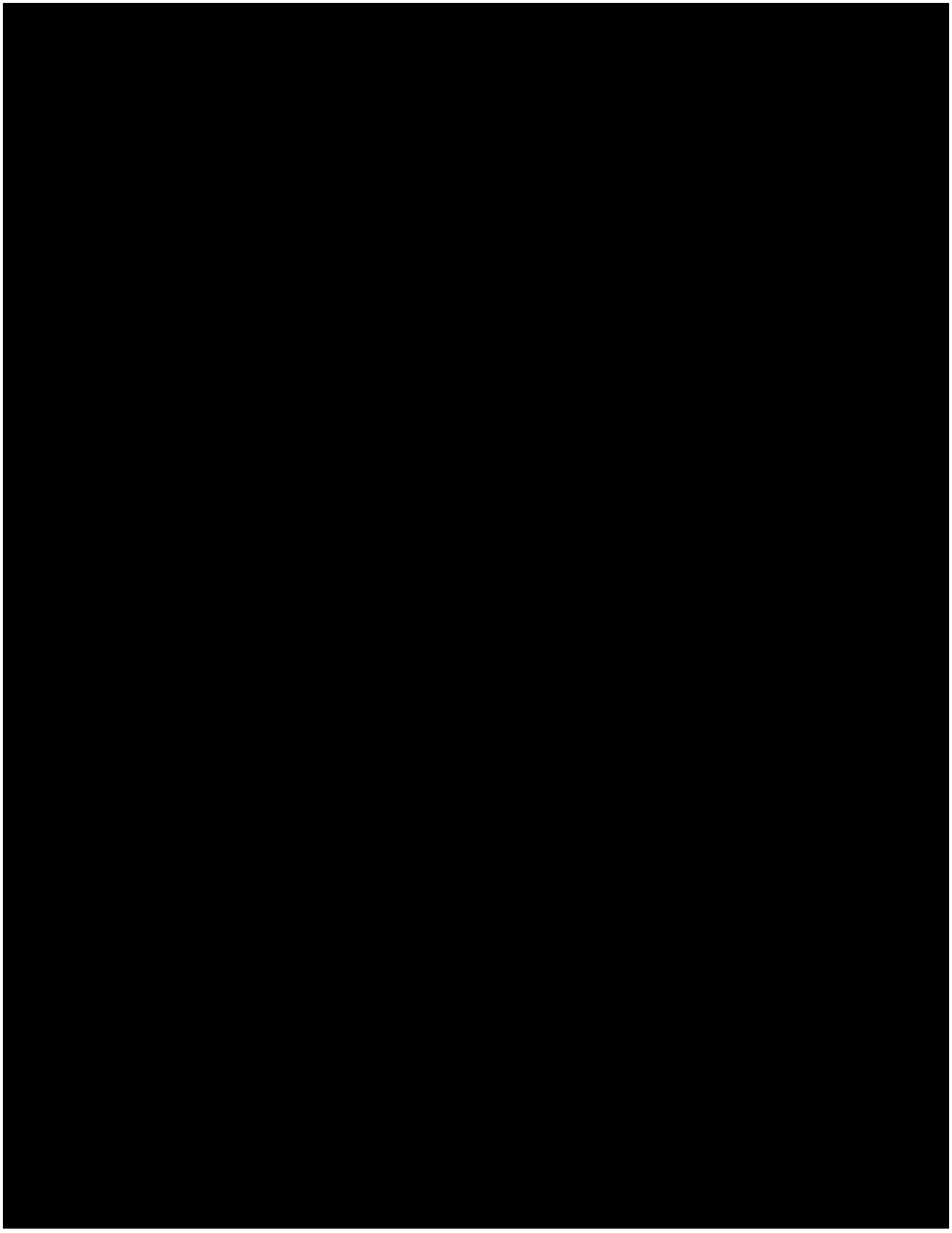
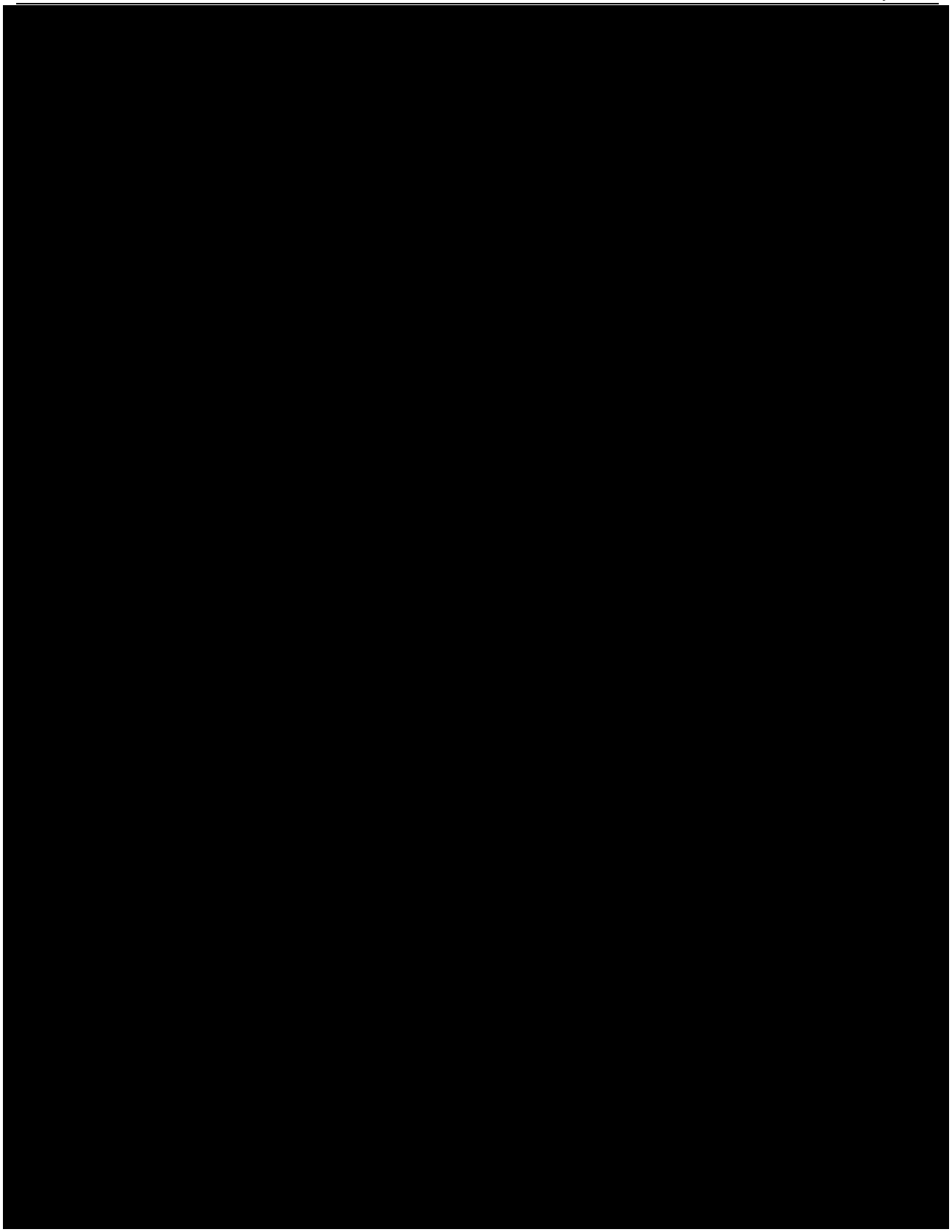


