Official Title of Study:

Phase 1/2a First-In-Human Study of BMS-986207 Monoclonal Antibody Alone and in Combination With Nivolumab or With Nivolumab and Ipilimumab in Advanced Solid Tumors

NCT Number: NCT02913313

Document Date (Date in which document was last revised): 06 January 2022

Protocol Number: CA020002
IND Number: 130,976
EUDRACT Number 2016-002263-34
Date: 12-Sep-2016
Revised Date: 06-Jan-2022

CLINICAL PROTOCOL CA020002

Phase 1/2a First-In-Human Study of BMS-986207 Monoclonal Antibody Alone and in Combination with Nivolumab or with Nivolumab and Ipilimumab in Advanced Solid Tumors

Short Title: An Investigational Immuno-therapy Study of BMS-986207 Given Alone and in Combination With Nivolumab or with Nivolumab and Ipilimumab

Protocol Amendment Number: 04

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to partners to which BMS has transferred obligations, eg, a Contract Research Organization (CRO).

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Protocol Amendment 04	06-Jan-2022	Revision to add to Part 1C lower dose levels of BMS-986207 (≤ 600 mg every 3 weeks) that may be tested. In Part 2C, the triplet combination of BMS-986207 + nivolumab + ipilimumab will be explored in first-line non-small cell lung cancer (1L NSCLC) participants with PD-L1 tumor cell positive expression ≥ 1%. Additional doses lower than the dose declared tolerable in Part 1C may be tested for dose optimization in Part 2C. Updates to contraception and pregnancy requirements in women of childbearing potential (WOCBP) and contraception requirements in males based on the available scientific evidence.
Protocol Amendment 03	05-Jan-2021	Revised to include 2 new treatment arms: Part 1C, BMS-986207 + nivolumab + ipilimumab in participants with advanced solid tumors and Part 2C, BMS-986207 + nivolumab + ipilimumab in participants with 1L NSCLC with tumor PD-L1 expression ≥ 50%.
Administrative Letter 05	02-Jul-2020	Updates to staff/contact information for the Medical Monitor
Administrative Letter 04	28-Aug-2018	Updates to staff/contact information for the Medical Monitor
Administrative Letter 03	27-Feb-2018	Updates to staff/contact information for the Medical Monitor
Administrative Letter 02	24-Aug-2017	Updates to staff/contact information for the Medical Monitor
Revised Protocol 02	06-Jul-2017	Addition of q4w dosing regimen
Administrative Letter 01	16-Mar-2017	Updates to staff/contact information for Medical Monitor/Study Director and Clinical Scientist Page 20, Section 2, Table 2.2 On Treatment Schedule of Activities: • Change in PK sampling schedule. C1D56 corresponds to C2D1 collection. C1D56 PK sample will not to be collected and will be removed with next protocol amendment. • Removal of C1D50 as there are no assessments/treatments to be done for study participants on this day. [redacted]
Revised Protocol 01	24-Oct-2016	Incorporates Amendment 02
Amendment 02	24-Oct-2016	Revisions/clarifications to protocol language: • Treatment of participants beyond initial progression modified to include radiographic assessment at 4-6 weeks to confirm initial disease progression (Section 8.1.1.1); • Required separate consent for retreatment of participants with progressive disease in follow-up (Section 5.1.3.4) • Inclusion Criteria for HCC participants:

Document	Date of Issue	Summary of Change
		radiographic evidence acceptable at enrollment with histologic confirmation required prior to initiation of study therapy; active hepatitis C infection with any viral load permitted, provided participants on anti-viral therapy; Participants must be ineligible for ablative techniques or liver transplant; Those who progressed after locoregional therapy, locoregional therapy must be completed at least 4 weeks prior to the baseline scan (Section 6.1). • Addition of d 29 safety ECG and removal of Day 50 timepoint from On Treatment Schedule of Activities Table and Clarification of Laboratory assessments in follow-up (Section 2); Confirmation of On Treatment C1D29 PK collection at hour 04:00 and PK [redacted] collections in Retreatment (Tables 9.5-2 [redacted]) • Clarified mandatory requirement for archived [redacted] • Addition of 60 minute monitoring post infusion of BMS 986207 for all 4 doses in Cycle 1 (section 7.1 and Schedule of Activities Table -section 2) • Added section: Discontinuation Due to Hypersensitivity (section 7.4.6) • Clarification of DLT criteria for Hypersensitivity Reaction to ≥ Grade 4 or Grade 3 that does not resolve to Grade 1 in < 6 hours (section 7.4.1.4) • Addition Preliminary Safety Cohort to Study Design (Appendix 13 and related study design text) • Clarified conditions for determination of MTD/RP2D (section 10.1.1).
Original Protocol	12-Sep-2016	Not applicable

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 04:

Key changes in this protocol amendment are the addition to Part 1C of lower dose levels of BMS-986207 (≤ 600 mg every 3 weeks) that may be tested in order to better estimate the tolerability of the optimal dose level of BMS-987207 in combination with nivolumab and ipilimumab. In addition, the triplet combination of BMS-986207 + nivolumab + ipilimumab will be explored in first-line non-small cell lung cancer (1L NSCLC) participants with PD-L1 tumor cell positive expression ≥ 1% (Part 2C). Additional doses lower than the dose declared tolerable in Part 1C may be tested for dose optimization in Part 2C. This will be examined in order to further develop the BMS-986207 program.

This protocol amendment also updates contraception and pregnancy requirements in women of childbearing potential (WOCBP) and contraception requirements in males based on the available scientific evidence.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 04

Section Number & Title	Description of Change	Brief Rationale
Synopsis	Revised to reflect the revisions in the body of the protocol.	For consistency throughout the protocol
Table 2-1: Screening - Schedule of Activities	Removed [redacted] from screening.	Align with Table 2-4 [redacted] that this test should be done on C1D1 instead.
Table 2-1: Screening - Schedule of Activities Section 6.1: Inclusion Criteria [redacted]	Changed current description of PD-L1 immunohistochemistry (IHC) results for Part 2C enrollment to increase clarity.	For better clarity for all global sites.
Section 3.1: Study Rationale Section 3.2.1.4: Preliminary Clinical Safety Profile Section 3.3: Benefit/Risk Assessment Figure 5.1.2.2-2: Treatments Cohorts in CA020002 Section 5.1.2.6: Safety Evaluation Phase of Part 1C Section 5.1.2.7: Cohort Expansion	Revised to reflect current knowledge regarding the safety and dose of BMS-986207. Clarification language added where necessary.	To reflect current knowledge regarding the safety and dose of BMS-986207.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
(Parts 2A, 2B, and 2C)		
Table 4.1: Objectives and Endpoints	[redacted]	
Figure 5.1.2.2-2: Treatments Cohorts in CA020002 5.5.2.2: Nivolumab	Dose for BMS-986207 changed from 1200 mg to 600 mg.	Due to the safety profile observed in participants in Part 1C who were treated with 1200 mg BMS-986207 Q3W + 360 mg nivolumab Q3W + 1 mg/kg ipilimumab Q6W (see Section 3.2.1.4).
Section 5.1.2.2: Treatment in Part 1C and Part 2C Figure 5.1.2.2-2: Treatments Cohorts in CA020002 Section 5.4.8: Rationale for Dose Escalation Phase Design Section 7.4: Dosage Modification	Text revised to include current testing dose of 600 mg BMS-986207 Q3W and that additional lower doses may be used. [redacted] Additional doses lower than the dose declared tolerable in Part 1C may be tested for dose optimization in Part 2C. Figure 5.1.2-2 updated to reflect dose of 600 mg BMS-986207 in Part 1C and the RP2D dose(s) of BMS-986207 in Part 2C. Intra-participant dosage modification has been clarified.	[redacted]
Section 5.2: Number of Participants	Participant numbers revised.	To align with statistical size determinations as discussed in Section 10: Statistical Considerations.
Section 5.2: Number of Participants Section 7.2: Method of Treatment Assignment Section 10.1.3.2: Cohort Expansion in Part 2C	Language revised to clarify handling of unconfirmed pre-existing PD-L1 results.	To clarify language about discordant test results that may be seen in Part 2C.
Section 5.4.4 Rationale for the Combination of BMS-986207,	Language added to justify inclusion of [redacted]	Inclusion of [redacted] will promote enrollment and capture the potential

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Nivolumab and Ipilimumab in NSCLC Table 5.4.7-1: Rationale for Tumor Selection	Language revised to clarify PD-L1 positive expression in NSCLC tumors.	benefit of BMS-986207 in a larger population.
Section 5.4.4: Rationale for the Combination of BMS-986207, Nivolumab, and Ipilimumab in NSCLC Section 5.5.2.1: BMS-986207 Table 7.1-2: Selection and Timing of Dose	Updates and reorganization of Section 5.4.4. Updated Section 5.5.2.1 with latest safety information on Part 1C at 1200 mg Q3W BMS-986207. Added additional doses of BMS-986207 to Table 7.1-2. Added footnote to Table 7.1-2 for dose de-escalation of BMS-986207.	Clarify further why the Triplet Combination is being examined in this study. Data from Part 1C indicated that the dose of 1200 mg Q3W BMS-986207 with nivolumab and ipilimumab was not tolerable in some participants and a lower dose was warranted.
Section 6.1: Inclusion Criteria	4)b) & 4)d) Updated WOCBP contraception criteria. 4)f) Updated male contraception criteria. Added 4)g) - 4)j).	Based on the available scientific evidence and regulatory guidance (FDA: International Council on Harmonisation [ICH] S6 [R1]), nivolumab, ipilimumab and BMS-986207 are not expected to have genotoxic potential.
Section 7.6.1: Prohibited and/or Restricted Treatments	Added sentence to clarify the non-live SARS-CoV-2 vaccination as a simple concomitant medication.	To provide increased clarity to study sites.
Section 9.2.5: Pregnancy Appendix 4: Women of Childbearing Potential Definitions and Methods of Contraception	Guidance revised to notification of pregnancy for 5 months following product administration. Additional guidance for completion of protocol procedures added. Removal of guidance to report pregnancy in female partners of male participants.	End of relevant systemic exposure is the time point 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. In this study, nivolumab has the longest half-life of 25 days compared to BMS-986207 (half-life of 14 days), and ipilimumab (half-life of 20 days). Using the half-life of nivolumab, the end of relevant systemic exposure is 125 days which is over 4 months. In order to simplify the

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
		contraception and pregnancy reporting guidance, 5 half-lives was updated to 5 months following product administration. Based on the available scientific evidence and regulatory guidance (FDA: International Council on Harmonisation [ICH] S6 [R1]), nivolumab, ipilimumab and BMS-986207 are not expected to have genotoxic potential.
[redacted]		
Section 10.1.3.2: Cohort Expansion in Part 2C Table 10.1.3.2-1: Operating characteristics of criteria for antitumor activity by ORR Table 10.1.3.2-2: Potential ORR in 1L NSCLC (≥ 1% PD-L1) and Exact 80% CI Table 10.2-1: Population for Analyses Table 10.3.1-1: Efficacy - Statistical Analysis	Updated [redacted] Updated to include that one or two doses are planned to be evaluated in Part 2C and a minimum of 20 participants are enrolled per dose level of BMS-986207. Statistical tables updated to reflect the change.	To align with changes to study rationale for Part 2C.
Throughout	Minor typographical errors corrected, or revisions made to increase readability.	Minor, therefore have not been summarized.

TABLE OF CONTENTS

1 SYNOPSIS

Protocol Title: Phase 1/2a First-In-Human Study of BMS-986207 Monoclonal Antibody Alone and in Combination with Nivolumab or with Nivolumab and Ipilimumab in Advanced Solid Tumors

Short Title: An Investigational Immuno-therapy Study of BMS-986207 Given Alone and in Combination With Nivolumab or with Nivolumab and Ipilimumab

Study Phase: Phase 1/2a

Rationale: BMS-986207, an anti-T cell immunoglobulin (Ig) and immunoreceptor tyrosine-based inhibitory motif (ITIM) domain (TIGIT) monoclonal antibody (mAb), is being studied alone and in combination with nivolumab or in combination with nivolumab and ipilimumab in humans with advanced solid tumors.

Tumors modulate and evade the host immune response through a number of mechanisms, including down regulation of tumor-specific antigen expression and presentation, secretion of anti-inflammatory cytokines, and upregulation of inhibitory ligands. Immunotherapeutic approaches such as checkpoint pathway blockade have demonstrated clinical efficacy in several cancers, including melanoma, renal cell, lung, and hormone-refractory prostate cancers. Following the success of anti-cytotoxic T-lymphocyte-associated protein (CTLA-4) and anti-programmed cell death 1 (PD-1) pathway-targeted agents in several cancers, the field of tumor immunotherapy is rapidly expanding, recognizing the potential value of combination therapies.

BMS-986207 is a fully human variant immunoglobulin G1 (IgG1) monoclonal antibody (mAb) that binds with high affinity to TIGIT (T cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain), a negative regulatory molecule that suppresses activation and functional responses in T cells and natural killer (NK) cells. TIGIT upregulation has been observed in cancer patients, in particular on T cells, and is co-expressed with [redacted] of T cell exhaustion. Binding of poliovirus receptor (PVR) and Nectin-2 (TIGIT ligands) to TIGIT results in suppression of T cell and NK cell function. These same ligands also bind with lower affinity to the stimulatory receptor CD226 (DNAX accessory molecule 1 [DNAM-1]) also expressed on effector T cells. Blockade of TIGIT with molecules like BMS-986207 therefore may increase the anti-tumor immune response both by removing the suppressive signal emanating from TIGIT and by freeing its ligands to bind to the stimulatory receptor CD226. Blockade of TIGIT-mediated inhibition of T and NK cell function is hypothesized to facilitate an increase in the amplitude and durability of responses against a number of malignancies.

[redacted]

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. For Part 2C, participants must have NSCLC, be treatment-naive, and have pre-existing or prior PD-L1 IHC results from testing of tumor tissue. PD-L1 expression must be tumor cell positive ≥ 1% for a participant to be eligible for enrollment.

Objectives and Endpoints: The primary and secondary objectives and endpoints for this study are shown in the table below.

Objectives	Endpoints
Primary	
• Part 1A, 1B, 2A, and 2B: To characterize the safety, tolerability, DLTs, and MTD/RP2D of BMS 986207 administered as monotherapy and in combination with nivolumab in participants with advanced solid tumors.	• Incidence of AEs, SAEs, AEs meeting protocol-defined DLT criteria, AEs leading to discontinuation, and death; Incidence of laboratory abnormalities.

Objectives	Endpoints
• Part 1C: To characterize the safety, tolerability, and DLTs of BMS-986207 in combination with nivolumab and ipilimumab in participants with advanced solid tumors.	• Incidence of AEs, SAEs, AEs meeting. protocol-defined DLT criteria, AEs leading to discontinuation, and death; Incidence of laboratory abnormalities.
• Part 2C: To evaluate the preliminary efficacy and safety of BMS-986207 in combination with nivolumab and ipilimumab in previously untreated participants with NSCLC whose tumors express ≥ 1% PD-L1 based on PD-L1 IHC results from central testing.	• ORR, mDOR, and PFSR at 24 weeks by RECIST v1.1 by investigator; Incidence of AEs, SAEs, AEs leading to discontinuation, and death.
Secondary • To assess the preliminary efficacy of BMS-986207 alone and in combination with nivolumab in advanced solid tumors (Parts 1A, 2A, 1B, and 2B) and in combination with nivolumab and ipilimumab in advanced solid tumors (Part 1C).	• ORR, mDOR, and PFSR at 24 weeks by RECIST v1.1
• To characterize the PK and immunogenicity of BMS-986207 when administered alone, in combination with nivolumab or in combination with nivolumab and ipilimumab.	• Summary measures of PK parameters of BMS-986207 and incidence of ADA to BMS-986207

Abbreviations: ADA, anti-drug antibody AE, adverse event; DLT, dose limiting toxicity; IHC, immunohistochemistry; mDOR, median duration of response; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD-L1, programmed death ligand 1; PFSR, progression-free survival rate; PK, pharmacokinetic; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended Phase 2 dose; SAE, serious adverse event.

OVERALL DESIGN

This is a Phase 1/2a, open-label study of BMS-986207 administered as a single agent, in combination with nivolumab, and in combination with both nivolumab and ipilimumab in participants with advanced solid tumors. The duration of the study will be approximately 6 years.