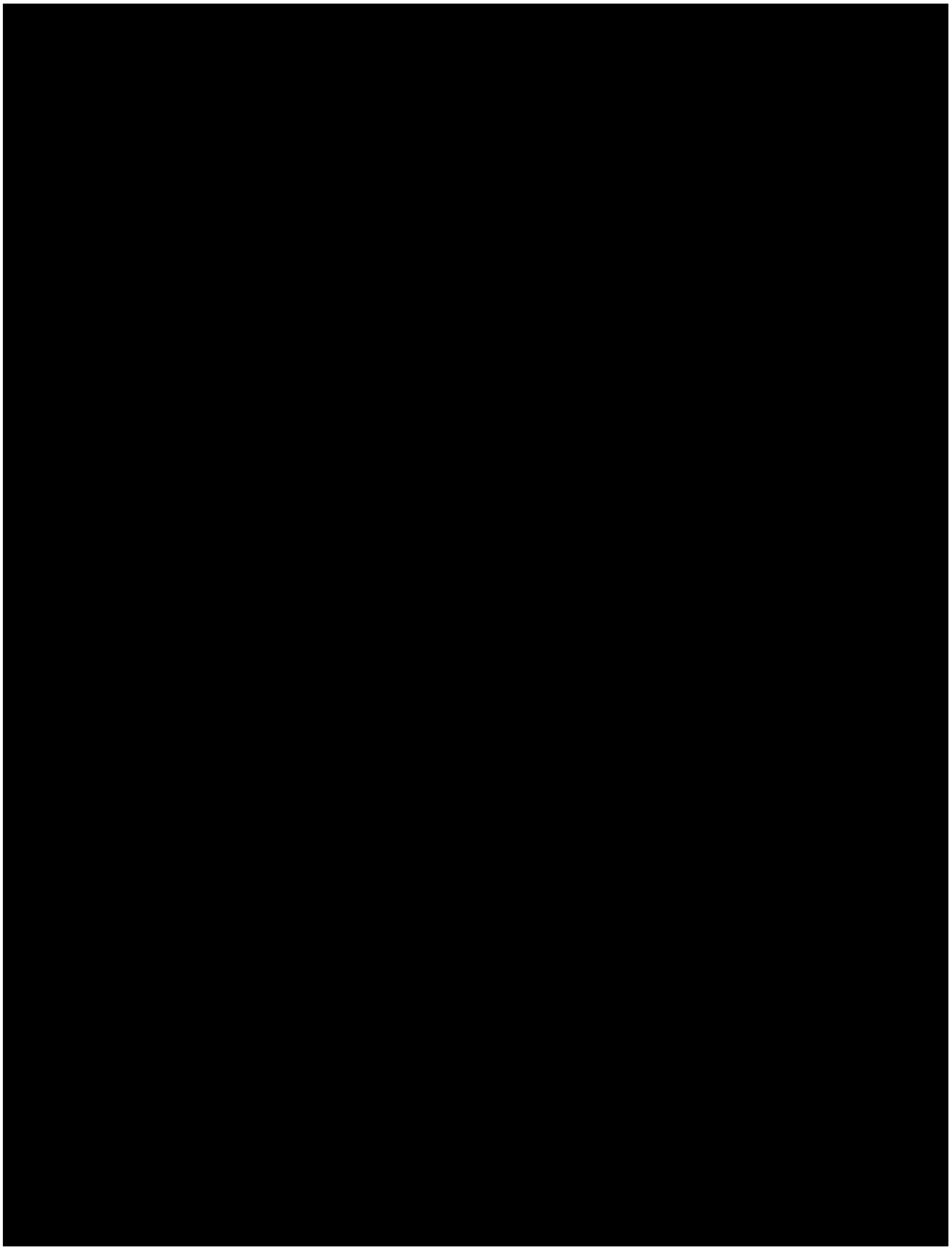
[redacted]

[redacted]









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APPENDIX 8 SCHEDULE OF ACTIVITIES, PHARMACOKINETICS SAMPLING SCHEDULE, AND BIOMARKER SAMPLING SCHEDULE FOR POTENTIAL ALTERNATIVE DOSE SCHEDULES IN CA043001

Detailed in the tables below are the on-treatment schedule of activities, pharmacokinetic (PK) sampling schedule, and biomarker sampling schedule for potential alternative [redacted] BMS-986288 dosing administration that may be explored in CA043001 following evaluation of preliminary safety, PK, and pharmacodynamic data from [redacted] administration (Section 2). Decisions to initiate exploration of these alternative dose schedules will be made after discussion and agreement between the Investigators and the BMS 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 [redacted] dosing schedule, and will not exceed a dose equivalent determined to be tolerable. 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 1: On-treatment Schedule of Activities for BMS-986288 Monotherapy Q3W Dosing Schedule in CA043001
- Table 2: PK and ADA Sampling Schedule for BMS-986288 IV Q3W Monotherapy in Dose Escalation (Part 1A) and BMS-986288 IV Q3W [redacted] Cohort Expansion (Part 2A)
- Table 3: Biomarker Sampling Schedule for BMS-986288 Monotherapy Q3W Dosing Schedule in CA043001
- Table 4: On-treatment Schedule of Activities for [redacted] Dosing Schedule for All Study Parts in CA043001
- Table 5: PK and ADA Sampling Schedule for BMS-986288 IV [redacted] (Part 1A and Part 2A)
- Table 6: PK and ADA Sampling Schedule for BMS-986288 IV [redacted] in Combination with Nivolumab IV [redacted] (Part 1B and Part 2B)
- Table 7: Biomarker Sampling Schedule for [redacted] Dosing Schedule for All Study Parts in CA043001

Table 1: On-treatment Schedule of Activities for BMS-986288 Monotherapy [redacted] Dosing Schedule in CA043001

Procedure	Cycle 1 ([redacted] days in length)			Cycle 2 ([redacted] days in length)			Cycle 3 and Cycle 4 ([redacted] days in length)	EOT[a,b]	Notes
	D1	[redacted] (± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	D1 (± 2 days)		
Safety Assessments									
ECOG Performance Status	X			X			X	X	
PE	X			X			X	X	For the site of [redacted] administration in [redacted], careful observation and examination of the [redacted] is required.[c]
Symptom-directed PE		X	X		X	X			For the site of [redacted] administration in [redacted], careful observation and examination of the [redacted] is required.[c]
Weight	X			X			X	X	
Vital Signs[d]	X	X	X	X	X	X	X	X	
Oxygen Saturation[d]	X			X			X		
ECG[e]	X			X			X	X	Triplicate ECGs performed at predose and EOI on C1D1 and C4D1 for Part 1A only. Single safety ECGs to be performed for all other time points.
[redacted]									

Table 1: On-treatment Schedule of Activities for BMS-986288 Monotherapy [redacted] Dosing Schedule in CA043001

Procedure	Cycle 1 ([redacted] days in length)			Cycle 2 ([redacted] days in length)			Cycle 3 and Cycle 4 ([redacted] days in length)	EOT[a,b]	Notes
	D1	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted] (± 2 days)	D1 (± 2 days)		
Laboratory Tests	X	X	X	X	X	X	X	X	There will be a 72-hour window for collection of laboratory tests on D1. If screening is within 72 hours of C1D1, laboratory tests performed at screening can be used for C1D1. Coagulation assessment at screening only. See Section 9.4.5 and Table 9.4.5-1 in the main protocol.
Urinalysis	X			X			For Cycle 3 and Cycle 4, as clinically indicated; microscopic urine reflex only for urinalysis positive for blood/protein/ leukocyte esterase.	X	
Pregnancy Test (WOCBP only)[g]	X			X			X	X	
Adverse Event Reporting and Concomitant Medication Assessments									
Monitor for Non-SAEs	Non-SAEs will be collected continuously starting with the first dose of study medication and through 100 days following last dose of study treatment.								See Appendix 3 and Section 9.2 in the main protocol. All AEs (SAEs or nonserious AEs) including those associated with SARS-CoV-2 infection must be collected continuously during the treatment period.
Monitor for SAEs	All SAEs must be collected continuously from the date of the participant's written consent until 100 days following last dose of study treatment.								See Appendix 3 and Section 9.2 in the main protocol. All AEs (SAEs or nonserious AEs) including those associated with SARS-CoV-2 infection

Table 1: On-treatment Schedule of Activities for BMS-986288 Monotherapy [redacted] Dosing Schedule in CA043001

Procedure	Cycle 1 ([redacted] days in length)			Cycle 2 ([redacted] days in length)			Cycle 3 and Cycle 4 ([redacted] days in length)	EOT[a,b]	Notes
	D1	[redacted] (± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	D1 (± 2 days)		
									must be collected continuously during the treatment period.
Concomitant Medications	X	X	X	X	X	X	X	X	
PK Assessments									
[redacted]	[redacted]								
Immunogenicity (ADA) Assessments	See Table 2 in Appendix 8 for the PK and immunogenicity sampling schedule and Section 9.5 in the main protocol.								
[redacted]	See Table 3 in Appendix 8 for the biomarker sampling schedule and Section 9.8 in the main protocol.								
Imaging Assessments									
Body Imaging[h]	See Section 9.1.1 in the main protocol. Contrast-enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease should occur [redacted] (± 7 days) starting from the first dose up until Week [redacted]. Imaging assessments should then occur [redacted] (± 7 days). For participants with cancer of the head and neck, a CT or MRI of the neck is required. For participants with TNBC without measurable lesions outside of the breast, contrast-enhanced MRI of the breasts should be performed.								
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. See Section 9.1.1.1 in the main protocol for further details.								
Bone Scan	As clinical indicated per local standards (see Section 9.1.1 in the main protocol).								

Table 1: On-treatment Schedule of Activities for BMS-986288 Monotherapy [redacted] Dosing Schedule in CA043001

Procedure	Cycle 1 ([redacted] days in length)			Cycle 2 ([redacted] days in length)			Cycle 3 and Cycle 4 ([redacted] days in length)	EOT[a,b]	Notes
	D1	[redacted] (± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	D1 (± 2 days)		
Biomarker Assessments									See Section 9.5 and Section 9.8 in the main protocol and Table 3 in Appendix 8.
[redacted]					X				Mandatory [redacted] must be performed at C2[redacted]; specimens may be collected within 3 days of the time point.
Required Post-progression [redacted]	A [redacted] is required upon confirmation of PD (within 7 days) except for: 1) participants who have an [redacted] 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 [redacted] and 3) participants who consent to be treated beyond progression will require the [redacted] only at the subsequent confirmation of progression.								See [redacted] in the main protocol.
Blood/Serum/Plasma Pharmacodynamic Sampling	See Table 3 in Appendix 8 for details of biomarker assessments.								See Section 9.5 and Section, 9.8 in the main protocol, Table 3 in Appendix 8, and refer to Laboratory Manual.
Exploratory Biomarker Assessments									See Section 9.5 and Section 9.8 in the main protocol and Table 3 in Appendix 8.
Clinical Treatment Supplies									
BMS-986288 Administration [redacted]	X			X			X		BMS-986288 to be supplied by BMS. BMS-986288 to be administered for up to a maximum of 4 doses.
[redacted]									
Clinical Outcomes Assessments (Part 2 Only)									
NSCLC-SAQ	X			X			X	X	Clinical outcomes assessments to be administered in Part 2 only. NSCLC-SAQ will only be
FACT GP5	X	X	X	X	X	X	X	X	

Table 1: On-treatment Schedule of Activities for BMS-986288 Monotherapy [redacted] Dosing Schedule in CA043001

Procedure	Cycle 1 ([redacted] days in length)			Cycle 2 ([redacted] days in length)			Cycle 3 and Cycle 4 ([redacted] days in length)	EOT[a,b]	Notes
	D1	[redacted]					D1 (± 2 days)		
		(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)			
EQ-5D-5L	X			X			X	X	administered to NSCLC participants. Data will be collected using electronic devices. See Section 9.1.2 in the main protocol.

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; EQ-5D-5L = 5-Level EQ-5D; FACT GP5 = Functional Assessment of Cancer Therapy Item GP5; hCG = human chorionic gonadotropin; IgG = immunoglobulin G; MRI = magnetic resonance imaging; NSCLC = non-small cell lung cancer; NSCLC-SAQ = Non-small Cell Lung Cancer Symptom Assessment Questionnaire; PD = progressive disease; PE = physical examination; PK = pharmacokinetic; [redacted] RECIST = Response Evaluation Criteria in Solid Tumors; [redacted] 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, C4D21) 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] In participants administered BMS-986288 [redacted], the Investigator or designated study staff will assess the proposed [redacted] for signs of local irritation and inflammation. The proposed [redacted] will be evaluated prior to all [redacted] doses and approximately [redacted] after the [redacted]. There are pre-specified [redacted] reactions of interest: [redacted] erythema; [redacted] pain, [redacted] pruritus, [redacted] hematoma, [redacted], and [redacted] induration. [redacted] reactions will be recorded as AEs on the appropriate page of the case report form. In addition, all participants will be contacted approximately 24 hours after each [redacted] for reporting of [redacted] reactions. The [redacted] will be also be evaluated at the next study visit.

[d] Vital signs will be obtained before the [redacted] of BMS-986288 and then every 15 minutes (± 5 minutes) until [redacted] after completion of the [redacted] for first 3 doses of study treatment on C1D1, C2D1, and C3D1; oxygen saturation to also be performed in conjunction with vital signs monitoring on these days. For C4, 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. ECGs to be performed in triplicate in association with time-matched PK sampling at predose and EOI on C1D1 and C4D1 for the BMS-986288 Monotherapy Escalation (Part 1A) only (see Section 9.4.4 of main protocol). Single safety ECGs to be performed for all other time points.

[redacted]

[g] 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).

[h] 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.

[i] Pre-treatment (screening) [redacted] can be performed optionally on C1D1. Mandatory [redacted] must be performed at C2D8; specimens may be collected within 3 days of the time point and must be obtained prior to administration of study treatments. Bone lesion [redacted] are unacceptable for submission. See [redacted] of main protocol.