The study comprises 2 parts. Part 1 includes dose escalation of BMS-986207 alone (Part 1A) and in combination with nivolumab (Part 1B) to determine the MTD/RP2D, as well as a select dose level of BMS-986207 in combination with nivolumab and ipilimumab (Part 1C) to evaluate safety and preliminary [redacted] activity of the triplet combination. Part 1B includes a substudy conducted at a single site under site-specific Amendments 6, 7, and 8 to evaluate the safety and preliminary efficacy of BMS-986207 in combination with nivolumab in PD-1 naive and relapsed/refractory participants with melanoma. Part 2 includes expansion cohorts to gather additional preliminary [redacted] activity, as well as additional safety, tolerability, PK, [redacted] information for BMS-986207 alone (Part 2A), in combination with nivolumab (Part 2B), and in combination with nivolumab and ipilimumab in NSCLC (Part 2C). Participants in each study phase will complete up to 4 periods in the study: screening, treatment, safety follow-up, and response/survival follow-up. The overall study design is illustrated in Figure 1 and the treatment cohorts are presented in Figure 2.

Screening: The screening period will last for up to 28 days, and will begin by establishing the participant's initial eligibility and signing of the informed consent form. Participants will be enrolled using an Interactive Response Technology (IRT).

Preliminary Safety Cohort: The Preliminary Safety Cohort precedes participant enrollment in Monotherapy-Dose Escalation (Part 1A) of the study. The first participant enrolled into monotherapy escalation will receive BMS-986207 starting at the 2-mg dose level, followed 2 weeks later with intra-participant dose escalation to the 6-mg dose level, and followed 2 weeks after that with intra-participant dose escalation to the 20-mg dose level. This first participant will be subject to a 5-day safety observation period after receiving the first 20-mg dose. If no dose-limiting toxicities (DLTs) or other safety concerns are observed, an additional 2 participants will be enrolled in the 20-mg dose cohort.

Treatment: Participants in Parts 1A, 1B, 2A, and 2B will be treated for up to 24 weeks (3 cycles) with monotherapy (Parts 1A and 2A) or combination therapy (Parts 1B and 2B). The treatment period will consist of up to 3 treatment

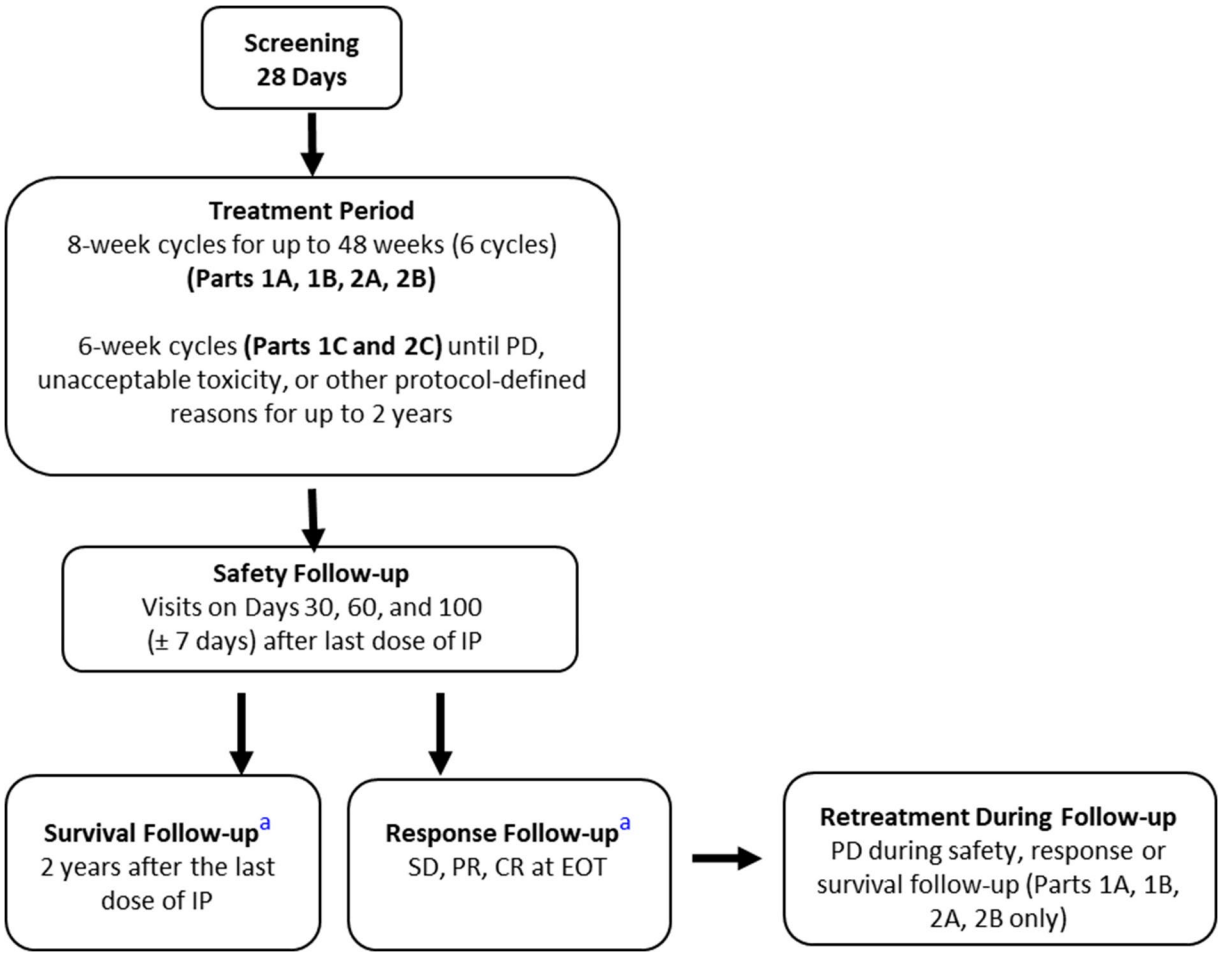
cycles of 8 weeks. Following each treatment cycle, the decision to treat a participant with additional cycles of study therapy (up to a maximum of 6 cycles), will be based on tumor assessment at the end of each cycle. In Parts 1C and 2C, nivolumab and BMS-986207 will be administered every 3 weeks and ipilimumab will be administered every 6 weeks until progression, unacceptable toxicity, or other reasons specified in the protocol for up to 2 years.

Each monotherapy treatment cycle will comprise 4 doses of BMS-986207 administered every 2 weeks (q2w) or 2 doses of BMS-986207 every 4 weeks (q4w) in Part 1A and 2A. BMS-986207 infusions will take place over 60 minutes and will require a 60 minute observation period after all infusions in Cycle 1 for each participant. For participants < 42 kg on the 1600 mg dose, the infusion time will be longer than 1 hour. In Parts 1B and 2B, each combination treatment cycle will comprise 4 doses of BMS-986207 administered q2w or 2 doses of BMS-986207 when administered q4w, each dose administered with nivolumab. In Part 1B and 2B, when both study drugs are given in combination, nivolumab will be given first, over a 30-minute infusion period, followed by BMS-986207 over a 60-minute infusion period, with a 60-minute observation period after all infusions in Cycle 1 for each participant, and at least 30 minutes after completion of the infusion of nivolumab. Tumor progression and response will be assessed using RECIST v1.1 criteria for solid tumors. The study design is shown in Figure 2.

The approximate number of evaluable participants will be 241. Approximately 100 of these participants will be treated with monotherapy and combination dose escalation (Part 1A and Part 1B, respectively). Approximately 36 participants will be treated (6 initial participants for safety evaluation followed by evaluation of approximately 12 additional participants per dose level) with BMS-986207, nivolumab, and ipilimumab in the Triplet Cohort (Part 1C). The remaining (up to 105) participants will be treated as part of dose expansion with up to 24 participants in Part 2A and 41 participants in Part 2B, and 40 participants with NSCLC [redacted] pre-existing or prior PD-L1 IHC results from testing of tumor tissue) considered to be response-evaluable, in Part 2C.

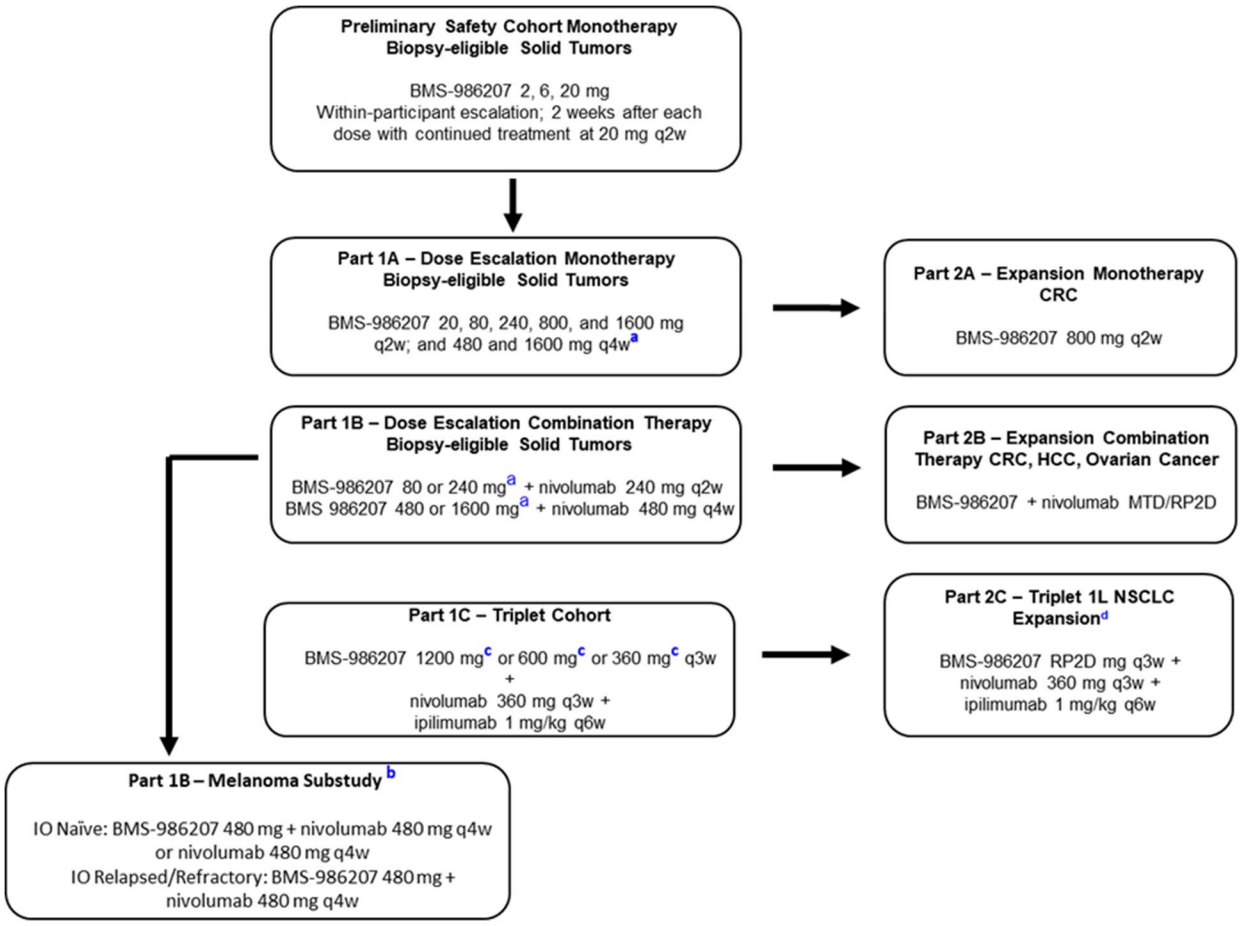
Study Design

Figure 1: Overall Study Design



Abbreviations: CR, complete response; EOT, end of treatment; IP, investigational product; PD, progressive disease; PR, partial response; SD, stable disease;

Figure 2: Treatment Cohorts in CA020002



Abbreviations: 1L NSCLC, first-line non-small cell lung cancer; BMS, Bristol-Myers Squibb; CRC, colorectal cancer; HCC, hepatocellular carcinoma; IO, immuno-oncology; MTD, maximum tolerated dose; q2w, every 2 weeks. q3w, every 3 weeks; q4w, every 4 weeks, q6w, every 6 weeks; RP2D, recommended phase 2 dose.

[a] Planned dose levels and dose schedules of BMS-986207 and/or nivolumab may be modified, and intermediate dose levels of BMS-986207 added, based upon the BLRM analysis and sponsor discretion and discussion with investigators. Once the safety (during the DLT evaluation) of a dose level has been established (Part 1A and/or Part 1B), additional participants (up to 15) may be added at that dose, to better characterize the safety, dose schedule, PK, [redacted]profile [redacted] assessments.

[b] Participants were enrolled at a single site under site-specific Amendments 6, 7, and 8. This substudy has been closed for enrollment.

[c] The safety profile of BMS-986207 1200 mg Q3W combined with nivolumab 360 mg Q3W and ipilimumab 1 mg/kg Q6W has been evaluated in 6 subjects. Of these subjects, 4 were DLT evaluable, and 2 developed DLTs. Per BOIN design, for all the remaining and future subjects, BMS-986207 was de-escalated to 600 mg Q3W (for details, see Section 3.2.1.4) Planned dose levels for BMS-986207 may be further modified based on generated data and additional doses, including 360 mg Q3W, may be assessed per BOIN design and for dose optimization analysis at Sponsor discretion and based upon discussion and agreement with investigators.

[d] Part 2C will enroll a minimum of 20 participants per dose level of BMS-986207. One or two doses are planned to be evaluated and selected from the range of doses assessed as tolerable and not exceeding the maximum tolerated dose in Part 1C. If two doses will be tested at the Sponsor's discretion, participants will be randomized in a 1:2 ratio schema between the highest dose selected in Part 1C and the next lower dose, after at least 10 participants will have been tested at the dose found safe in Part 1C.

TREATMENT

Preliminary Safety Cohort: The Preliminary Safety Cohort precedes participant enrollment in Monotherapy - Dose Escalation (Part 1A) of the study. The first participant enrolled into monotherapy escalation will receive BMS-986207 starting at the 2 mg dose level, followed 2 weeks later with intra-participant dose escalation to the 6 mg dose level, followed 2 weeks after that with intra-participant dose escalation to the 20 mg dose level. This first participant will be subject to a 5-day safety observation period after receiving the first 20 mg dose. If there are no DLTs or other safety concerns observed, an additional 2 participants will be enrolled in the 20 mg dose cohort.

Dose Escalation (Part 1A and Part 1B): Approximately 35 participants are expected to be treated during each dose escalation part of the study guided by Bayesian Logistic Regression Model (BLRM). Each participant will be administered intravenous (IV) doses of BMS-986207 per the cohort assignment as described below.

In Part 1A (monotherapy dose escalation), the planned flat dose levels for BMS-986207 are 20, 80, 240, 800, and 1600 mg (assuming an 80 kg participant) q2w, in 8-week cycles, for up to 3 cycles of study therapy (24 weeks). In addition, a q4wk schedule of BMS-986207 will be evaluated at flat doses of 480 mg and 1600 mg (assuming an 80 kg participant). Enrollment of the first q4w cohort will be guided by the safety, PK, [redacted] analysis from the q2wk cohorts. Following each treatment cycle, the decision to treat a participant with additional cycles of study therapy (up to a maximum of 6 cycles), will be based on tumor assessment at the end of each cycle.

In Part 1B, (combination therapy dose escalation), BMS-986207 and nivolumab will be administered at flat doses of 80 and 240 mg BMS-986207 q2w and 240 mg nivolumab q2w. In addition, BMS-986207 will be administered at flat doses of 480, and 1600 mg q4w in combination with nivolumab administered at 480 mg q4w. Study drugs will be administered in 8-week cycles, for up to 3 cycles of study therapy (24 weeks). Following each treatment cycle, the decision to treat a participant with additional cycles of study therapy (up to a maximum of 6 cycles), will be based on tumor assessment at the end of each cycle.