Table 2: PK and ADA Sampling Schedule for BMS-986288 IV [redacted] Monotherapy in Dose Escalation (Part 1A) and BMS-986288 IV [redacted] Cohort Expansion (Part 2A)

Study Day of Sample Collection (1 Cycle = [redacted])	Event	Time (Relative to Start of BMS-986288 [redacted])[a] Hour:Minute	BMS-986288 PK [redacted] Sample	BMS-986288 ADA [redacted] Sample
C1D1	Predose[b]	00:00	X	X
	EOI	See note[c]	X	
		[redacted]	X	
C1[redacted]			X	
C1[redacted]			X	
C1[redacted]			X	
C1[redacted]			X	
C2[redacted]	Predose[b]	00:00	X	X
	EOI	See note[c]	X	
C2[redacted][d] (± 3 days)		168:00	X	
C3D1	Predose[b]	00:00	X	X
	EOI	See note[c]	X	
C4D1	Predose[b]	00:00	X	X
	EOI	See note[c]	X	
		[redacted]	X	
C4[redacted]			X	
C4[redacted]			X	
C4[redacted]			X	
C4[redacted]			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: ADA = anti-drug antibody; C = Cycle; D = Day; EOI = end of infusion; EOT = end of treatment; IV = intravenous; [redacted].

[a] Every effort should be taken to collect the sample as close to the designated time as possible. The actual time of collection should be recorded.

[b] Predose: All predose samples should be taken within 30 minutes prior to the start of the infusion/administration.

[c] EOI PK samples should be collected when all study drug has been infused. If a flush is administered to clear the IV lines of the drug and to ensure delivery of the entire drug dose, then draw the EOI PK sample within approximately 15 minutes after end of the flush. Do not draw EOI samples from the same IV access through which the drug was

administered. Refer to the Pharmacy Manual for infusion duration. If the EOI is delayed beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.

[d] Sample should be collected with [redacted] (see Table 3 in Appendix 8).

Table 3: Biomarker Sampling Schedule for BMS-986288 Monotherapy [redacted] Dosing Schedule in CA043001

Study Day of Sample Collection [redacted]	**Time (Relative to BMS-986288 Dose) Hour:Min**	[redacted]						
Screening								X
C1D1	00:00[c]	X	X	X	X	X	X	
	EOI[d]	X						
C1[redacted]	[redacted]	X				X	X	
C1[redacted]		X				X	X	
C1[redacted]		X				X	X	
C2D1	00:00[c]	X						
	EOI[d]	X						
C2[redacted][b] (± 3 days)	168:00	X	X	X	X	X	X	X
C2D15 (± 2 days)	336:00	X				X	X	
C3D1	00:00[c]	X				X	X	
	EOI[d]	X						
C3D8 (± 2 days)	168:00	X		X	X			
C3D15 (± 2 days)	336:00	X						
C4D1	00:00[c]	X	X	X	X			
EOT or at Progression		X	X	X	X	X	X	X

Abbreviations: C = cycle; CXDY = Cycle X Day Y, as an example; D = day; EOI = end of infusion; EOT = end of treatment; [redacted].

[a] Instructions for the collection and processing [redacted] will be provided in the Laboratory Manual.

[b] Pre-treatment (screening) [redacted] can be performed optionally on C1D1. Mandatory [redacted] to be performed at C2D8; specimens may be collected within 3 days of the time point and must be obtained prior to administration of study treatments. C2D8 biomarker collections should occur at the same time as [redacted]. Adjust the biomarker collection in accordance with the [redacted] collection. An optional additional [redacted] can be collected on-treatment if the Investigator and the Medical Monitor (or designee) find it indicated. A [redacted] is required upon confirmation of PD (within 7 days) except for participants: 1) who have an [redacted] 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 [redacted], and 3) participants who consent to be treated beyond progression will require the [redacted] only at the subsequent confirmation of progression. Bone lesion [redacted] are unacceptable for submission.

[c] All predose samples should be taken prior to the start of the infusion/administration.

[d] EOI samples should be taken after the infusion/administration of study treatment. Refer to the Pharmacy Manual for infusion duration. EOI is defined as the end of infusion/administration.

Table 4: On-treatment Schedule of Activities for [redacted] Dosing Schedule for All Study Parts in CA043001

Procedure	Cycle 1 ([redacted] days in length)				Cycle 2 ([redacted] days in length)				Cycles 3 and Beyond (each cycle [redacted] days in length)	EOT[a,b]	Notes
	D1	[redacted] (± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	D1 (± 2 days)		
Safety Assessments											
ECOG Performance Status	X				X				X	X	
PE	X				X				X	X	For the site of [redacted] administration in [redacted], careful observation and examination of the [redacted] is required.[c]
Symptom-directed PE		X	X	X		X	X	X			For the site of [redacted] administration in [redacted], careful observation and examination of the [redacted] is required.[c]
Weight	X				X				X	X	
Vital Signs[d]	X	X	X	X	X	X	X	X	X	X	
Oxygen Saturation[d]	X				X				X		
ECG[e]	X				X				X	X	Triplicate ECGs performed at predose and EOI on C1D1 and C5D1 for Part 1A only. Single safety ECGs to be performed for all other time points.

Table 4: On-treatment Schedule of Activities for [redacted] Dosing Schedule for All Study Parts in CA043001

Procedure	Cycle 1 ([redacted] days in length)				Cycle 2 (2[redacted] days in length)				Cycles 3 and Beyond (each cycle [redacted] days in length)	EOT[a,b]	Notes
	D1	D[redacted] (± 2 days)	D[redacted] (± 2 days)	D[redacted] (± 2 days)	D1 (± 2 days)	D[redacted] (± 2 days)	D[redacted] (± 2 days)	D[redacted] (± 2 days)	D1 (± 2 days)		
[redacted]											
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 9.4.5 and Table 9.4.5-1 in the main protocol.
Urinalysis	X				X				As clinically indicated; microscopic urine reflex only for urinalysis positive for blood/protein/ leukocyte esterase.		

Table 4: On-treatment Schedule of Activities for [redacted] Dosing Schedule for All Study Parts in CA043001

Procedure	Cycle 1 ([redacted] days in length)				Cycle 2 ([redacted] days in length)				Cycles 3 and Beyond (each cycle [redacted] days in length)	EOT[a,b]	Notes
	D1	[redacted] (± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	D1 (± 2 days)		
Pregnancy Test (WOCBP only)[h]	X				X				X	X	
Adverse Event Reporting and Concomitant Medication Assessments											
Monitor for Non-SAEs	Non-SAEs will be collected continuously starting with the first dose of study medication and through 100 days following last dose of study treatment.										See Appendix 3 and Section 9.2 in the main protocol. All AEs (SAEs or nonserious AEs) including those associated with SARS-CoV-2 infection must be collected continuously during the treatment period.
Monitor for SAEs	All SAEs must be collected continuously from the date of the participant's written consent until 100 days following last dose of study treatment.										See Appendix 3 and Section 9.2 in the main protocol. All AEs (SAEs or nonserious AEs) including those associated with SARS-CoV-2 infection must be collected continuously during the treatment period.
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	

Table 4: On-treatment Schedule of Activities for [redacted] Dosing Schedule for All Study Parts in CA043001

Procedure	Cycle 1 ([redacted] days in length)				Cycle 2 ([redacted] days in length)				Cycles 3 and Beyond (each cycle [redacted] days in length)	EOT[a,b]	Notes
	D1	[redacted]							D1 (± 2 days)		
		(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)			
PK Assessments											
[redacted]											
Immunogenicity (ADA) Assessments	See Table 5 and Table 6 in Appendix 8 for the PK and immunogenicity sampling schedule and Section 9.5 in the main protocol.										
[redacted]	See Table 5 and Table 6 in Appendix 8 for the biomarker sampling schedule and Section 9.8 in the main protocol.										
Imaging Assessments											
Body Imaging[i]	See Section 9.1.1 in the main protocol. Contrast-enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease should occur [redacted] (± 7 days) starting from the first dose up until Week 48. Imaging assessments should then occur [redacted] (± 7 days). For participants with cancer of the head and neck, a CT or MRI of the neck is required. For participants with TNBC without measurable lesions outside of the breast, contrast-enhanced MRI of the breasts should be performed.										
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	As clinically indicated per local standards (see Section 9.1.1 in the main protocol).										