Planned dose levels may be modified, or intermediate dose levels added, based upon the BLRM analysis. Part 1B, combination dose escalation, will be initiated after at least 3 dose levels (ie, 20, 80, and 240 mg dose cohorts), have been found to be tolerable in Part 1A, monotherapy dose escalation. The starting dose of BMS-986207 in Part 1B will be at least 1 dose level below a dose that was demonstrated to be tolerated in Part 1A. At no time will the dose for BMS-986207 in Part 1B exceed the highest tolerated dose in Part 1A. BLRM may indicate evaluation of intermediate dose levels that fall in-between the planned dose levels. Any dose level increment will be limited to approximately a 3-fold increase. Subsequently, escalation in Parts 1A and 1B may be done in parallel.

Participants with biopsy eligible solid tumors will be enrolled in Parts 1A and 1B. Specifically participants with tumor types where the microbiome has been implicated, in preclinical or clinical data, to mediate TIGIT inhibition, such as but not limited to, CRC and squamous cell carcinoma of the head and neck (SCCHN), will be enrolled in Part 1A. Once the safety (during the dose limiting toxicity [DLT] evaluation) of a dose level has been established (Part 1A and/or Part 1B), additional participants (up to a total of 15) may be added at that dose level, to better characterize the safety, PK, [redacted] profile.

Sentinel Participant: For all dose escalation cohorts, a sentinel participant approach will be used with a 5-day interval between the treatment initiation of the first participant and the treatment of subsequent participants in that dose level. The first participant in both Part 1A, starting at the 20-mg dose level, and Part 1B will receive Cycle 1 Day 1 dose of study drug(s), and be observed for 5 days before additional participants receive study drugs. The first participants to be dosed in all subsequent dose-level cohorts will also be subject to a 5-day sentinel period. Initially, 3 participants will be enrolled at the start of each dose-escalation cohort, in accordance with the sentinel participant approach above. However, to allow for any unforeseen discontinuations (such as disease progression) before the 4-week DLT period is completed, an extra participant may be enrolled at each dose-escalation cohort. Therefore, there will be a total of 4 participants (3+1) at the start of each dose-escalation cohort, providing the fourth participant is able to start the first day of dosing within approximately 1 week of the third participant in the same dose-escalation cohort.

Triplet Cohort (Part 1C): Approximately 36 participants will be treated (6 initial participants for safety evaluation followed by evaluation of approximately 12 additional participants for each dose level tested) with BMS-986207, nivolumab, and ipilimumab in the Triplet Cohort (Part 1C). BMS-986207 will be administered at 600 mg q3w and/or 360 mg q3w and nivolumab will be administered at 360 mg q3w. Ipilimumab, at a dose of 1 mg/kg, will be given q6w. A dose of 1200 mg BMS-986207 administered every 3 weeks has been tested per Amendment 03 but due to the

DLTs observed no additional participants will be tested at this dose (see Section 3.2.1.4). Study drugs will be administered in 6-week cycles until disease progression, unacceptable toxicity, or other reasons as specified in the protocol for up to 2 years. Treatment beyond initial investigator-assessed RECIST v1.1 defined progression is permitted if the subject has investigator-assessed clinical benefit and is tolerating the treatment.

The DLT period in Part 1C will be 42 days (6 weeks). The DLT safety monitoring during the dose evaluation phase, including the potential decision to de-escalate to a lower dose, will be based on the Bayesian optimal interval (BOIN) design framework with a dose-limiting toxicity (DLT) rate of 30% (24%, 36%).

Subjects who do not complete the DLT observation period for reasons other than DLTs may be replaced. De-escalation may be considered if the safety and tolerability profiles for the selected BMS-986207 dose are deemed unacceptable, after discussion between the investigator (s) and the Sponsor/Medical Monitor.

Cohort Expansion (Part 2A, 2B, and 2C): In the cohort expansion part of the study, additional safety, tolerability, preliminary efficacy, PK, [redacted] information, regarding BMS-986207 alone and in combination with nivolumab, will be sought. Continuous evaluation of toxicity events will be performed throughout enrollment in the expansion cohorts. If, at any time, the aggregate rate of treatment-related toxicities meeting DLT criteria exceeds 33% across all participants treated in cohort expansions, reassessment of enrollment will take place. Depending on the nature and grade of the toxicity and after assessing the risk/benefit ratio, a new dose(s) for all cohorts may be initiated at a previously tested lower dose level or at a dose level intermediate to previously tested lower dose levels.

In Part 2A, only CRC will be evaluated in cohort expansion with BMS-986207 as monotherapy. In Part 2B, the 3 disease-restricted populations, ovarian cancer, CRC and HCC, will be investigated in cohort expansions with BMS-986207 in combination with nivolumab. A Fleming 2-stage design framework will be used as a guide in cohort expansion.

During the expansion phase, participants with CRC who have disease progression on BMS-986207 monotherapy will be able to cross over to combination treatment (BMS-986207 + nivolumab), once the CRC expansion arms are enrolling. This cross-over option is not applicable during the escalation phases. CRC participants with disease progression who cross over to combination treatment will undergo the same efficacy and safety assessments as the main cohort.

The purpose of Part 2C is to gather preliminary efficacy information regarding BMS-986207 in combination with nivolumab and ipilimumab in participants with advanced, treatment-naive NSCLC whose tumors expres[redacted] to assess optimal dose selection for RP2D. These subjects will be treated with BMS-986207 q3w at a dose not to exceed the dose declared tolerable in Part 1C, nivolumab 360 mg q3w, and ipilimumab 1 mg/kg q6w. Additional doses lower than the dose declared tolerable might be tested for dose optimization in Part 2C.

Part 2C may begin once there is sufficient safety data from a minimum of 6 participants in Part 1C.

Continuous evaluation of toxicity events will also be performed in this part of the study If, at any time, the aggregate rate of treatment-related toxicities meeting DLT criteria exceeds 33%, the findings will be discussed and further enrollment may be interrupted. Depending on the nature and grade of the toxicity, and after assessing the risk/benefit ratio, a new dose for all participants may be initiated at a lower dose level.

Participants with an outcome of unconfirmed progressive disease, 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 either: 1) completion of the maximum number of cycles, 2) confirmed PD, 3) clinical deterioration suggesting that no further benefit from treatment is likely, 4) intolerability to therapy, or 5) the participant meets criteria for discontinuation of study therapy. 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 in settings where benefit/risk justify discontinuation of study therapy.

Dose Limiting Toxicities: For the purpose of guiding dose escalation, DLTs will be defined based on the incidence, intensity, and duration of adverse events (AEs) for which no clear alternative cause is identified. DLT period will be 28 days (4 weeks) in Part 1A and Part 1B and 42 days (6 weeks) in Part 1C.

For the purpose of participant management, any AE that meets DLT criteria, regardless of the cycle in which it occurs, will lead to discontinuation of study drug unless the investigator determines that 1 of the agents must be discontinued due to toxicity attributed to that agent alone. Participants experiencing a DLT will not be retreated with study drug,

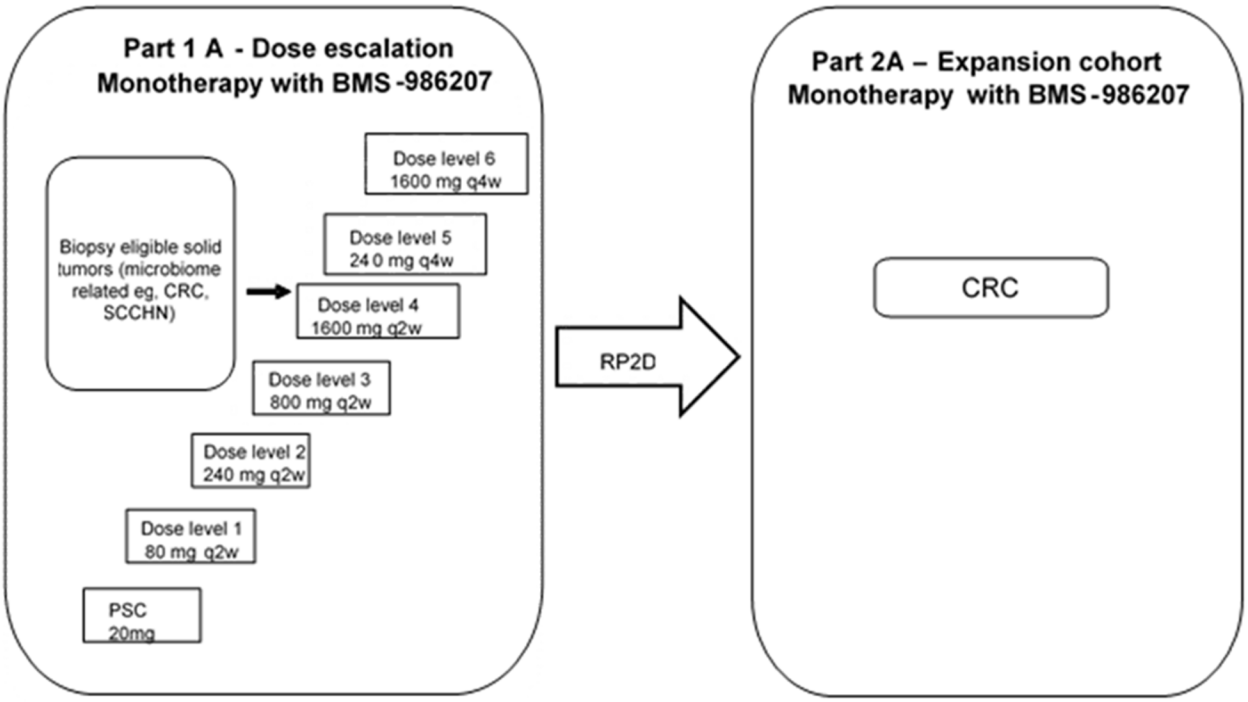
and will enter the safety follow-up period of the study. Following the last treatment with investigational product (IP), participants who withdraw from the study during the DLT evaluation interval for reasons other than a DLT may be replaced with a new participant at the same dose level.

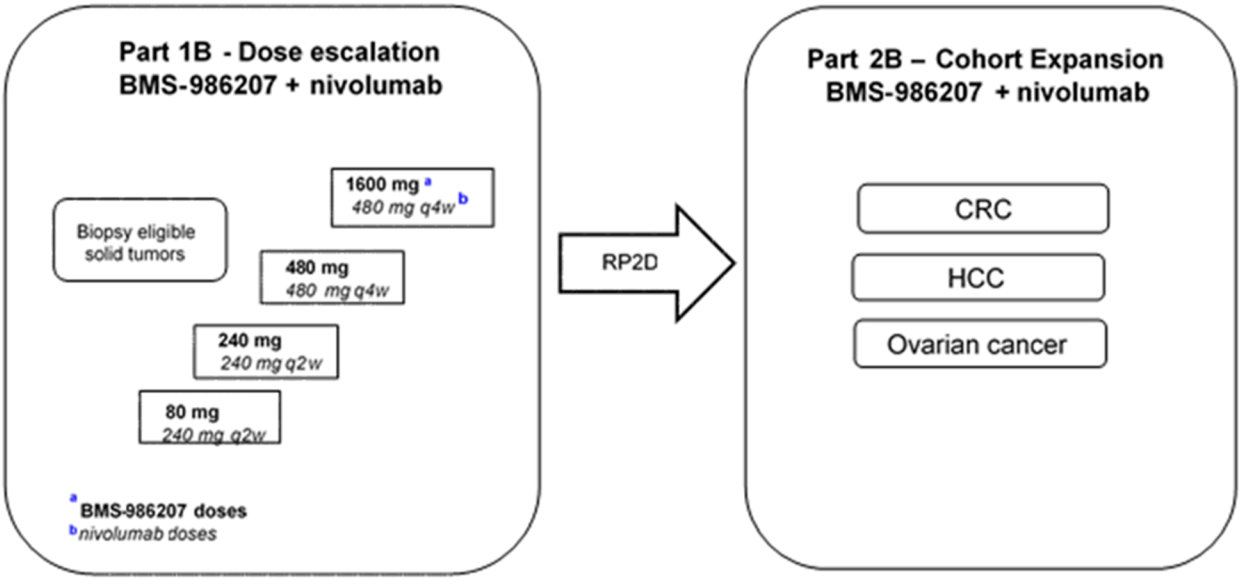
Treatment with Additional Cycles beyond 24 Weeks: Participants in Parts 1A, 1B, 2A, or 2B with ongoing disease control (CR, PR, SD) or unconfirmed progressive disease, and completing approximately 24 weeks of treatment, may be eligible for an additional 3 cycles of study therapy in both the monotherapy (Parts 1A and 2A) and combination therapy (Parts 1B and 2B) parts beyond the initial 24 weeks, at discretion of the Investigator and BMS Medical Monitor. Upon completion of 3 cycles of study therapy (or up to a maximum of 6 cycles if applicable), all participants will enter the safety follow-up period.

The cohort expansion phase of the study is shown in the figure below.

Schematic of Dose Escalation and Cohort Expansion Phases of the Study

Prior to initiating Part 1A (Monotherapy -Dose Escalation), a preliminary safety cohort will be tested in which a single participant will undergo an intra-participant dose escalation to establish safety over the 2- to 20-mg dose range of BMS-986207. Thereafter, standard dose escalation panels as monotherapy and combination therapy with nivolumab will proceed as described below.





Abbreviations: CRC, colorectal cancer; HCC, hepatocellular carcinoma; PSC, preliminary safety cohort; RP2D, recommended Phase 2 dose, q2w, every 2 weeks; q4w, every 4 weeks; SCCHN, squamous cell carcinoma of the head and neck.

FOLLOW-UP PERIODS

Safety Follow-up: After the end-of-treatment (EOT) visit, all participants will be evaluated for any new AEs for at least 100 days after the last dose of therapy. Follow-up visits will occur at Day 30, 60, and 100 (± 7 days) after the last dose or date of discontinuation.

Survival Follow-up: In parallel with the safety follow-up period, participants in Parts 1A, 1B, 2A and 2B will enter the survival follow-up period. Participants will be followed by telephone every 12 weeks from discontinuation of study drug/EOT visit for a period of 2 years, or until death, lost to follow-up, withdrawal of consent, or conclusion of the study, whichever comes first. Both the response and survival follow-up periods will occur simultaneously during the 2 year follow-up period. Radiological tumor assessments for participants who have ongoing clinical benefit may continue to be collected after participants complete the survival phase of the study. In Parts 1C and 2C, the survival follow-up period will continue for 2 years following the last dose of study drug or until death, lost to follow-up, withdrawal of consent, or conclusion of the study, whichever comes first. Survival follow-up visits will occur every 12 weeks (±7 days) until 2 years after the last dose of study drug.

Response Follow-up: Participants with SD, PR, or CR at the time of study drug discontinuation will continue to have radiologic and clinical tumor assessments every 12 weeks for the first year after discontinuation of study drug/EOT visit. Subsequently, they will continue to receive tumor assessment scans per standard-of-care guidelines, or, at a minimum, every 6 months up to 2 years following the last dose of study drug, or until disease progression or withdrawal of study consent.

Retreatment: Retreatment may be allowed for participants in Parts 1A, 1B, 2A, or 2B with disease progression during response follow-up. Participants completing approximately 3 cycles of study therapy (or up to a maximum of 6 cycles, if applicable), and entering the response follow-up with ongoing disease control (CR, PR, or SD), may be eligible for retreatment.

TREATMENTS ADMINISTERED

The description and storage information of the drugs used in this open-label study are shown in the table below.

Product Description Class and Dose Form	Potency	Blinding	Packaging Appearance	Storage Conditions (per label)
BMS-986207 for injection	160 mg/vial (20 mg/ml)	None	Vial	2 to 8°C. Protect from light and freezing.
Nivolumab (BMS-936558) solution for injection	100 mg/vial (10 mg/ml)	None	Vial	2 to 8°C. Protect from light and freezing.
Ipilimumab (BMS-734016) solution for injection	200 mg (5 mg/ml)	None	Vial	2 to 8°C. Protect from light and freezing.

In Parts 1A, 1B, 2A, and 2B, the initial treatment period is up to 24 weeks (3 cycles) of dosing and the number of 8-week cycles will depend on tumor assessment at each cycle. Following each treatment cycle, the decision to treat a participant with the next cycle of study therapy, up to a maximum of 48 weeks (6 cycles) of treatment, will be based on safety/benefit and tumor assessment. For Parts 1C and 2C, the treatment period is up to a maximum of 2 years in the absence of disease progression or unacceptable toxicity. Upon completion of these treatment, participants will enter a safety follow-up period.