Table 4: On-treatment Schedule of Activities for [redacted] Dosing Schedule for All Study Parts in CA043001

Procedure	Cycle 1 ([redacted] days in length)				Cycle 2 ([redacted] days in length)				Cycles 3 and Beyond (each cycle [redacted] days in length)	EOT[a,b]	Notes
	D1	[redacted]							D1 (± 2 days)		
		(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)			
[redacted]											
[redacted]		X							X		A mandatory [redacted] must be performed at C1D8; specimens may be collected within 3 days of the time point. While not preferred, if a [redacted] at C1D8 is not collected, then a [redacted] at C3D5 (± 3 days) must be performed.
Required Post-progression [redacted]	A [redacted] is required upon confirmation of PD (within 7 days) except for: 1) participants who have an [redacted] 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 [redacted]; and 3) participants who consent to be treated beyond progression will require the [redacted] only at the subsequent confirmation of progression.										See [redacted] in the main protocol.
Blood/Serum/Plasma Pharmacodynamic Sampling	See Table 7 in Appendix 8 for details of biomarker assessments.										See Section 9.5 and Section 9.8 in the main protocol and refer to Laboratory Manual.
Exploratory Biomarker Assessments											See Section 9.5 and Section 9.8 in the main

Table 4: On-treatment Schedule of Activities for [redacted] Dosing Schedule for All Study Parts in CA043001

Procedure	Cycle 1 ([redacted] days in length)				Cycle 2 ([redacted] days in length)				Cycles 3 and Beyond (each cycle [redacted] days in length)	EOT[a,b]	Notes
	D1	[redacted] (± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	D1 (± 2 days)		
											protocol and Table 7 in Appendix 8.
Clinical Treatment Supplies											
BMS-986288 Administration [redacted]	X								X (Every other cycle starting at Cycle 3 [eg, C3, C5, C7, etc])		BMS-986288 to be supplied by BMS.
Nivolumab Administration [redacted] (Part 1B, [redacted] Arm B, Part 2B)	X				X				X		Nivolumab to be supplied by BMS.
[redacted]											
Clinical Outcomes Assessments (Part 2 Only)											
NSCLC-SAQ	X				X				X	X	

Table 4: On-treatment Schedule of Activities for [redacted] Dosing Schedule for All Study Parts in CA043001

Procedure	Cycle 1 ([redacted] days in length)				Cycle 2 ([redacted] days in length)				Cycles 3 and Beyond (each cycle [redacted] days in length)	EOT[a,b]	Notes
	D1	[redacted] (± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	D1 (± 2 days)		
FACT GP5	X	X	X	X	X	X	X	X	X	X	Clinical outcomes assessments to be administered in Part 2 only. NSCLC-SAQ will only be administered to NSCLC participants. Data will be collected using electronic devices. See Section 9.1.2 in the main protocol.
EQ-5D-5L	X				X				X	X	

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; EQ-5D-5L = 5-Level EQ-5D; FACT GP5 = Functional Assessment of Cancer Therapy Item GP5; hCG = human chorionic gonadotropin; IgG = immunoglobulin G; MRI = magnetic resonance imaging; NSCLC = non-small cell lung cancer; NSCLC-SAQ = Non-small Cell Lung Cancer Symptom Assessment Questionnaire; PD = progressive disease; PE = physical examination; PK = pharmacokinetic; [redacted] RECIST = Response Evaluation Criteria in Solid Tumors; [redacted] SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; [redacted] 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] In participants administered BMS-986288 or nivolumab [redacted], the Investigator or designated study staff will assess the proposed [redacted]. The proposed [redacted] will be evaluated prior to all [redacted] doses and approximately [redacted]. There are pre-specified [redacted] will be recorded as AEs on the appropriate page of the case report form. In addition, all participants will be contacted approximately 24 hours after each [redacted] for reporting of [redacted] reactions. The [redacted] will be also be evaluated at the next study visit.

[d] Vital signs will be obtained before the [redacted] of BMS-986288 and then every 15 minutes (± 5 minutes) until [redacted] after completion of the infusion for first 3 doses of study treatment on C1D1, C3D1, and C5D1; oxygen saturation to also be performed in conjunction with vital signs monitoring on these days. For all cycles after C5 and for the 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.

[e] ECGs should be recorded after the participant has been supine for at least 5 minutes and prior to blood draws. ECGs to be performed in triplicate in association with time-matched PK sampling at predose and EOI on C1D1 and C5D1 for the BMS-986288 Monotherapy Escalation (Part 1A) only (see Section 9.4.4 of the main protocol). Single safety ECGs to be performed for all other time points.

[redacted]

[g] Eye exam is to be performed every other cycle prior to dosing, starting with Cycle 3 (ie, Cycle 3, Cycle 5, etc.) and at EOT.

[h] Serum/urine to be collected within 24 hours prior to BMS-986288 or nivolumab dosing. For BMS-986299 monotherapy this would be collected prior to Day 1 of odd cycles (eg, Cycle 1, Cycle 3, Cycle 5, etc), for BMS-986288 in combination with nivolumab this would be collected prior to Day 1 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).

[i] 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.

[j] Mandatory [redacted] must be performed at C1D8; specimens may be collected within 3 days of the time point. While not preferred, if a [redacted] at C1D8 is not collected, then a [redacted] at C3D5 (± 3 days) must be performed. [redacted] are not required to be collected at both C1D8 and C3D5. Bone lesion [redacted] are unacceptable for submission. See [redacted] of the main protocol.

Table 5: PK and ADA Sampling Schedule for BMS-986288 IV [redacted] (Part 1A and Part 2A)

Study Day of Sample Collection (1 Cycle = [redacted])	Event	Time (Relative to Start of BMS-986288 Infusion) Hr:Min[a]	BMS-986288 PK [redacted] Sample	BMS-986288 ADA [redacted] Sample
C1D1	Predose[b]	00:00	X	X
	EOI	See note[c]	X	
		04:00	X	
C1[redacted]		[redacted]	X	
C1[redacted]			X	
C1[redacted]			X	
C1[redacted]			X	
C1[redacted]			X	
C2D1		672:00	X	X
C2[redacted] (± 2 days)		840:00	X	
C3D1	Predose[b]	00:00	X	X
	EOI	See note[c]	X	
C3D5[d]		96:00	X	
C4D1		672:00	X	X
C5D1	Predose[b]	00:00	X	X
	EOI	See note[c]	X	
		[redacted]	X	
C5[redacted]			X	
C5[redacted]			X	
C5[redacted]			X	

Table 5: PK and ADA Sampling Schedule for BMS-986288 IV [redacted] (Part 1A and Part 2A)

Study Day of Sample Collection (1 Cycle = [redacted])	Event	Time (Relative to Start of BMS-986288 Infusion) Hr:Min[a]	BMS-986288 PK [redacted] Sample	BMS-986288 ADA [redacted] Sample
C5[redacted]		[redacted]	X	
C5[redacted]			X	
C6D1		672:00	X	
C7D1	Predose[b]	00:00	X	X
Every fourth cycle after C7 until EOT (C11D1, C15D1, C19D1, etc until EOT)	Predose[b]	00:00	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; EOI = end of infusion; EOT = end of treatment; IV = intravenous; PK = pharmacokinetics; [redacted].