Details of the dose escalation and cohort expansion phase in this study are given in the study design section and the schematic above. For Parts 1A, 1B, 2A and 2B intra-participant dose escalation/reduction of BMS-986207, nivolumab, or ipilimumab is not permitted in this study in order to allow better evaluation of the extended safety and efficacy at individual dose levels and schedules. For intra-participant dose reduction of BMS-986207 in Part 1C and 2C see Section 5.1.2.6 and Section 5.1.2.7, respectively.

Study treatment will be dispensed at the study visits. For participants on combination treatment, a 30-minute infusion of nivolumab will be followed by a 30-minute observation period, followed by a 60-minute infusion of BMS-986207, with a 60-minute observation period after all infusions in Cycle 1 for each participant. For participants < 42 kg receiving the 1600-mg dose of BMS-986207 or <38 kg receiving the 1200-mg dose of BMS-986207, the infusion time will be longer than 1 hour. For participants in Part 1C or Part 2C, a 30-minute infusion of nivolumab will be followed by a 30-minute observation period; followed by a 30-minute infusion of ipilimumab, a 30-minute observation period, and by a 60-minute infusion of BMS-986207.

Treatment Assignment: In this open-label study, no blinding will be required. Enrolled participants will be assigned sequential participant numbers via IRT starting with [redacted] (eg, [redacted]). Enrolled participants meeting the inclusion criteria will be eligible to be dosed. In the expansion phase only, participants with CRC will be randomized in a 1:1 manner to either BMS-986207 monotherapy or combination therapy with BMS-986207 and nivolumab to eliminate the possibility of enrollment bias.

STUDY ASSESSMENTS AND ANALYSES:

Safety Assessments: Safety assessments will be based on reported AEs and the measurement results of vital signs, ECGs, physical examinations, and clinical laboratory tests. AEs will be coded using the most current version of the 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 the last dose of BMS-986207 in the case of monotherapy, and the last dose of BMS-986207 and nivolumab, and the last dose of BMS-986207, nivolumab, and ipilimumab for combination therapy. A central/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 National Cancer Institute Common Terminology Criteria for Adverse Events v4.03.

PK Assessments: Pharmacokinetics of BMS-986207 will be derived from serum concentration versus time data. The pharmacokinetic parameters that will be assessed, following the intensive PK collection, are: maximum observed serum concentration (Cmax), time of maximum observed serum concentration (Tmax), area under the plasma concentration-time curve (AUC) from time zero to the time of the last quantifiable concentration (AUC[0-T]), AUC in 1 dosing interval (AUC[tau]), observed concentration at the end of a dosing interval (Ctau), total body clearance (CLT), average concentration over a dosing interval (Css-avg), accumulation index (AI), effective elimination half-life that explains the degree of accumulation observed for a specific exposure measure (T-HALFeff), [redacted]. Individual participant PK parameter values will be derived by noncompartmental methods by a validated PK analysis program. Actual times will be used for the analyses.

Immunogenicity Assessments: Serum samples for BMS-986207, [redacted] anti-drug antibody (ADA) will be collected from all participants at specified time points.

[redacted]

Efficacy Assessments: Efficacy assessments for the [redacted] activity of BMS-986207, alone, in combination with nivolumab, or in combination with nivolumab and ipilimumab will be based on tumor measurements, using RECIST v1.1, with computer tomography and/or magnetic resonance imaging, as appropriate, at baseline, every 8 weeks (± 1 week) for Parts 1A, 1B, 2A, and 2B or every 6 weeks for Part 1C and Part 2C during the treatment period, and every 12 weeks thereafter during the response follow-up period.

2. SCHEDULE OF ACTIVITIES

Study assessments and procedures are shown in Table 2-1, Table 2-2, Table 2-3, Table 2-4, Table 2-5, and Table 2-6.

Abbreviations used in the protocol are shown in Appendix 1.

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

If a subject has a delay in study drug administration for any reason, then assessments and laboratory tests (with the exception of any tests needed to ensure subject safety) should be correspondingly delayed with the exception of tumor assessments (see Table 2-2, Table 2-3, and Table 2-4) regardless of dosing delays).

Table 2-1: Screening - Schedule of Activities

Procedure	Screening Visit (Day -28 to -1)	Notes
Eligibility Assessments		
Informed Consent	X	A participant is considered enrolled only when a protocol-specific informed consent is signed.
IRT Participant Assignment	X	Following obtainment of consent, sites will use IRT for participant number assignment. Subsequent visits will be registered into IRT system for drug supply. See Section 5.1.1
Inclusion/Exclusion Criteria	X	See Sections 6.1 and 6.2
Medical History	X	Include any toxicities or allergy related to previous treatments
Prior Cancer Therapies	X	
Concomitant Medications	X	
ECOG Performance Status	X	
Safety Assessments		
PE	X	If the screening PE is performed within 72 hours prior to dose administration 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
ECGs	X	ECGs should be recorded after the participant has been supine for at least 5 minutes, and prior to blood draws. Screening ECG to be collected as a single reading (Section 9.4.3)
Laboratory Tests[a]	X	See Clinical Laboratory Assessments in Section 9.4.4 and Table 9.4.4-1
Urinalysis	X	Screening only; microscopic urine reflex only for urinalysis positive for blood/protein/leukocyte
Serology	X	Includes hepatitis C antibody, reflex HCV RNA viral load, hepatitis B surface antigen. HIV-1 and HIV-2 antibody should be tested if mandated by local requirement. **For HCC participants**: hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody, hepatitis B DNA PCR, hepatitis C antibody and hepatitis C RNA PCR, and hepatitis D antibody testing for those with concurrent hepatitis B infection. See Section 9.4.4 and Table 9.4.4-1.

Table 2-1: Screening - Schedule of Activities

Procedure	Screening Visit (Day -28 to -1)	Notes
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 taken within 24 hours of dosing (C1D1), a further pregnancy test is not required.
FSH	X	Women only, as needed to document postmenopausal status.
Adverse Event Reporting		
Assessment of Signs/Symptoms/ Clinical Complaints	X	All AEs (SAEs or non-serious AEs) associated with SARS-CoV-2 infection collected from time of onset.
Monitor for Serious Adverse Events	X	All SAEs must be collected from the date of participant's written consent until 100 days after discontinuation of dosing.
Tumor Assessments		
CT/MRI	X	Refer to Imaging Assessment details in Section 9.4.5
MRI Brain		MRI scan of the brain required at screening only if participant is symptomatic or has history of brain metastasis
Bone Scan		May be used to evaluate presence of metastatic lesions; should not be used as modality for assessment of measurable disease
Dispense Study Drug	X	Study drugs (BMS-986207, nivolumab, and ipilimumab [Parts 1C and 2C only]) to be supplied by BMS, and in assigned vials per IRT
[redacted]		

Table 2-1: Screening - Schedule of Activities

Procedure	Screening Visit (Day -28 to -1)	Notes
[redacted]		

Abbreviations: AE, adverse event; [redacted] BMS, Bristol-Myers Squibb; C, cycle; CLIA, Clinical Laboratory Improvements Amendments; CT, computed tomography; D, day; DNA, deoxyribonucleic acid; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; [redacted] FSH, follicle stimulating hormone; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; HIV, human immunodeficiency virus; IgG, immunoglobulin G; [redacted] IRT, Interactive Response Technology, MRI, magnetic resonance imaging; [redacted] PCR, polymerase chain reaction; PE, physical examination; RNA, ribonucleic acid; SAE, serious adverse events; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WOCBP, women of childbearing potential,

[a] There will be a 72 hour window at screening prior to C1D1 for the collection of laboratory tests,

[redacted]

Table 2-2: On Treatment - Schedule of Activities - q2w and q4w Dosing - Cycles 1 to 3 (Parts 1A, 1B, 2A, and 2B)

Procedure	Cycle 1								Cycles 2 to 3							EOT[a, b]
	D1	D2	D5	D8	D15	D22	D29	D43	D1	D2	D5	D8	D15	D29	D43	
Safety Assessments																
ECOG Performance Status	X															
PE	X								X							X
Symptom Directed PE				X	X	X	X	X					X	X	X	
Weight	X				X		X	X	X					X		
Vital Signs[c]	X			X	X	X	X	X	X				X	X	X	
Oxygen Saturation[c]	X				X											
ECGs[d]	X						X		X					X		X
Laboratory Tests[e]	X			X	X[k]	X	X	X[k]	X				X[k]	X	X[k]	
Urinalysis	As clinically indicated; microscopic urine reflex only for urinalysis positive for blood/protein/leukocyte esterase															
Pregnancy Test (WOCBP only)[f]	X				X		X	X	X				X	X	X	X
Adverse Event Reporting																
Monitor for Non-Serious Adverse Events (Appendices 3 and 4)	X	Non-Serious AEs will be collected starting with the first dose of study medication and through 100 days following last dose of study drug.														
Monitor for Serious Adverse Events (Appendices 3 and 4)	X	All SAEs must be collected from the date of the participant's written consent until 100 days following the last dose of study drug.														
Concomitant Medications	X				X		X	X	X				X	X	X	
Pharmacokinetic (PK) Assessments																
Serial Serum PK and Immunogenicity Sampling	See Table 9.5-2 and Table 9.5-3 of pharmacokinetic and immunogenicity sampling schedule and Section 9.5.															

Table 2-2: On Treatment - Schedule of Activities - q2w and q4w Dosing - Cycles 1 to 3 (Parts 1A, 1B, 2A, and 2B)

Procedure	Cycle 1								Cycles 2 to 3							EOT[a, b]
	D1	D2	D5	D8	D15	D22	D29	D43	D1	D2	D5	D8	D15	D29	D43	
Imaging Assessments																
CT/MRI[g]	Tumor imaging assessment to be performed q8w from baseline/screening ± 1 week[a]															
[redacted]																

Abbreviations: AE, adverse event; [redacted] BMS, Bristol Myers Squibb; C, cycle; D, day; [redacted] ECG; electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EOI, end of infusion; EOT, end of treatment; HCG, human chorionic gonadotrophin; IRT, Interactive Response Technology; IU, international units; MRI, magnetic resonance imaging; PE, physical examination; PK, pharmacokinetic; q2w, every 2 weeks; q4w, every 4 weeks, q8w, every 8 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event, WOCBP, women of childbearing potential.

[a] End of treatment (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, Cycle 3 Day 43) and the start of the safety follow-up period. For participants that 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), does not need to be repeated and will be considered the start of the safety follow-up period.

[c] For BMS-986207, vital signs will be obtained before the infusion and then every 15 minutes (± 5 minutes) until 60 minutes after completion of all infusions in Cycle 1; oxygen saturation to also be performed in conjunction with vital signs monitoring on these days. For nivolumab, vital signs will be obtained before the infusion and then every 30 minutes (± 10 minutes) until the start of BMS-986207 infusion or per institution guidelines for administration of nivolumab. The 30-minute post nivolumab infusion vital signs may correspond to the pre-infusion BMS-986207 vital signs. In the event BMS-986207 administration is delayed, nivolumab vital signs will be obtained until 60 minutes after completion of the 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. Obtainment of vital signs surrounding study drug administration(s) from Cycle 2 on as per institutional practice/Investigator discretion. For participants < 42 kg on the 1600 mg dose, the infusion time will be 90 minutes. Details of study drug preparation are found in the Pharmacy Manual, a document that will be provided separately to the site.

[d] 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 PK sampling, at predose, EOI, and 4-hr post dose, on day 1 of both C1 and C2 for dose escalation phase only (see Table 9.5-2). Single safety ECGs to be done on Day 1 and Day 29 of all treatment cycles where ECG not performed in conjunction with PK sampling.

[e] There will be a 72-hour window for collection of all laboratory tests. See Section 9.4.4 and Table 9.4.4-1.

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

[g] Same imaging modality to be used for all assessments, per RECIST v1.1 (Appendix 5). Tumor assessment to be performed prior to initiating next cycle of treatment. Unconfirmed PR/CR must be confirmed at least 4 weeks after initial assessment finding (Section 9.4.5)

[k] Pregnancy testing on D15 and D43 time points only for q2w dosing.

Table 2-3: On Treatment - Schedule of Activities - q2w and q4w Dosing - Cycles 4-6 (Parts 1A, 1B, 2A, and 2B)

Procedure	Cycles 4, 5 and 6					EOT[a, b]
	D1	D8	D15	D29	D43	
Safety Assessments						
PE	X					X
Symptom Directed PE			X	X	X	
Weight	X			X		
Vital Signs[c]	X		X	X	X	
ECGs[d]	X			X		X
Laboratory Tests[e]	X		X	X	X	
Urinalysis	As clinically indicated; microscopic urine reflex only for urinalysis positive for blood/protein/leukocyte esterase					
Pregnancy Test (WOCBP only)[f]	X		X[i]	X	X[i]	X
Adverse Event Reporting						
Monitor for Non-Serious Adverse Events (Appendices 3 and 4)	Non-Serious AEs will be collected starting with the first dose of study medication and through 100 days following last dose of study drug.					
Monitor for Serious Adverse Events (Appendices 3 and 4)	All SAEs must be collected from the date of the participant's written consent until 100 days following the last dose of study drug.					
Concomitant Medications	X		X	X	X	
Pharmacokinetic (PK) Assessments						
Serial Serum PK and Immunogenicity Sampling	See Table 9.5-2 and Table 9.5-3 of pharmacokinetic and immunogenicity sampling schedule and Section 9.5.					
[redacted]						

Table 2-3: On Treatment - Schedule of Activities - q2w and q4w Dosing - Cycles 4-6 (Parts 1A, 1B, 2A, and 2B)

Procedure	Cycles 4, 5 and 6					EOT[a, b]
	D1	D8	D15	D29	D43	
Imaging Assessments						
CT/MRI[g]	Tumor imaging assessment to be performed q8w from baseline/screening ± 1 week[b]					
Clinical Drug Supplies						
BMS-986207 and Nivolumab Infusion [h]	X		X	X	X	
BMS-986207 and Nivolumab Infusion [h]	X			X		

Abbreviations: AE, adverse event; BMS, Bristol Myers Squibb; CR, complete response; CT, computed tomography; D, day; ECG; electrocardiogram; EOT, end of treatment; HCG, human chorionic gonadotropin; IRT, Interactive Response Technology; IU, international unit; MRI, magnetic resonance imaging; PE, physical examination; PK, pharmacokinetic; PR, partial response; q2w, every 2 weeks; q4w, every 4 weeks; q8w, every 8 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event; WOCBP, women of childbearing potential.

[a] End of treatment (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, Cycle 3 Day 43) and the start of the safety follow-up period. For participants that 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), does not need to be repeated and will be considered the start of the safety follow-up period.

[c] Obtainment of vital signs surrounding study drug administration(s) from Cycle 2 on as per institutional practice/Investigator discretion.

[d] ECGs should be recorded after the participant has been supine for at least 5 minutes, and prior to blood draws. Single safety ECGs to be done on Day 1 and Day 29 of all treatment cycles where ECG not performed in conjunction with PK sampling.

[e] There will be a 72-hour window for collection of all laboratory tests. See Section 9.4.4 and Table 9.4.4-1.

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

[g] Same imaging modality to be used for all assessments, per RECIST v1.1 (Appendix 5). Tumor assessment to be performed prior to initiating next cycle of treatment. Unconfirmed PR/CR must be confirmed at least 4 weeks after initial assessment finding (Section 9.4.5)

[h] Study drugs, BMS-986207 and nivolumab, to be supplied by BMS; vials assigned by IRT should be used. In limited instances, scheduled drug administration can occur outside of the indicated timeframes but the Sponsor should always be notified first.

[i] Pregnancy testing on D15 and D43 time points only for q2w dosing.

[redacted]

Table 2-4: On Treatment- Schedule of Activities -Triplet Cohort (Part 1C) and Triplet NSCLC Expansion (Part 2C)

Procedure	Cycle 1 Visit Window = -3 Days for C1D1, ± 3 Days for All Others						Each Subsequent Cycle			
	D1	D8	D15	D22	D29	D36	D1 (± 3 Days)	D22 (± 3 Days)	EOT	Notes 1 Cycle = 6 weeks
Safety Assessments										
PE	X						X		X	
Physical Measurements	X			X			X	X		See Appendix 8: For C1D21 and each subsequent cycle D1 and D21 weight only
Symptom-directed PE		X	X		X	X				To include signs and symptoms
Vital Signs and Oxygen Saturation	X	X	X	X	X	X	X	X		
ECGs	X						X		X	ECGs should be recorded after the participant has been supine for at least 5 minutes, and prior to blood draws. Single safety ECGs to be done on Day 1 of all treatment cycles.
Adverse Event Assessments	Continuously during the study									All SAEs must be collected from the date of the participant's written consent until 100 days following the last dose of study drug. All AEs (including SAEs and non-serious AEs), including those associated with SARS-CoV-2 infection, must be collected continuously during the treatment period.
Review of Concomitant Medications	X	X	X	X	X	X	X	X	X	

Table 2-4: On Treatment- Schedule of Activities -Triplet Cohort (Part 1C) and Triplet NSCLC Expansion (Part 2C)

Procedure	Cycle 1 Visit Window = -3 Days for C1D1, ± 3 Days for All Others						Each Subsequent Cycle			
	D1	D8	D15	D22	D29	D36	D1 (± 3 Days)	D22 (± 3 Days)	EOT	Notes 1 Cycle = 6 weeks
Pregnancy Test (WOCBP only)	X			X			X	X	X	For WOCBP; serum/urine pregnancy test to be performed (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG), see Section 9.2.5.
ECOG Performance Status	X						X			Confirm status prior to randomization and on C1D1
Laboratory Assessments										
Chemistry and hematology tests	X			X			X	X		Within 72 hrs prior to dosing. See 9.4.4 and Table 9.4.4-1.
[redacted]										

Table 2-4: On Treatment- Schedule of Activities -Triplet Cohort (Part 1C) and Triplet NSCLC Expansion (Part 2C)

Procedure	Cycle 1 Visit Window = -3 Days for C1D1, ± 3 Days for All Others						Each Subsequent Cycle			
	D1	D8	D15	D22	D29	D36	D1 (± 3 Days)	D22 (± 3 Days)	EOT	Notes 1 Cycle = 6 weeks
[redacted]										
Efficacy Assessments										
Body Imaging	Contrast enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease should occur every 6 weeks starting from date of first dose (± 7 days) for the first 12 months (week 48), then every 12 weeks (± 7 days) until the end of year 2, then every 12 weeks (± 14 days) thereafter until disease progression or treatment discontinuation, whichever occurs later. See Section 9.1 and Section 5.1.4 for further details.									
Brain Imaging	Participants with a history of brain metastasis or symptoms should have a surveillance MRI study per standard of care (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 for further details.									
Pharmacokinetic (PK) and Immunogenicity Assessments										
PK and Immunogenicity Samples	See Section 9.5 and Table 9.5-4.									
Clinical Drug Supplies										
IWRS Vial Assignment	X			X			X			Within 1 day prior to dosing
Study Drug Treatments										
BMS-986207	X			X			X	X		BMS-986207 to be administered q3W. For participants < 38 kg on the 1200 mg dose, the infusion time will be longer than 1 hour (approximately 90 minutes). For participants with a bodyweight of > 250 kg the dosing of BMS-986207 will occur the

Table 2-4: On Treatment- Schedule of Activities -Triplet Cohort (Part 1C) and Triplet NSCLC Expansion (Part 2C)

Procedure	Cycle 1 Visit Window = -3 Days for C1D1, ± 3 Days for All Others						Each Subsequent Cycle			
	D1	D8	D15	D22	D29	D36	D1 (± 3 Days)	D22 (± 3 Days)	EOT	Notes 1 Cycle = 6 weeks
										day after dosing of nivolumab and ipilimumab when these drugs are administered on the same day (ie, D2 and D22 of each cycle).Details of study drug preparation are found in the Pharmacy Manual.
Nivolumab	X			X			X	X		Nivolumab to be administered q3W
Ipilimumab	X						X			Ipilimumab to be administered q6W

Abbreviations: AE, adverse event; BMS, Bristol-Myers Squibb; C, cycle; CT, computed tomography; D, day; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; EOT, end of treatment; hCG, human chorionic gonadotropin [redacted] IU, international units; IWRS, Interactive Web Response System, MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; PE, physical exam; PK, pharmacokinetics; q3w, every 3 weeks; q6w, every 6 weeks; SAE, serious adverse events; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WOCBP, women of childbearing potential

NOTES:

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

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

Table 2-5: Follow-up Procedural Outline (All Participants)

Procedure	Safety Follow-up			Survival Follow-up	Response Follow-up[a]	
	Follow-up 1 30 Days[b] (± 7 days)	**Follow-up 2 60 Days (± 7 days)**	**Follow-up 3 100 Days (± 7 days)**	**All Participants - Commence with Start of Safety Follow-up: Follow-up Every 12 Weeks until 2 Years After LAST Dose of Study Drug**	**Commences with Start of Safety Follow-up: Follow-up Done Every 12 Weeks for 1 Year After LAST Dose of Study Drug**	**Notes**
Safety Assessments						
Physical Examination	X	X	X			
Vital Signs	X	X	X			Includes body temperature, seated/supine blood pressure, and heart rate.
Laboratory Tests[c]	X	X	X			Lab tests also as clinically indicated; See laboratory assessments in Section 9.4.4 and Table 9.4.4-1
Urinalysis	As clinically indicated. See Section 9.4.4					
Pregnancy Test	X	X	X			For WOCBP; serum/urine pregnancy test to be performed (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG), (Section 9.2.5.
Adverse Event Reporting and Concomitant Medication Assessments						
Monitor for Non-Serious Adverse Events	X	X	X			Non-Serious AEs will be collected starting with the first dose of study medication and through 100 days after discontinuation of dosing (Appendices 3 and 4).

Table 2-5: Follow-up Procedural Outline (All Participants)

Procedure	Safety Follow-up			Survival Follow-up	Response Follow-up[a]	
	Follow-up 1 30 Days[b] (± 7 days)	**Follow-up 2 60 Days (± 7 days)**	**Follow-up 3 100 Days (± 7 days)**	**All Participants - Commence with Start of Safety Follow-up: Follow-up Every 12 Weeks until 2 Years After LAST Dose of Study Drug**	**Commences with Start of Safety Follow-up: Follow-up Done Every 12 Weeks for 1 Year After LAST Dose of Study Drug**	**Notes**
Monitor for Serious Adverse Events	X	X	X			All SAEs must be collected from the date of the participant's written consent until 100 days post discontinuation of dosing. Participants will be followed for all SAEs and all AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection until resolution, the condition stabilizes, the event is otherwise explained, the event is deemed irreversible, the participant is lost to follow-up (as defined in Section 8.3), or for suspected cases, until SARS-CoV-2 infection is ruled-out.
Concomitant Medication Assessments	X	X	X			

Table 2-5: Follow-up Procedural Outline (All Participants)

Procedure	Safety Follow-up			Survival Follow-up	Response Follow-up[a]	
	Follow-up 1 30 Days[b] (± 7 days)	Follow-up 2 60 Days (± 7 days)	Follow-up 3 100 Days (± 7 days)	All Participants - Commence with Start of Safety Follow-up: Follow-up Every 12 Weeks until 2 Years After LAST Dose of Study Drug	Commences with Start of Safety Follow-up: Follow-up Done Every 12 Weeks for 1 Year After LAST Dose of Study Drug	Notes
[redacted]						
Pharmacokinetic (PK) Assessments						
Serial Serum PK and Immunogenicity Sampling	See Table 9.5-2 and Table 9.5-3 for pharmacokinetic and immunogenicity sampling schedule and Section 9.5.					
[redacted]						
Efficacy Assessments						
Tumor/Response Assessments			X		X	Contrast enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease should occur every 8 weeks (6 weeks for Parts 1C and 2C) starting from date of first dose (± 7 days) for the first 12 months (week 48), then every 12 weeks (± 7

Table 2-5: Follow-up Procedural Outline (All Participants)

Procedure	Safety Follow-up			Survival Follow-up	Response Follow-up[a]	
	Follow-up 1 30 Days[b] (± 7 days)	Follow-up 2 60 Days (± 7 days)	Follow-up 3 100 Days (± 7 days)	All Participants - Commence with Start of Safety Follow-up: Follow-up Every 12 Weeks until 2 Years After LAST Dose of Study Drug	Commences with Start of Safety Follow-up: Follow-up Done Every 12 Weeks for 1 Year After LAST Dose of Study Drug	Notes
						days) until the end of year 2, then every 12 weeks (± 14 days) thereafter until disease progression or treatment discontinuation, whichever occurs later. See Section 9.1 for further details.
Brain Imaging					X	As clinically indicated
Bone Scan					X	As clinically indicated
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.

Abbreviations: AE, adverse event; CR, complete response; CT, computed tomography; EOT, end of treatment; hCG, human chorionic gonadotropin; [redacted] IU, international units; MRI, magnetic resonance imaging; PK, pharmacokinetic; PR, partial response;; SAE, serious adverse event; SARS-CoV 2, severe acute respiratory syndrome coronavirus-2; SD, stable disease; WOCBP, women of childbearing potential.

[a] Only participants with SD, PR, or CR at EOT visit. After first year of response follow-up, participants will continue to receive tumor assessment scans as per standard-of-care guidelines, or at a minimum of every 6 months for a total of 2 years response follow-up after the last dose of study drug.

[b] Follow-up visits at Days 30, 60 (± 7days), and 100 (± 10days) should occur relative to the last dose of study drug or date of discontinuation.

[c] For details of laboratory tests, see Section 9.4.4 and Table 9.4.4-1.

[redacted]

Table 2-6: Retreatment Day 0 Procedural Outline (Parts 1A, 1B, 2A, 2B only)

Procedure	Day 0[a,b]	Notes
Eligibility Assessments	X	Participants must meet eligibility criteria and discussion with BMS Medical Monitor should occur.
Safety Assessments		
Physical Examination	X	If the screening physical examination is performed within 72 hours of dosing on re-treatment Cycle 1/ Day 1, then a single examination may count as both the screening and predose evaluations.
ECOG Performance Status	X	
Physical Measurements	X	Weight only
Vital Signs and Pulse Oximetry	X	Includes body temperature, respiratory rate, seated/supine blood pressure, and heart rate. Blood pressure, respiratory rate, and heart rate should be measured after the participant has been seated quietly for at least 5 minutes.
Laboratory Tests[c]	X	**Laboratory tests must be completed within 2 weeks of retreatment Cycle 1/Day 1 unless otherwise noted.** For laboratory assessments, see Section 9.4.4 and Table 9.4.4-1
Urinalysis	X	See Section 9.4.4
Serology Tests	X	Repeat the following if > 6 months since last treatment: serum for hepatitis C antibody, hepatitis B surface antigen, HIV-1 and HIV-2 antibody (screening, and as mandated by local requirement), and hepatitis C RNA (reflex). **For HCC participants**: hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody, hepatitis B deoxyribonucleic acid (DNA) polymerase chain reaction (PCR), hepatitis C antibody, and hepatitis C ribonucleic acid (RNA) PCR and hepatitis D antibody testing for those with concurrent hepatitis B infection.
Thyroid Function Tests	X	TSH with free T3 and free T4 (reflex only)
[redacted]		
Serial Serum PK Sampling		PK/ADA sampling to be done at predose on Day 1 of all cycles; @ EOT and 30 and 60 day followup visits. PK sampling to be performed w/SAEs, with addition of ADA if suspected hypersensitivity reaction. No dose delay PK sampling to be done in Retreatment.
Serum Pregnancy Test	X	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 retreatment provided results are available prior to starting study therapy. If pregnancy test taken within 24 hours of dosing (retreatment C1D1), a further pregnancy test is not required.

Table 2-6: Retreatment Day 0 Procedural Outline (Parts 1A, 1B, 2A, 2B only)

Procedure	Day 0[a,b]	Notes
[redacted]		
FSH	X	Women only, as needed to document postmenopausal status
Efficacy Assessments		
Tumor Assessments	X	CT with contrast is the preferred modality (MRI if CT is not feasible). Previous CT scan within 28 days can be used for this timepoint.
Brain Imaging	X	Brain imaging (CT/MRI) for participants with history or symptoms of brain metastases and who have not had brain imaging within 30 days of anticipated first retreatment dose.
Bone Scan	X	As clinically indicated (eg, participants with history or symptoms of bone metastases), but bone scans will not be considered a modality for the assessment for measurable disease.
Clinical Drug Supplies		
Participant Registration for Retreatment via IRT	X	Ensure participant continues to meet eligibility for protocol treatment.

Abbreviations:; ADA, antidrug antibody; BMS, Bristol Myers Squibb; C1D1, Cycle 1 Day 1; CT, computed tomography DNA, deoxyribonucleic acid; ECOG, Eastern Cooperative Oncology Group; EOT, end of treatment; FSH, follicle stimulating hormone; HCC, hepatocellular carcinoma; HIV, human immunodeficiency virus; IRT, Interactive Response Technology; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; PK, pharmacokinetic; RNA, ribonucleic acid; SAE, serious adverse event;TSH, thyroid stimulating hormone; T3, triiodothyronine; T4, thyroxine; WOCBP, women of child bearing potential.

[a] All procedures for retreatment eligibility will be performed within 28 days prior to retreatment Cycle 1/Day 1 dosing.

[b] All participants entering retreatment will follow the same time and events table as previously assigned. Limited PK/[redacted] samples will be collected.

[c] For details of laboratory tests, see Section 9.4.4 and Table 9.4.4-1.

[redacted]

3. INTRODUCTION

This is a Phase 1/2a, first-in-human (FIH), dose escalation study of BMS-986207, an anti-T cell immunoglobulin (Ig) and immunoreceptor tyrosine-based inhibitory motif (ITIM) domain (TIGIT) monoclonal antibody (mAb), alone, in combination with nivolumab (anti-programmed cell death 1 [PD-1]), and in combination with nivolumab and ipilimumab (anti-cytotoxic T-lymphocyte associated protein 4 [CTLA-4] antibody) in humans with advanced solid tumors.

3.1 Study Rationale

Antibody-based therapy for cancer is well established and constitutes an important strategy for the treatment of patients with hematological malignancies and solid tumors. [1] In addition to the targeting of antigens involved in cancer cell proliferation and survival, antibodies can function either to activate or antagonize immunological pathways involved in cancer immune surveillance. The anti-cancer, antigen-specific immune response is the result of a complex dynamic interplay between antigen-presenting cells, T-lymphocyte cells, and the target cancer cells.[2] The critical balance of T cell activity that dictates whether endogenous anti-cancer immune responses will be effective is thought to be controlled by antigen-specific stimuli sensed by the T cell receptor and by the combined activity of both positive (co-stimulatory) and negative (co-inhibitory) T cell surface molecules.[3] Within the past decade, antibodies against these key receptors have been designed and evaluated in the clinic with encouraging results, heralding the onset of immunotherapy as a key pillar of anti-cancer therapy.[4]

Tumors modulate and evade the host immune response through a number of mechanisms, including down regulation of tumor-specific antigen expression and presentation, secretion of anti-inflammatory cytokines, and upregulation of inhibitory ligands. Immunotherapeutic approaches such as checkpoint pathway blockade have demonstrated clinical efficacy in several cancers, including melanoma, renal cell, lung, and hormone-refractory prostate cancers. [5] Following the success of CTLA-4 and anti-PD-1 pathway-targeted agents in several cancers, the field of tumor immunotherapy is rapidly expanding, recognizing the potential value of combination therapies.[6]

TIGIT is a 26-kDa type I transmembrane immunoglobulin superfamily member with a single extracellular IgV domain, an intracellular domain containing immunoglobulin tail tyrosine motif and ITIM, and a growth factor receptor-bound protein binding site. In healthy individuals, TIGIT is expressed on a subset of memory CD4+ and CD8+ T cells and on the majority of regulatory T cells (Tregs) and NK cells. In the settings of chronic viral infections and cancer, TIGIT is strongly upregulated on CD8+ T cells and has been associated with other [redacted] of T cell exhaustion, including PD-1, CTLA-4, lymphocyte-activation gene 3 (LAG-3), and T cell immunoglobulin and mucin domain-containing-3 (TIM-3).[7,8] In human tumors, TIGIT is expressed on the majority of tumor-infiltrating Tregs and CD8+ T cells, and to a lesser extent on CD4+ T effectors.[8]

TIGIT ligands poliovirus receptor (PVR) and Nectin-2 are highly expressed on many tumors and tumor-infiltrating myeloid cells, and likely contribute to the immunosuppressive tumor

microenvironment. Upon ligand engagement, TIGIT can partially suppress T cell and natural killer (NK) cell activation. [9] Furthermore, TIGIT agonism leads to Treg stabilization and increased interleukin 10 production by Tregs.[10,11] TIGIT competes for ligand binding with costimulatory receptor DNAX accessory molecule 1 (DNAM-1, also CD226), which has been shown to be involved in tumor immune surveillance, and TIGIT co-expression on the cell surface has been linked to decreased DNAM-1 signaling.[8,12]

In ex vivo experiments using peripheral blood mononuclear cells (PBMC) from melanoma patients, antibody blockade of TIGIT/PVR interaction on tumor antigen-stimulated CD8+ T cells resulted in increased proliferation and cytokine production. This activity was further enhanced when combined with PD-1 blockade.[13]Comparable studies were conducted using PBMC from human immunodeficiency virus (HIV) positive patients with similar results.[14] Studies at BMS have shown that TIGIT blockade on NK cells results in increased activation and lysis of PVR-expressing tumor cells in a DNAM-1 expression dependent manner. BMS-986207, a fully human anti-TIGIT mAb, was designed with an inert isotype (termed IgG1.1) to eliminate fragment crystallizable region (Fc) effector function, which is intended to increase anti-tumor immune response by decreasing inhibitory signals and allowing increased DNAM-1 co-stimulation on intra-tumoral CD8+ T cells. Based on preclinical models, blockade of PD1/programmed death-ligand 1 (PD-L1) pathway is expected to enhance or synergize with TIGIT blockade.