[a] Every effort should be taken to collect the sample as close to the designated time as possible. The actual time of collection should be recorded.

[b] Predose: All predose samples should be taken within 30 minutes prior to the start of the infusion of BMS-986288.

[c] EOI PK samples should be collected when all study drug has been infused. If a flush is administered to clear the IV lines of the drug and to ensure delivery of the entire drug dose, then draw the EOI PK sample within approximately 15 minutes after end of the flush. Do not draw EOI samples from the same IV access through which the drug was administered. Refer to the Pharmacy Manual for infusion duration. If the EOI is delayed beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.

[d] Sample should be collected with [redacted] (see Table 7 in Appendix 8). C3D5 PK sample is only collected if participant is scheduled for corresponding [redacted], while C1D[redacted] PK sample should be collected irrespective of corresponding [redacted].

Table 6: PK and ADA Sampling Schedule for BMS-986288 IV [redacted] in Combination with Nivolumab IV [redacted] (Part 1B and Part 2B)

Study Day of Sample Collection (1 Cycle = [redacted])	Event	Time (Relative to Start of Nivolumab Infusion) Hr:Min[a]	BMS-986288 PK [redacted] Sample	Nivolumab PK [redacted] Sample	BMS-986288 ADA [redacted] Sample	Nivolumab ADA [redacted] Sample
C1D1	Predose[b]	00:00	X	X	X	X
	EOI	See note[c]	X	X		
		04:00	X			
C1[redacted]		[redacted]	X			
C1[redacted]			X			
C1[redacted]			X			
C1[redacted]			X			
C1[redacted]			X			
C2D1	Predose[b]	00:00	X	X	X	X
C2[redacted] (± 2 days)		168:00	X	X		
C3D1	Predose[b]	00:00	X	X	X	X
	EOI	See note[c]	X	X		
C3D5[d]		96:00	X			
C4D1	Predose[b]	00:00	X	X	X	X
C5D1	Predose[b]	00:00	X	X	X	X
	EOI	See note[c]	X	X		
		04:00	X			
C5[redacted]		[redacted]	X			
[redacted]			X			

Table 6: PK and ADA Sampling Schedule for BMS-986288 IV [redacted] in Combination with Nivolumab IV [redacted] (Part 1B and Part 2B)

Study Day of Sample Collection (1 Cycle = [redacted])	Event	Time (Relative to Start of Nivolumab Infusion) Hr:Min[a]	BMS-986288 PK [redacted] Sample	Nivolumab PK [redacted] Sample	BMS-986288 ADA [redacted] Sample	Nivolumab ADA [redacted] Sample
C5[redacted]		[redacted]	X			
C5[redacted]			X			
C5[redacted]			X			
C6D1	Predose[b]	00:00	X	X	X	X
C7D1	Predose[b]	00:00	X	X	X	X
Every fourth cycle after C7 until EOT (C11D1, C15D1, C19D1, etc until EOT)	Predose[b]	00:00	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; EOI = end of infusion; EOT = end of treatment; IV = intravenous; PK = pharmacokinetics; [redacted].

[a] Every effort should be taken to collect the sample as close to the designated time as possible. The actual time of collection should be recorded.

[b] Predose: All predose samples should be taken within 30 minutes prior to the start of the infusion of nivolumab.

[c] EOI PK samples should be collected when all study drug has been infused. If a flush is administered to clear the IV lines of the drug and to ensure delivery of the entire drug dose, then draw the EOI PK sample within approximately 15 minutes after end of the flush. Do not draw EOI samples from the same IV access through which the drug was administered. Refer to the Pharmacy Manual for infusion duration. If the EOI is delayed beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.

[d] Sample should be collected with [redacted] (see Table 7 in Appendix 8). C3D5 PK sample is only collected if participant is scheduled for corresponding [redacted], while C1D[redacted] PK sample should be collected irrespective of corresponding[redacted].

Table 7: Biomarker Sampling Schedule for [redacted] Dosing Schedule for All Study Parts in CA043001

Study Day of Sample Collection (1 Cycle = [redacted])	Time (relative to BMS-986288 dose) Hour:Min	[redacted]						
Screening								X
C1D1	00:00[c]	X	X	X	X	X	X	
	EOI[d]	X						
C1D2	24:00	X				X	X	
C1D8[b] (± 3 days)	168:00	X	X	X	X	X	X	X
C1D15 (± 2 days)	336:00	X				X	X	
C1D22 (± 2 days)	504:00	X						
C2D1[e]	672:00	X				X	X	
C2D8 (± 2 days)	840:00	X				X	X	
C2D15 (± 2 days)	984:00	X				X		
C2D22 (± 2 days)	1152:00	X				X		
C3D1	00:00[c]	X						
	EOI[d]	X						
C3D5[b] (± 3 days)	96:00	X	X	X	X	X	X	X
C3D15 (± 2 days)	336:00	X				X	X	
C3D22 (± 2 days)	840:00	X						

Table 7: Biomarker Sampling Schedule for [redacted] Dosing Schedule for All Study Parts in CA043001

Study Day of Sample Collection (1 Cycle = [redacted])	Time (relative to BMS-986288 dose) Hour:Min	[redacted]						
C4D1[e]	672:00	X	X	X	X			
C5D1 and beyond: D1 (every other cycle until EOT)	00:00[c]	X						
Every 6 months from C1D1								
EOT or at progression		X		X	X	X	X	X
30-day Follow-up								

Abbreviations: C = cycle; D = Day; EOI = end of infusion; EOT = end of treatment; [redacted].

[a] Instructions for the collection and processing [redacted] will be provided in the Laboratory Manual.

[b] Mandatory on-treatment [redacted] to be performed at C1D8; specimens may be collected within 3 days of the time point and must be obtained prior to administration of study treatments. While not preferred, if a [redacted] at C1D8 is not collected, then a [redacted] at C3D5 (± 3 days) must be performed. [redacted] are not required to be collected at both C1D8 and C3D5. An optional additional [redacted] can be collected on-treatment if the Investigator and the Medical Monitor (or designee) find it indicated. A [redacted] is required upon confirmation of PD (within 7 days) except for participants: 1) who have an [redacted] 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 [redacted], and 3) participants who consent to be treated beyond progression will require the [redacted] only at the subsequent confirmation of progression. [redacted] are unacceptable for submission.

[c] All predose samples should be taken prior to the start of the infusion/administration.

[d] EOI samples should be taken after the infusion/administration of BMS-986288. Refer to the Pharmacy Manual for infusion duration. EOI is defined as the end of [redacted] or [redacted] administration.

[e] For cohorts with BMS-986288 administered in combination with nivolumab (Part 1B, [redacted] Arm B, and Part 2B), nivolumab will continue to be administered [redacted], hence samples should be collected prior to nivolumab administration. Instructions for the collection and processing [redacted] will be provided in the Laboratory Manual.

APPENDIX 9 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 10 NYHA 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 11 COUNTRY-SPECIFIC REQUIREMENTS/DIFFERENCES

Section	Original Language	Country-specific Language or Differences
Section 6.1: Inclusion Criteria	Must have received, and then progressed, relapsed, or been intolerant to, at least 1 standard treatment regimen in the advanced or metastatic setting	France: Must have received, and then progressed, relapsed, or been intolerant to, at least 1 standard chemotherapy-based treatment regimen in the advanced or metastatic setting
Section 6.1: Inclusion Criteria	All participants with adenocarcinoma must have known EGFR, ALK, KRAS, and ROS1 status (when testing is available as per country/region standard of care practices). Participants with an activating EGFR mutation, ALK translocation, or ROS1 mutation must have received appropriate inhibitor therapy (as available per country/region standard of care).	France: All participants with adenocarcinoma must have known EGFR, ALK, KRAS, and ROS1 status (when testing is available as per country/region standard of care practices). Regardless of histology, all participants with a known activating EGFR mutation, ALK translocation, or ROS1, or KRAS mutation must have received appropriate inhibitor therapy (as available per country/region standard of care).

APPENDIX 12 PROTOCOL AMENDMENT SUMMARY OF CHANGE HISTORY

Overall Rationale for Protocol Amendment 02, 22-Jul-2021

Key changes in this protocol amendment are the addition of new dose levels for dose escalation (Part 1) and the addition of clinical outcomes assessments and new indications for dose expansion (Part 2).

This protocol amendment updates toxicity management based on CTCAE v5. Previously, toxicity management was based on CTCAE v4 and adverse event reporting was based on CTCAE v5. This update was made to ensure consistency with adverse event reporting and the most up-to-date CTCAE version. This protocol amendment also incorporates SARS-CoV-2 assessment requirements to address the COVID-19 pandemic with regard to study conduct. The contraceptive and pregnancy requirements have been updated based on the available scientific evidence and regulatory guidance.

Lastly, this protocol amendment incorporates changes from the approved Administrative Letter 02, which are not detailed in the Summary of Key Changes table below.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	Updated contact information for the Clinical Trial Physician - Medical Monitor and Clinical Scientist	To provide current study information
Synopsis	Revised to match relevant protocol revisions below	For consistency throughout the protocol
Table 2-1 Screening Schedule of Activities for All Study Parts [redacted]	Revised screening [redacted] requirements	Updated to provide flexibility around the screening sample that is collected and ensure that fresh [redacted] collection could be prioritized. If a fresh screening sample is not available, the alternative would be a relatively recent archival sample. [redacted] ensure enough material for biomarker assays.
2 Schedule of Activities 3.3 Benefit-Risk Assessment Table 4-1 Objectives and Endpoints 6.2 Exclusion Criteria (2.f, 2.h, and 3.e.xvi-xviii)	Added protocol text to address SARS-CoV-2 infection and vaccination during study participation	Added guidance to address serum collection and AE monitoring related to COVID-19

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
6.4.1 Retesting During Screening or Lead-In Period 7.4 Dosage Modification (and relevant subsections) 7.7.1 Prohibited and/or Restricted Treatments 9.2 Adverse Events (and relevant subsections) Table 9.8.4-1 Biomarker Sampling Schedule for [redacted] Dosing Schedule for All Study Parts 9.8.4.1 Exploratory Serum and Plasma Biomarkers		
2 Schedule of Activities 9.2.1 Time Period and Frequency for Collecting AE and SAE Information 9.4 Safety	Specified that AE and SAE collection will be done "continuously" and from "last dose" of study treatment	For clarity, as the date of discontinuation of dosing may be different from the date of last dose
2 Schedule of Activities Table 4-1 Objectives and Endpoints 5.4.5 Rationale for Quality of Life Evaluation 9.1.2 Clinical Outcomes Assessments (and relevant subsections) Table 10.2-1 Populations for Analyses 10.3.7 Other Analyses	Added collection of clinical outcomes assessments in Part 2 only	To assess quality of life for new indications
3.2.3 Ipilimumab 3.2.4 Nivolumab Combined with Ipilimumab	Added text on ipilimumab and the combination of nivolumab and ipilimumab	Added information based on new scientific findings
3.3 Benefit-Risk Assessment 5.1.5 Data Monitoring Committee and Other External Committees	Changed Global Pharmacovigilance and Epidemiology (GPVE) to Worldwide Patient Safety (WWPS) Changed Medical Surveillance Team (MST) to Safety Management Team (SMT)	Updated to align with current BMS nomenclature
5.1 Overall Design Figure 5.1-1 Study Design Schematic 5.1.2.3 The Expansion Phase of BMS-986288 [redacted] (Part 2A) and	Added 2 doses to each Part 1 cohort Added text indicating that Part 2 dosing will be selected from the	Added to further explore the MTD Updated Part 2 dosing regimen based on new study design for Part 2

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
BMS-986288 in Combination with Nivolumab (Part 2B) 5.5.2 Rationale for BMS-986288 Maximum Dose Table 7.1-1 Selection and Timing of Dose 7.2 Method of Treatment Assignment [redacted]	range of doses that are tolerable in Part 1	
5.1.2.3 The Expansion Phase of BMS-986288 [redacted] (Part 2A) [redacted] Nivolumab (Part 2B) 6.1 Inclusion Criteria (2.d.ii.3.b)	Removed allowance for prior anti-CTLA-4 therapy in up to 20% of [redacted] participants	To enroll a more homogenous cohort
5.1.4 Treatment Beyond Progression 9.1.1 Imaging Assessment for the Study	Added instruction to continue radiographic assessment for the duration of treatment beyond progression Added instruction to perform imaging assessments that may demonstrate tumor response or progression at unscheduled time points	To clarify the timing of follow-up requirements
Figure 5.1-1 Study Design Schematic 5.2 Number of Participants 6.1 Inclusion Criteria (2.d.ii.2 and 2.e) 10.1.4 The BMS-986288 [redacted] Cohort Expansion (Part 2A) 10.1.5 The BMS-986288 in Combination with Nivolumab Cohort Expansion (Part 2B)	Specified number of participants for each Part 2 cohort and added inclusion criteria detail for Part 2A and Part 2B	Updated number of participants and inclusion criteria based on new study design for Part 2
6.1 Inclusion Criteria (1.a and 1.b)	Added that "a legally acceptable representative" may also sign the informed consent form	Updated to allow for participants' legally acceptable representatives to sign/date IRB/IEC-approved consent forms
6.1 Inclusion Criteria (2.c.v.2 and 2.c.v.3)	Added KRAS status requirement to participants with [redacted] in Part 1	Updated to collect baseline KRAS status in Part 1 [redacted] participants due to the evolving treatment landscape