The purpose of this study is to evaluate the safety, tolerability, and preliminary efficacy of intravenous (IV) doses of BMS-986207, administered as monotherapy, in combination with nivolumab, and as of Protocol Amendment 03, in combination with nivolumab and ipilimumab, in participants with advanced solid tumors. This study will also determine the maximum tolerated dose (MTD)/recommended Phase 2 dose (RP2D) of BMS-986207 to be used in future monotherapy and combination studies. Further details on the scientific rationale for the study design are presented in Section 5.4.

BMS-986207 was well tolerated as monotherapy and in combination with nivolumab.[19] Preliminary data from the CA020002 study have, thus far, shown some clinical benefit in participants with melanoma (2 participants with partial response [PR]) and prostate cancer (1 participant with PR) when BMS-986207 was combined with nivolumab. No clinical benefit was observed in any participants who received BMS-986207 monotherapy (unpublished results).

Other tumor types in this study included colorectal cancer (CRC), ovarian, breast, gastric, and urothelial cancer.

Recently, reports in the literature have shown comparable efficacy results with anti-TIGIT agents in combination with anti-PD-(L)1 agents, pembrolizumab and atezolizumab, in most tumor types.[15,16] Best responses, however, were observed in those studies in 1L and previously treated NSCLC participants whose tumors expressed PD-L1. A randomized Phase 2 study comparing the anti-TIGIT agent tiragolumab plus atezolizumab versus placebo plus atezolizumab in PD-L1-positive 1L Stage IV NSCLC patients demonstrated improvement in the overall response rate (ORR; 37% vs. 21% with atezolizumab alone). The treatment regimen was well tolerated, with safety similar to that seen in the placebo plus atezolizumab treatment (see Section 5.4.4 for more details).[16] In addition, recent data presented from a Phase 1 study (NCT02964013) of the anti-TIGIT antibody vibostolimab plus pembrolizumab in participants with anti-PD-(L)1-naive NSCLC demonstrated anti-tumor activity (ORR 29% and 46% in patients with PDL1-positive disease).[17] These data suggest that combining anti-TIGIT with anti-PD-(L)1 can be safe, tolerable, and have clinical benefits in PD-L1-positive 1L NSCLC patients.[17]

As of 20-Oct-2021, the safety profile of BMS-986207 1200 mg Q3W in combination with nivolumab 360 mg Q3W and ipilimumab 1 mg/kg Q6W has been evaluated in 6 subjects with multiple metastatic solid tumors in CA020002 Part 1C. Of the 4 dose-limiting toxicity (DLT)-evaluable participants, 2 participants reported DLTs (Grade 3 encephalitis and Grade 3 bullous dermatitis [n = 1 each]). Per Bayesian optimal interval (BOIN) design, in all the remaining and future subjects, BMS-986207 was de-escalated to a lower dose (600 mg Q3W). For details, see Section 3.2.1.4.

The combination of nivolumab +/- ipilimumab is approved in 17 countries as 1L treatment for patients with metastatic non-small cell lung cancer (NSCLC) expressing PD-L1 ≥ 1% (eg, United States, Canada, etc.) or both PD-L1 ≥ 1% and < 1% (e.g. Japan, Argentina). This regimen is also recommended by the European Society for Medical Oncology and National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology as a 1L treatment option for metastatic NSCLC regardless of PD-L1 expression.[18] Data from BMS CheckMate 227, a randomized, open-label Phase 3 study in participants with treatment-naive NSCLC, demonstrated that the combination of nivolumab plus ipilimumab was safe and tolerable and improved overall survival (OS) compared to chemotherapy alone (PD-L1 ≥ 1% overall survival [OS] 29% vs. 18%, hazard ratio [HR] 0.76; 95% confidence interval [CI]: 0.65 to 0.90).[33] Thus, the nivolumab and ipilimumab combination is an appropriate backbone for exploring the effects of BMS-986207 in PDL1-positive 1L NSCLC. Using this triplet combination in NSCLC participants allows the combination of a checkpoint inhibitor-responsive patient population (NSCLC) with a checkpoint inhibitor combination (nivolumab + ipilimumab) that has been demonstrated to work as an appropriate therapy for this patient population.

In the present study, to further evaluate whether TIGIT inhibition together with cancer immunotherapies can enhance [redacted] immune activity, the safety of this triplet combination will be tested in a small group of participants across all tumor types. Once safety is established,

1L NSCLC participants whose tumor cells express ≥ 1% PD-L1 will be treated with BMS-986207 plus nivolumab and ipilimumab.

It is anticipated that anti-TIGIT antibody (BMS-986207), administered as a single agent, in combination with anti-PD1 antibody (nivolumab), or in combination with nivolumab and anti-CTLA-4 antibody (ipilimumab) will demonstrate adequate safety and tolerability, as well as a favorable risk/benefit profile, to support further clinical testing. No prospective hypotheses are being formally evaluated.

3.2 Background

3.2.1 BMS-986207

BMS-986207 is a fully human immunoglobulin G1 (IgG1) mAb that binds with high affinity to TIGIT (T cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain), a negative regulatory molecule that suppresses activation and functional responses in T cells and NK cells. The antibody is engineered to negate Fc gamma receptor (FcγR) binding by the introduction of 5 specific amino acid mutations. TIGIT upregulation has been observed in cancer patients, in particular on T cells and is co-expressed with [redacted] of T cell exhaustion. Binding of PVR and Nectin-2 (TIGIT ligands) to TIGIT results in suppression of T cell and NK cell function. Blockade of TIGIT therefore may increase the immune anti-tumor response both by removing the suppressive signal emanating from TIGIT as well as by freeing its ligands to bind to the stimulatory receptor CD226 (DNAM-1), which shares these ligands. BMS-986207 blocks interaction of TIGIT with its ligands and thereby may induce or enhance anti-tumor immune responses.

3.2.1.1 Nonclinical Pharmacology

BMS-986207 binds recombinant TIGIT with an equilibrium dissociation constant (K_D) of [redacted] and to cell surface TIGIT on activated CD8+ T cells with a half-maximal effective concentration (EC50) of [redacted]. The antibody binds to recombinant cynomolgus monkey TIGIT with and EC50 of [redacted] and to activated cynomolgus monkey CD8+ T with an EC50 of [redacted] BMS-986207 inhibits the binding of PVR and Nectin-2 to TIGIT in a dose-dependent manner with an EC50 of [redacted]. BMS-986207 blocked the inhibitory activity of TIGIT/PVR interaction in a Jurkat cell line reporter assay, a T cell peptide stimulation assay, and an NK cell redirected lysis assay. In the Jurkat and NK cell assays, TIGIT blockade alone resulted in increased nuclear factor-kappa-B (NF-κB) luciferase signals and increased lysis of target cells, respectively. In the T cell peptide stimulation assay, the effect of TIGIT blockade was strongest when combined with PD-1 blockade, and resulted in increased interferon gamma (IFNγ) secretion and an elevated percentage of IFNγ–producing T cells.

Due to its engineered inert Fc region, as expected, BMS-986207 does not induce antibody-dependent cellular cytotoxicity (ADCC)- or antibody-dependent cellular phagocytosis (ADCP)-mediated killing of TIGIT-expressing target cells. In addition, BMS-986207 does not bind complement 1q (C1q). Based on these findings, BMS-986207-induced depletion of TIGIT-expressing cells is not expected. BMS-986207 showed no unexpected binding in 8 cynomolgus

tissue types tested. Additionally, BMS-986207 did not mediate spontaneous cytokine secretion at detectable levels in fresh whole blood samples from 8 normal human donors. These data suggest that BMS-986207 treatment does not lead to cytokine release syndrome (CRS) in whole blood.

A number of mouse studies were undertaken to examine the role of TIGIT blockade in tumor settings. An MC38 colon adenocarcinoma murine tumor study in PD-1/TIGIT double knockout (KO) mice suggested dual blockade of TIGIT and PD-1 may be beneficial in the treatment of cancer through enhanced antitumor immunity. PD-1/TIGIT double KO mice showed superior tumor rejection as compared to the other groups. There were no tumor-free mice in the groups of TIGIT KO mice or wild-type mice. In the CT26 colon murine tumor model and the A20 B cell lymphoma murine model, TIGIT blockade with a surrogate antibody in combination with PD-1 blockade or CTLA-4 by surrogate antibodies resulted in anti-tumor responses. In these models, the combination of PD-1 blockade or CTLA-4 blockade with TIGIT blockade resulted in a greater number of tumor-free mice than either agent alone.

The in vitro and in vivo data indicating that TIGIT blockade can enhance T cell and NK cell activation, and that TIGIT blockade (together with PD-1 or CTLA-4 blockade) enhances anti-tumor immune activity, support the development of BMS-986207 for the treatment of cancer.

3.2.1.2 Nonclinical Pharmacokinetics

The pharmacokinetics (PK) of BMS-986207 were evaluated in cynomolgus monkeys in 2 studies [redacted] Following a single IV dose of 1, 10, and 100 mg/kg [redacted] or 0.5 and 3 mg/kg [redacted] BMS-986207 serum concentrations exhibited biexponential decline, dose-proportional increase in systemic exposure, low total body serum clearance ([redacted]), low volume of distribution at steady-state [redacted] and long apparent half-life [redacted] The Vss is similar to the reported plasma volume in monkeys, indicating limited extravascular distribution. The presence of anti-drug antibodies (ADAs) was observed in all except 1 monkeys. Anti-drug-antibodies were detected as early as Day 7 and their appearance appeared to correlate with an accelerated decline in BMS-986207 serum concentrations.

In mice, a dose dependent tumor efficacy was observed with a combination of 10A7-mIgG1 D265A (anti-mouse TIGIT with a D265A mutated inert mIgG1 isotype; the surrogate antibody for BMS-986207) and 4H2-mIgG1 D265A (mAb to mouse PD-1 Clone 4H2, isotype mouse IgG1-D265A); either antibody had little or no tumor efficacy. Therefore, PK of 10A7-mIgG1 D265A in combination with 4H2-mIgG1 D265A were evaluated in mice. After multiple intraperitoneal (IP) doses of 10A7-mIgG1 D265 (10 mg/kg) alone or in combination with anti-mPD-1-mIgG1 D265A (7.5 mg/kg) at 0.3, 1, and 3 mg/kg to female BALB/c mice bearing CT26 tumors, 10A7-mIgG1 D265A exhibited a dose-proportional increase in exposure. Fitting the exposures to a 1-compartment PK model with an absorption compartment yielded an estimated apparent CLTs [redacted].

3.2.1.3 Nonclinical Toxicology

The nonclinical safety of BMS-986207 was evaluated in vitro in a human tissue cross-reactivity study and cytokine release and lymphocyte activation assays with human cells, and in an in vivo

1-month intermittent repeat-dose IV toxicity study in cynomolgus monkeys. The cynomolgus monkey was selected as the toxicology species because BMS-986207 binds to TIGIT expressed on activated cynomolgus monkey T cells with a similar affinity as TIGIT expressed on activated human T cells [redacted] and is pharmacologically active in monkeys; it does not bind rodent TIGIT.

In a Good Laboratory Practice (GLP)-compliant tissue cross-reactivity study in normal human tissues fluoresceinated BMS-986207 produced membrane and cytoplasmic staining of mononuclear cells in human lymphoid tissues and select non-lymphoid tissues. This staining was expected based on TIGIT expression by mononuclear cell types, such as T cells and NK cells. No unexpected tissue cross-reactivity was observed. BMS-986207 did not induce cytokine release or increase the expression of activation [redacted] on human T, B, or NK cells in an in vitro human peripheral blood mononuclear cell cytokine release and cell activation assay, suggesting a low risk of BMS-986207-induced CRS in humans.

In a 1-month pivotal toxicity study in monkeys, BMS-986207 was administered IV as a slow bolus at doses of 0, 10, 30, or 100 mg/kg (once weekly [qw]× 5 doses). BMS-986207 was clinically well tolerated by all monkeys at 30 and 100 mg/kg doses while 3 out of 10 monkeys in the 10 mg/kg dose group exhibited signs of ADA mediated hypersensitivity reactions immediately after dosing on study days 22 and/or 29 (fourth and/or fifth dose). The clinical signs were transient, accompanied by increases in serum cytokine levels and complement activation, and no treatment was required for the affected monkeys. The timing, type of clinical observations, correlative complement activation are consistent with the formation of treatment-emergent ADA, a common response by monkeys to a foreign protein. This immunogenicity is not considered to be predictive for ADA responses in humans (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [ICH] S6). [redacted] responses were observed at all doses and included NK cell activation and CD8+ T cell activation and proliferation, and were generally dose-independent. Based on the lack of directly BMS-986207-related adverse findings, the no-observed-adverse-effect level (NOAEL) was considered to be [redacted]. In addition, for determination of the maximum recommended human starting dose, [redacted] was also considered the highest non-severely toxic dose (HNSTD). The HNSTD/NOAEL of [redacted] than the proposed starting dose in humans (1 mg/kg) with a corresponding plasma [redacted] of the projected human AUC (0-336),ss at 1 mg/kg [redacted]

Overall, the nonclinical toxicology assessment of BMS-986207 has demonstrated an acceptable safety profile, supporting clinical use in oncology patients.

3.2.1.4 Preliminary Clinical Safety Profile

Overall, based on preliminary data as of 21-Jan-2021, the safety profile of BMS-986207 as monotherapy (n = 42) or in combination with nivolumab (n = 30) is manageable at the doses tested.[19] [redacted] no new serious adverse events (SAEs) or treatment-related adverse events (AEs) had been reported for BMS-986207 monotherapy or in

combination with nivolumab. BMS-986207 was evaluated as a monotherapy at doses ranging from 20 mg to 1600 mg q2w (20 mg: n = 3; 80 mg: n = 3; 240 mg: n = 4; 800 mg: n = 28; 1600 mg: n = 4.). A single participant was dosed using an intra-participant dose escalation approach at 2, 6, and 20 mg. Escalation in this participant occurred 2 weeks after each dose with continued treatment at 20 mg q2w. There was no relationship between the incidence, severity, or causality of AEs and BMS-986207 dose level. A majority of treatment-related AEs were of Grade 1 to Grade 2, with 5 treatment-related Grade 3 to Grade 4 AEs (Grade 3 elevated aspartate aminotransferase, n = 1; Grade 3 hypertension, n = 1; Grade 3 hyponatremia, n = 2; Grade 3 hyperglycemia, n = 1). Infusion-related AEs were reported in 1 participant, which were managed based on the updated protocol guidelines. There were no drug-related SAEs with monotherapy. A total of 26 deaths were reported in participants treated with BMS-986207 monotherapy. All deaths were due to complications from disease progression except for 1 death attributed to aspiration pneumonia. All were considered by the Investigator to be not related to study drugs.