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
6.1 Inclusion Criteria (2.c.vii.2)	Removed inclusion criterion requiring that participants with [redacted] in Part 1 have no more than 3 prior total systematic treatment regimens	To allow more lines of treatment in the current treatment environment
6.1 Inclusion Criteria (4.e, 4.f, and 4.g) 9.2.5 Pregnancy	Removed language related to half-lives, fetal toxicity, and contraception requirements for male participants Removed requirements for pregnancy and sexual activity reporting and surveillance in female partners of male participants	Based on the available scientific evidence and regulatory guidance (FDA: International Council on Harmonisation [ICH] S6 [R1]), nivolumab and BMS-986288 are not expected to have genotoxic potential at relevant systemic concentrations sufficient to produce a risk of fetal toxicity in WOCBP partners of male participants who have exposure to a male participant's seminal fluid
6.2 Exclusion Criteria (2.g; 2.i; 3.e.iii; 3.e.v; 3.e.x; and 3.e.xiii through 3.e.xv)	Revised exclusion criteria regarding complementary medicine Revised exclusion criteria regarding prior radiotherapy Revised exclusion criteria regarding timing of systemic treatment with corticosteroids or other immunosuppressive medications Revised exclusion criteria regarding chronic hepatitis and HBV, HCV, and HIV infection	Changed complementary medicine criteria based on regulatory guidance Clarified prior radiotherapy relevant exclusion Clarified the different requirement of corticosteroids and other immunosuppressive medications Changed viral infection criteria based on regulatory guidance
7.4 Dosage Modification (and relevant subsections) Table 7.4.3.1-1 Adverse Event Criteria for Delay, Resume, and Discontinue of Nivolumab and/or BMS-986288	Added text specifying that when criteria to resume treatment are met, both study treatments are resumed on the same day Added table for AE criteria for delaying, resuming, or discontinuing nivolumab and/or BMS-986288	Clarified that both study treatments should resume on the same day for combination therapy Updated study treatment dose delay, resumption, and discontinuation criteria to align with CTCAE v5 and

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
	Added definition of DLTs and moved DLT information to Table 7.4.3.1-1	reorganized table for readability Added DLT information to AE table for greater convenience
7.4.5 Management of Drug-related Infusion Reactions	Revised text to indicate that Grade 3 or 4 infusion reactions are to be reported through the standard AE/SAE reporting process and do not need to be reported separately to the BMS Medical Monitor	To reflect current practice
7.5 Preparation/Handling/Storage/ Accountability	Specified that when combination therapy is administered, nivolumab is to be administered first	Clarified the study drug administration procedure
9.2.3 Follow-up of AEs and SAEs	Specified that after initial AE/SAE report, the investigator must follow each participant at subsequent visits/contacts	Clarified the follow-up expectation for AEs/SAEs
Table 9.5-2 PK and ADA Sampling Schedule for BMS-986288 [redacted] Monotherapy in Dose Escalation (Part 1A) and BMS-986288 IV [redacted] Cohort Expansion (Part 2A) Table 9.5-3 PK and ADA Sampling Schedule for BMS-986288 [redacted] in Combination with Nivolumab [redacted] in Dose Escalation (Part 1B) and BMS-986288 [redacted] in Combination with Nivolumab [redacted] Cohort Expansion (Part 2B)	Revised EOI footnote to allow 15-minute window	To reflect current practice
10.3.8.1 Bayesian Continuous Monitoring for Treatment-related Toxicities Meeting DLT Criteria in Part 2 Table 10.3.8.1-1 Monitoring Boundaries for Treatment-related Toxicities Meeting DLT Criteria in Part 2	Set up Bayesian continuous monitoring framework to assist clinical interpretation of safety signals in Part 2 expansion participants Provided safety monitoring boundaries for treatment-related toxicities meeting DLT criteria in a table	To ascertain safety signals (by quantitative framework for monitoring DLT) that may occur during Part 2 expansion in BMS-986288 as monotherapy and/or in combination with nivolumab in study participants

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Appendix 2 Study Governance Considerations	Updated first paragraph for Monitoring section to further describe that details on monitoring can be found in the monitoring plan Added section on dissemination of clinical study data	Clarified expectations
Appendix 4 Women of Childbearing Potential Definitions and Methods of Contraception	Updated contraception guidance and removed additional measures required for male participants	Aligned methods of contraception with updates made to male contraceptive requirements in Section 6.1
Appendix 6 Management Algorithms for IO Agents	Updated the IO agent management algorithms to align with CTCAE v5	Updated toxicity management algorithms for immune-mediated AEs to align with CTCAE v5 and the updated Nivolumab IB Addendum 01
[redacted]		
Appendix 8 Schedule of Activities, Pharmacokinetics Sampling Schedule, and Biomarker Sampling Schedule for Potential Alternative Dose Schedules in CA043001	Added protocol text to address SARS-CoV-2 infection and vaccination during study participation Specified that AE and SAE collection will be done "continuously" and from "last dose" of study treatment Added collection of clinical outcomes assessments in Part 2 only. Included additional text to indicate that if other indications are included then other indication-specific patient-	Added guidance to address serum collection and AE monitoring related to COVID-19 For clarity, as the date of discontinuation of dosing may be different from the date of last dose Added clinical outcomes assessments to assess quality of life for new indications

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
	reported outcomes will also be included in future protocol amendments Revised EOI footnotes to allow 15-minute window	To reflect current practice
All	Removed some instances of "randomization" and/or added "treatment allocation" Specified participants with "cutaneous" melanoma for this study Minor formatting and typographical corrections and additional revisions to align the protocol with respect to the key changes outlined above	For clarification. In this open-label study, treatment assignment is by allocation, not randomization Updated for consistency of melanoma tumor subtype within the document Corrections for clarity and consistency within the document were minor and therefore have not been summarized

Overall Rationale for the Revised Protocol 01, 11-Jun-2019

The primary reasons for these changes are to address questions provided by the United States Food and Drug Administration, incorporate Administrative Letter 01, and ensure that the protocol is consistent with internal BMS policies and operating procedures.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
2 and Appendix 8: Schedule of Activities	Updated notes and footnotes [redacted].	Clarified expectations and timing [redacted]
6.1: Inclusion Criteria	Require additional prior treatments for eligible participants with [redacted], removed language pertaining to participant refusal from inclusion criteria, and removed option of replacing participants based on tumor mutational burden status.	Inclusion criteria updated to ensure that participants receive appropriate prior therapy.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
6.2: Exclusion Criteria; 7.4.1: Dose-limiting Toxicities; 7.4.5: Management of Drug-related Infusion Reactions; 9.4: Safety; 10.3.2: Safety Analyses	Updated National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events (CTCAE) from v4.03 to v5.0.	Updated NCI CTCAE criteria to current version 5.0.
7.1: Schedule of Dose for Each Investigational Product	Updated footnote "a" in Table 7.1-1 to include additional details on infusion times.	Clarified infusion times for BMS-986288 per Administrative Letter 01.
7.4.1.3: Hematologic Dose-Limiting Toxicities; 7.4.4: Exceptions to Permanent Discontinuation Criteria	Additional hematologic dose-limiting toxicity criteria provided.	Added for participant safety.
7.4.2: Management Algorithms for Immuno-oncology Agents	Added encephalitis as an example of a neurological immune-mediated adverse event and cardiac management algorithms.	Added for participant safety.
9.8.5: Additional Research Collection	Provided additional details for additional research collection.	Clarified expectations for additional research collection.
Appendix 2: Study Governance Considerations	Addressed language around serious breach, clinical study report, and scientific publications.	Modified for clarity and consistency with internal BMS policies and operating procedures.
Appendix 6: Management Algorithms for IO Agents	Added treatment algorithm for myocarditis.	Added for participant safety.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
All	Minor formatting, typographical corrections, and 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.