The safety profile of BMS-986207 in combination with nivolumab was evaluated at the following doses: 80 mg BMS-986207 + 240 mg nivolumab q2w (n = 4), 240 mg BMS-986207 + 240 mg nivolumab q2w (n = 4), 480 mg BMS-986207 + 480 mg nivolumab q4w (n = 18), and 1600 mg BMS-986207 + 480 mg nivolumab q4w (n = 4). There was no relationship between the incidence, severity, or causality of AEs and the combination regimen dose levels. Most AEs were of Grade 1 and Grade 2. With combination therapy, treatment-related AEs were similar to those expected from nivolumab alone.[19] A total of 13 deaths occurred in participants treated with combination therapy. All deaths were due to complications from disease progression and all were considered by the Investigator to be not related to study drug.

As of 20-Oct-2021, the safety profile of BMS-986207 1200 mg Q3W in combination with nivolumab 360 mg Q3W and ipilimumab 1 mg/kg Q6W was assessed in 6 participants. Of the 6 treated participants (the first participant was a sentinel participant), 4 participants were DLT evaluable. Based on preliminary data, 2 out of the 4 DLT-evaluable participants reported experiencing DLTs. One participant was a 79-year-old female with second-line (2L) pancreatic cancer who was reported to have Grade 3 encephalitis. The patient received the triplet combination once on Day 1. On Day 22, treatment was held for Grade 2 pneumonitis, which began on Day 12. On Day 40, treatment was discontinued due to disease progression. On Day 41, Grade 3 encephalitis, a DLT, was reported, treated with corticosteroids and mycophenolate mofetil, and had improved to Grade 2 on Day 53. The participant died on Day 118 due to disease progression. The Grade 2 pneumonitis and Grade 2 encephalitis did not resolve. The second participant was a 73-year-old female with fourth-line (4L) melanoma who received the triplet once on Day 1 and developed Grade 3 bullous dermatitis, a DLT, on Day 21. Treatment with corticosteroids and mycophenolate mofetil was consequently initiated, and dermatitis resolved on Day 49. A total of 2 deaths were reported, and both were attributed to disease progression and not related to study intervention. Based on the BOIN design, ongoing participants in the first cohort, as well as future participants in the next cohort, in the dose evaluation for Study CA020002 will dose de-escalate to BMS986207 600 mg Q3W in combination with nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W.

3.2.2 Nivolumab

Nivolumab (also referred to as BMS-936558, MDX1106, or ONO-4538) is a human monoclonal antibody (immunoglobulin G4 [IgG4]-S228P) that targets the programmed death-1 (PD-1) cluster of differentiation 279 (CD279) cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes. Binding of PD-1 to its ligands, programmed death–ligands 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T cell responses to both foreign antigens as well as self-antigens. Nivolumab is expressed in Chinese hamster ovary (CHO) cells and is produced using standard mammalian cell cultivation and chromatographic purification technologies. The clinical study product is a sterile solution for parenteral administration.

Nivolumab is approved for the treatment of several types of cancer in multiple regions including the United States (US, Dec-2014), the European Union (EU, Jun-2015), and Japan (Jul-2014).

Nivolumab has demonstrated durable responses exceeding 6 months as monotherapy in several tumor types, including NSCLC, melanoma, renal cell carcinoma (RCC), Classical Hodgkin Lymphoma (cHL), small-cell lung cancer (SCLC), gastric cancer, squamous cell carcinoma of the head and neck (SCCHN), urothelial cancer, hepatocellular carcinoma (HCC), and CRC. In confirmatory trials, nivolumab as monotherapy demonstrated a statistically significant improvement in OS as compared with the current standard of care in patients with advanced or metastatic NSCLC, unresectable or metastatic melanoma, advanced RCC, or recurrent or metastatic SCCHN. Details of the clinical activity in these various malignancies are provided in the US prescribing information (USPI) and Summary of Product Characteristics (SmPC).[34,20]

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

3.2.3 Ipilimumab

Ipilimumab (BMS-734016, MDX010, MDX-CTLA4) is a fully human monoclonal immunoglobulin (Ig) G1 kappa specific for human cytotoxic T-lymphocyte antigen 4 (CTLA-4, cluster of differentiation [CD] 152), which is expressed on a subset of activated T cells. CTLA-4 is a negative regulator of T cell activity. Ipilimumab is a monoclonal antibody (mAb) that binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T cell activation and proliferation, including the activation and proliferation of tumor-infiltrating T effector cells. Inhibition of CTLA-4 signaling can also reduce T-regulatory cell (Treg) function, which may contribute to a general increase in T cell responsiveness, including the anti-tumor response.

3.2.4 Nivolumab Combined with Ipilimumab Clinical Activity

Multiple clinical studies have evaluated nivolumab combined with ipilimumab 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 RCC, previously untreated metastatic NSCLC expressing [redacted] and microsatellite instability-high or mismatch repair deficient colorectal cancer. Details of the clinical activity in these various malignancies are provided in the USPI and SmPC.[34,20]

3.3 Benefit/Risk Assessment

Through the CA020002 study, some initial evidence of clinical benefit has been observed in patients with advanced cancer especially when used in combination with PD-1 inhibition. Recent reports with other anti-TIGIT antibodies have shown similar clinical benefit when used in combination with PD-1/PD-L1 inhibitors.[15,16] Prior to these studies, the evaluation of risk was based on information from nonclinical studies with BMS-986207 in monkeys (Section 5.5.1.3) and potential effects based on the proposed mechanism of action. The nonclinical toxicology assessment of BMS-986207 has demonstrated an acceptable safety profile, supporting clinical use in oncology patients. Because BMS-986207 blocks interaction of TIGIT with nectin-2 or PVR, it has the potential to remove an inhibitory signal to T cells and NK cells. TIGIT expression is limited to lymphoid cells, so the principal effects are anticipated to be related to the effects of inflammatory cells in specific tissues. Similar to other Immuno-Oncology (I-O) drugs, a general principle is to monitor for immune-mediated adverse reactions in various organ systems. Noninflammatory etiologies should be considered and discussions with the BMS Medical Monitor should be used to guide treatment. Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

In vitro treatment of human mononuclear cells with BMS-986207 did not induce [redacted] of lymphocyte activation or cytokine release. Moreover, there was no evidence for CRS in cynomolgus monkeys treated with BMS-986207. To assess for unanticipated potential effects of lymphocyte activation, a sentinel participant will be monitored for 5 days at each dose level for Parts 1A and 1B.

Novel monoclonal antibodies such as BMS-986207 have the potential to induce anti-idiotype antibodies that can be neutralizing or non-neutralizing. BMS-986207 is a fully human antibody and the clinical experience with other human mAb I-O agents is that infusion-related reactions or hypersensitivity reactions occur at a frequency of < 10% and are generally low grade. Severe infusion-related reactions or anaphylaxis are rare and occur at a frequency of approximately 0.1%. For the proposed clinical study of BMS-986207, the administration will start with a single participant enrolled into monotherapy escalation, receiving BMS-986207 starting at the 2 mg dose level, followed 2 weeks later with intra-participant dose escalation to the 6 mg dose level, followed 2 weeks after that with intra-participant dose escalation to the 20 mg dose level. This first participant was subject to a 5-day safety observation period after receiving the first 20 mg dose. This study design was intended to thoroughly assess the risk of any immediate hypersensitivity

reactions. As of 21-Jan-2021, 1 participant out of 42 treated participants in monotherapy (2.4%) was noted to have an infusion-related reaction (Grade 1) with BMS-986207 treatment.[19]

All BMS-986207 infusions 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 will undergo observation and assessment for signs of infusion reaction for 60 minutes post infusion after all infusions of BMS-986207 in Cycle 1.

In combination therapy, BMS-986207 may potentiate immune-mediated adverse reactions caused by nivolumab and ipilimumab. The safety profile of nivolumab monotherapy is well defined and is based on experience with greater than 23,500 patients evaluated in clinical trials. 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 (BMS-986558) IB.[21] Management algorithms for nivolumab-induced AEs involving gastrointestinal, renal, pulmonary, hepatic, endocrinopathy, skin, neurologic systems, and myocarditis are included in the protocol.

As of 23-Mar-2021, more than 30,000 participants have been enrolled in ipilimumab monotherapy and combination therapy studies, including compassionate use programs, in several cancer types, allowing the safety profile to be well defined. 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 ipilimumab (BMS-734016, MDX-010) IB. [22] Management algorithms for ipilimumab- induced AEs are included in the protocol.

The safety profile of nivolumab and nivolumab plus ipilimumab is characterized by immune-related toxicities, such as diarrhea, rash, pneumonitis, liver toxicity, and endocrinopathies. The frequencies and intensities of these events are variable and depend on the specific doses and schedule used. In the dosing schedules selected, these events were mostly low grade and manageable with the use of corticosteroids. Nivolumab and ipilimumab combination therapy has shown improved efficacy over either agent alone in melanoma.

Overall, the safety profiles of nivolumab monotherapy, ipilimumab monotherapy, and the combination of the two are manageable and generally consistent across completed and ongoing clinical trials. There was no MTD reached at any dose of nivolumab tested up to 10 mg/kg. Most AEs were low-grade (Grade 1 to 2) with relatively few related high-grade (Grade 3 to 4) AEs. There was no pattern in the incidence, severity, or causality of AEs with respect to nivolumab dose level.

A pattern of immune-related AEs has been defined, for which management algorithms have been developed; these are provided in Appendix 6. Most high-grade events were manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in these algorithms.

Participants with newly diagnosed metastatic or recurrent NSCLC represent a great unmet need. Recent studies from other agencies using anti-TIGIT antibodies in combination with PD-1/PD-L1 inhibition have shown some clinical benefit in PD-L1 positive 1L NSCLC.[15,16] These anti-TIGIT

antibodies, have differed from BMS-986207 as they have wild type Fc regions while BMS-986207 has an inert Fc region. This inert Fc region may provide less toxicity in participants when used as monotherapy or in combination with PD-1/PD-L1 or CTLA-4 inhibitors.

The potential benefit of combination immunotherapy of BMS-986207 plus nivolumab plus ipilimumab in first line treatment of NSCLC is not yet known. The safety profile of nivolumab and ipilimumab plus BMS-986207 is expected to have no new categories of AEs compared to BMS-986207 monotherapy, nivolumab monotherapy, ipilimumab monotherapy, or nivolumab plus ipilimumab combination therapy. The frequencies and intensities of these AEs in the nivolumab and ipilimumab plus BMS-986207 combination may be higher. Preliminary data of CA020002 Part 1C, as per 20-Oct-2021, revealed that 2 out of 4 DLT-evaluable participants experienced DLTs with the combination of BMS-986207 1200 mg Q3W, nivolumab 360 mg Q3W, and ipilimumab 1 mg/kg Q6W (Grade 3 encephalitis and Grade 3 bullous dermatitis, see Section 3.2.1.4 for more details).[19] Per BOIN design, BMS-986207 dose of 1200 mg Q3W was reduced to 600 mg due to the reported DLTs. If needed, BMS-986207 dosing will be further reduced in the setting of SAEs or worsening AE profiles. When BMS-986207 was combined with nivolumab, participants with melanoma (1 participant with a complete response [CR], 2 participants with partial response [PR]), and prostate cancer (1 participant with PR) experienced clinical benefit (unpublished results). When 1200 mg BMS-986207 was combined with nivolumab and ipilimumab (n = 6 treated participants), PR was observed in one participant with CRC and stable disease (SD) with NSCLC (post PD-1 therapy). No clinical benefit was observed in any participants who received BMS-986207 monotherapy (unpublished results). Other tumor types in this study included pancreatic, ovarian, breast, gastric, and urothelial cancer. In efforts to reduce toxicity associated with ipilimumab, a lower dose of 1 mg/kg at a 6-week dosing interval will be used. This dose of ipilimumab is currently approved for the treatment of 1L NSCLC in combination with nivolumab or with nivolumab and 2 cycles of chemotherapy.

Patients who develop immune-related AEs may require prolonged treatment with high dose corticosteroids and other immunosuppressive agents. This could increase the risk of opportunistic infections. Immune-related AE management algorithms in the protocol recommend antibiotic prophylaxis against opportunistic infections in such situations.

The clinical studies of BMS-986207 have been designed to minimize the overall risk to participants. Complete blood counts and chemistry (including liver enzyme) tests will be carried out prior to administration of study therapy and on a weekly basis during the first 4 weeks of treatment. 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 4 weeks of treatment. Due to the potential risk of exaggerated inflammatory response, participants with auto-immune disorders, who are at risk for flare of auto-immunity, will be excluded.

[redacted]

[redacted]

Continuous safety assessments will be utilized by the Investigators and Sponsor to determine whether dose modification, additional safety measures, or termination of the study is required at any time. In addition, AEs and SAEs will be reviewed on an ongoing basis by the BMS Medical Monitor and World Wide Patient Safety (WWPS) representatives to monitor for any safety signals or trends. As BMS-986207 is an experimental agent, it is possible that unforeseen, unknown, or unanticipated reactions may occur. However, based on the nonclinical safety profile of BMS-986207, and with a 91-fold exposure margin built into the planned starting dose of 1 mg/kg (or 80 mg based an average body weight of 80 kg in cancer patients), the potential safety risks are expected to be minimized.

[redacted]

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. 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 8.1.

[redacted]

4. OBJECTIVES AND ENDPOINTS

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

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Primary	
• Part 1A, 1B, 2A, and 2B: To characterize the safety, tolerability, DLTs, and MTD/RP2D of BMS-986207 administered as monotherapy and in combination with nivolumab in participants with advanced solid tumors.	• Incidence of AEs, SAEs, AEs meeting protocol-defined DLT criteria, AEs leading to discontinuation, and death; Incidence of laboratory abnormalities.
• Part 1C: To characterize the safety, tolerability, and DLTs of BMS-986207 in combination with nivolumab and ipilimumab in participants with advanced solid tumors.	• Incidence of AEs, SAEs, AEs meeting protocol-defined DLT criteria, AEs leading to discontinuation, and death; Incidence of laboratory abnormalities.
• Part 2C: To evaluate the preliminary efficacy and safety of BMS-986207 in combination with nivolumab and ipilimumab in previously untreated participants with NSCLC whose tumors express ≥ 1% PD-L1 based on PD-L1 IHC results from central testing.	• ORR, mDOR, and PFSR at 24 weeks by RECIST v1.1 by Investigator; Incidence of AEs, SAEs, AEs leading to discontinuation, and death.

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Secondary	
• To assess the preliminary efficacy of BMS-986207 alone and in combination with nivolumab, in advanced solid tumors (Parts 1A, 2A, 1B, and 2B) and in combination with nivolumab and ipilimumab in advanced solid tumors (Part 1C).	• ORR, mDOR, and PFSR at 24 weeks by RECIST v1.1
• To characterize the PK and immunogenicity of BMS-986207 when administered alone, in combination with nivolumab or in combination with nivolumab and ipilimumab.	• Summary measures of PK parameters of BMS-986207 and incidence of ADA to BMS-986207
[redacted]	

Abbreviations: ADA, anti-drug antibody AE, adverse event; DLT, dose limiting toxicity; IHC, immunohistochemistry; mDOR, median duration of response; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; ORR, objective response rate; [redacted] PD-L1, programmed death ligand 1; PFSR, progression-free survival rate; PK, pharmacokinetic; RECIST, Response Evaluation Criteria in Solid Tumors; [redacted] RP2D, recommended Phase 2 dose; [redacted] SAE, serious adverse event; [redacted].

AEs and laboratory values will be graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03.

5. STUDY DESIGN

5.1 Overall Design

This is a Phase 1/2a, open-label study of BMS-986207, administered as a single agent, in combination with nivolumab, and in combination with both nivolumab and ipilimumab in participants with advanced solid tumors. The duration of the study will be approximately 6 years.

The study comprises 2 parts. Part 1 includes dose escalation of BMS-986207 alone (Part 1A) and in combination with nivolumab (Part 1B) to determine the MTD/RP2D, as well as a select dose level of BMS-986207 in combination with nivolumab and ipilimumab (Part 1C) to evaluate safety and preliminary [redacted] activity of the triplet combination. Part 1B includes a substudy conducted at a single site under site-specific Amendments 6, 7, and 8 to evaluate the safety and preliminary efficacy of BMS-986207 in combination with nivolumab in PD-1 naive and relapsed/refractory participants with melanoma. Part 2 includes expansion cohorts to gather additional preliminary [redacted] activity, as well as additional safety, tolerability, PK, [redacted] information for BMS-986207 alone (Part 2A), in combination with nivolumab (Part 2B), and in combination with nivolumab and ipilimumab in NSCLC (Part 2C). Participants in each study phase will complete up to 4 periods in the study: screening, treatment, safety follow-up, and response/survival follow-up. The overall study design is shown in Figure 5.1.2.2-1.

5.1.1 Screening Period

The screening period for all parts of the study will be up to 28 days, and begins by establishing the participant's initial eligibility and signing of the informed consent form (ICF). See Appendix 2 for details of the informed consent process and other study governance considerations. Participants will be enrolled using an Interactive Response Technology (IRT), and the screening assessments are shown in Table 2-1.

If a participant exceeds the 28-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.

5.1.2 Treatment Period

Treatment cohorts are illustrated in Figure 5.1.2.2-2.

5.1.2.1 Treatment in Parts 1A, 1B, 2A, and 2B

Participants will be treated for up to 24 weeks (3 cycles) with monotherapy as will participants treated with combination therapy (Parts 1B and 2B). The treatment period will consist of up to 3 treatment cycles of 8 weeks. Following each treatment cycle, the decision to treat a participant with additional cycles of study therapy (up to a maximum of 6 cycles), will be based on tumor assessment at the end of each cycle. Weekly study visits will be performed for the first 4 weeks following the first dose of study drug, followed by study visits q2w thereafter.

Following a preliminary, within-patient dose escalation, safety cohort, each monotherapy treatment cycle will comprise 4 doses of BMS-986207 administered q2w or 2 doses of BMS-986207 administered q4w. BMS-986207 infusions will take place over 60 minutes and will require a 60 minute observation period following the completion of the infusion for the first four doses of Cycle 1 for each participant. A 60-minute post infusion safety observation period is considered appropriate given BMS-986207 is a fully human monoclonal antibody that is an antagonist (not an agonist) and has a low likelihood of resulting in infusion reactions. For participants < 42 kg on the 1600 mg dose, the infusion time will be longer than 1 hour (approximately 90 minutes; see Pharmacy Manual for more detail). In Parts 1B and 2B, each combination treatment cycle will comprise 4 doses of BMS-986207 administered q2w or 2 doses of BMS-986207 when administered q4w, each dose administered in combination with nivolumab.

Nivolumab will be given first, over a 30-minute infusion period, followed by BMS-986207 over a 60-minute infusion period, beginning at least 30 minutes after completion of the infusion of nivolumab.

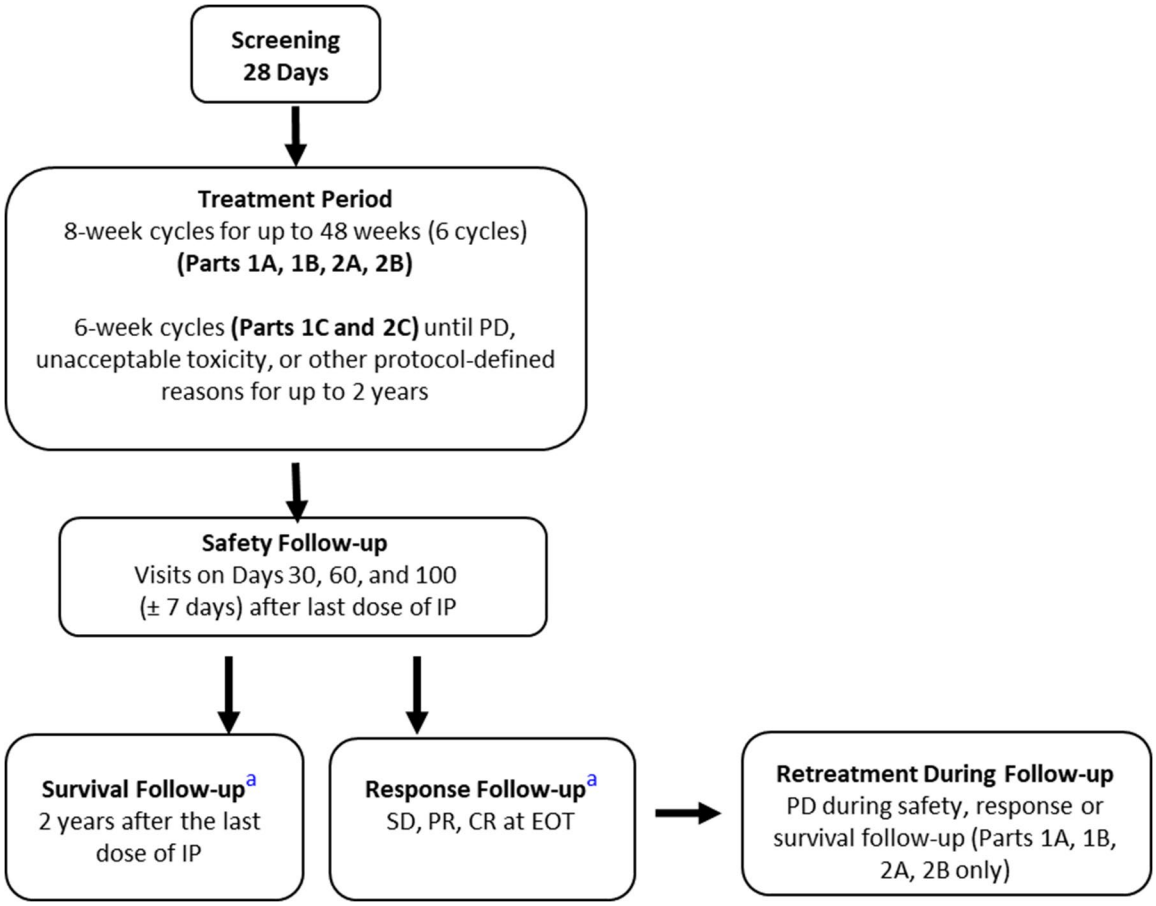
Additional infusion details are given in the Pharmacy Manual. Tumor progression and response endpoints will be assessed using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria for solid tumors (Appendix 5).

5.1.2.2 Treatment in Part 1C and Part 2C

In Part 1C (Triplet cohort) and Part 2C (Triplet NSCLC Expansion), each treatment cycle is equal to 6 weeks. Nivolumab (360 mg) will be administered every 3 weeks and ipilimumab (1 mg/kg) will be administered every 6 weeks at least 30 minutes after completion of the nivolumab infusion. BMS-986207 will be administered every 3 weeks at 600 mg and/or 360 mg and will be tested in Part 1C per BOIN design and for dose optimization. A dose not to exceed the dose declared tolerable in Part 1C will be used in Part 2C. Additional doses lower than the dose declared tolerable in Part 1C might be tested for dose optimization in Part 2C. A dose of 1200 mg BMS-986207 administered every 3 weeks has been tested per Amendment 03 but due to the DLTs observed no additional participants will be tested at this dose (see Section 3.2.1.4).

Treatment will occur until disease progression, unacceptable toxicity, or other reasons as specified in Section 8.1 for up to 2 years. Treatment beyond initial investigator-assessed RECIST v1.1 defined progression is permitted if the participant has investigator-assessed clinical benefit and is tolerating the treatment, as specified in Section 5.1.4.

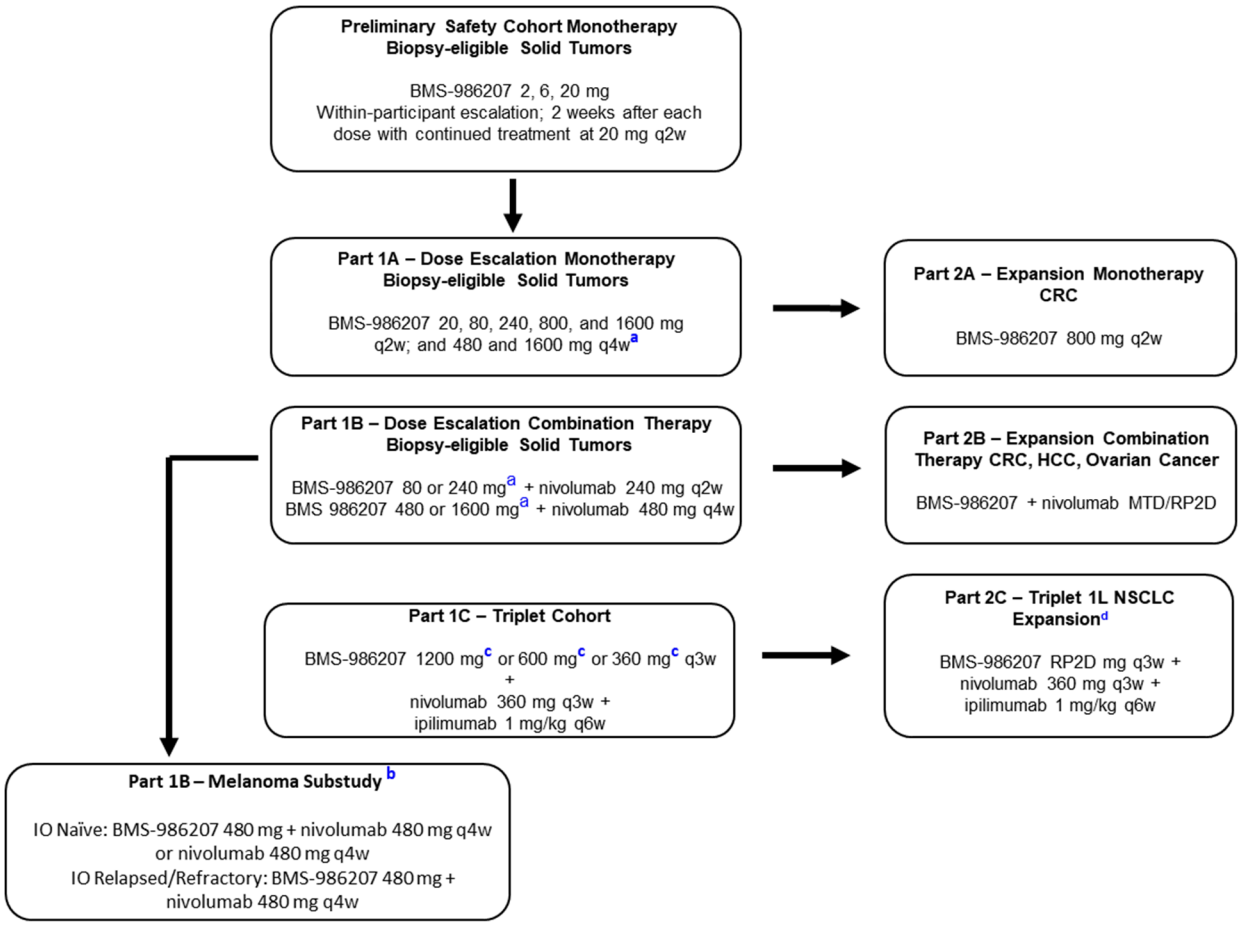
Figure 5.1.2.2-1: Overall Study Design Schematic



Abbreviations: CR, complete response; EOT, end of treatment; IP, investigational product; PD, progressive disease; PR, partial response; SD, stable disease.

[a] Details of the response and survival follow-up periods are given in Sections 5.1.3.2 and 5.1.3.3, respectively.

Figure 5.1.2.2-2: Treatment Cohorts in CA020002



Abbreviations: 1L NSCLC, first-line non-small cell lung cancer; BMS, Bristol-Myers Squibb; CRC, colorectal cancer; HCC, hepatocellular carcinoma; IO, immuno-oncology; IP, investigational product; MTD, maximum tolerated dose; q2w, every 2 weeks. q3w, every 3 weeks; q4w, every 4 weeks, RP2D, recommended phase 2 dose.

[a] Planned dose levels and dose schedules of BMS-986207 and/or nivolumab may be modified, and intermediate dose levels of BMS-986207 added, based upon the BLRM analysis and sponsor discretion and discussion with Investigators. Once the safety (during the DLT evaluation) of a dose level has been established (Part 1A and/or Part 1B), additional participants (up to 15) may be added at that dose, to better characterize the safety, dose schedule, PK, [redacted]profile [redacted] assessments.

[b] Participants were enrolled at a single site under site-specific Amendments 6, 7, and 8. This substudy has been closed for enrollment.

[c] The safety profile of BMS-986207 1200 mg Q3W combined with nivolumab 360 mg Q3W and ipilimumab 1 mg/kg Q6W has been evaluated in 6 subjects. Of these subjects, 4 were DLT evaluable, and 2 developed DLTs. Per BOIN design, in all the remaining and future subjects in Part 1C, BMS-986207 was de-escalated to 600 mg Q3W (for details, see Section 3.2.1.4). Planned dose levels for BMS-986207 may be further modified based on generated data and additional doses, including 360 mg Q3W, may be assessed per BOIN design and for dose optimization analysis at sponsor discretion and based upon discussion and agreement with investigators.

[d] Part 2C will enroll a minimum of 20 participants per dose level of BMS-986207. One or two doses are planned to be evaluated and selected from the range of doses assessed as tolerable and not exceeding the maximum tolerated dose in Part 1C. If two doses will be tested at the sponsor's discretion, participants will be randomized in a 1:2 ratio schema between the highest dose selected in Part 1C and the next lower dose, after at least 10 participants will have been tested at the dose found safe in Part 1C.

5.1.2.3 Preliminary Safety Cohort & Dose Escalation (Part 1A and 1B)

Approximately 35 participants are expected to be treated during each dose escalation part of the study guided by Bayesian Logistic Regression Model (BLRM). Each participant will be administered IV doses of BMS-986207 per the cohort assignment as follows:

- The Preliminary Safety Cohort precedes participant enrollment in Monotherapy - Dose Escalation (Part 1A) of the study. The first participant enrolled into monotherapy escalation will receive BMS-986207 starting at the 2 mg dose level, followed 2 weeks later with intra-participant dose escalation to the 6 mg dose level, followed 2 weeks after that with intra-participant dose escalation to the 20 mg dose level, This first participant will be subject to a 5-day safety observation period after receiving the first 20 mg dose. No other intra-participant dose escalation is planned for this study. If there are no DLTs or other safety concerns observed, an additional 2 participants will be enrolled in the 20 mg dose cohort. Please refer to Appendix 13 for complete details of the Preliminary Safety Cohort
- In Part 1A (monotherapy dose escalation), the planned flat dose levels for BMS-986207 are 20, 80, 240, 800 and 1600 mg (assuming an 80kg participant) q2w, in 8-week cycles, for up to 3 cycles of study therapy (24 weeks). In addition, a q4w schedule of BMS-986207 will be evaluated at flat doses of 480 mg and 1600 mg (assuming an 80kg participant). Enrollment of the first q4w cohort will be guided by the safety, PK, [redacted] analysis from the q2w cohorts. Following each treatment cycle, the decision to treat a participant with additional cycles of study therapy (up to a maximum of 6 cycles), will be based on tumor assessment at the end of each cycle.
- In Part 1B, (combination therapy dose escalation), BMS-986207 and nivolumab will be administered at flat doses of 80 and 240 mg BMS-986207 q2w with 240 mg nivolumab q2w. In addition, BMS-986207 will be administered at flat doses of 480 and 1600 mg q4w in combination with nivolumab administered at 480 mg q4w. Study drugs will be administered in 8-week cycles, for up to 3 cycles of study therapy (24 weeks). Following each treatment cycle, the decision to treat a participant with additional cycles of study therapy (up to a maximum of 6 cycles), will be based on tumor assessment at the end of each cycle.

Planned dose levels and dose schedules of BMS-986207 and/or nivolumab may be modified, and intermediate dose levels of BMS-986207 added, based upon the BLRM analysis and/or sponsor discretion and discussion with the Investigators. Once the safety (during the DLT evaluation) of a dose level has been established (Part 1A and/or Part 1B), additional participants (up to 15) may be added at that dose, to better characterize the safety, dose schedule, PK, [redacted] profile [redacted] assessments. Part 1B combination dose escalation will be initiated after at least 3 dose levels have been found to be tolerable in Part 1A monotherapy dose escalation. The starting dose of BMS-986207 in Part 1B will be at least 1 dose level below a dose that was demonstrated to be tolerated in Part 1A. At no time will the dose for BMS-986207 in Part 1B exceed the highest tolerated dose in Part 1A. Escalation within Parts 1A and 1B, within the constraints cited above, may be done in parallel.

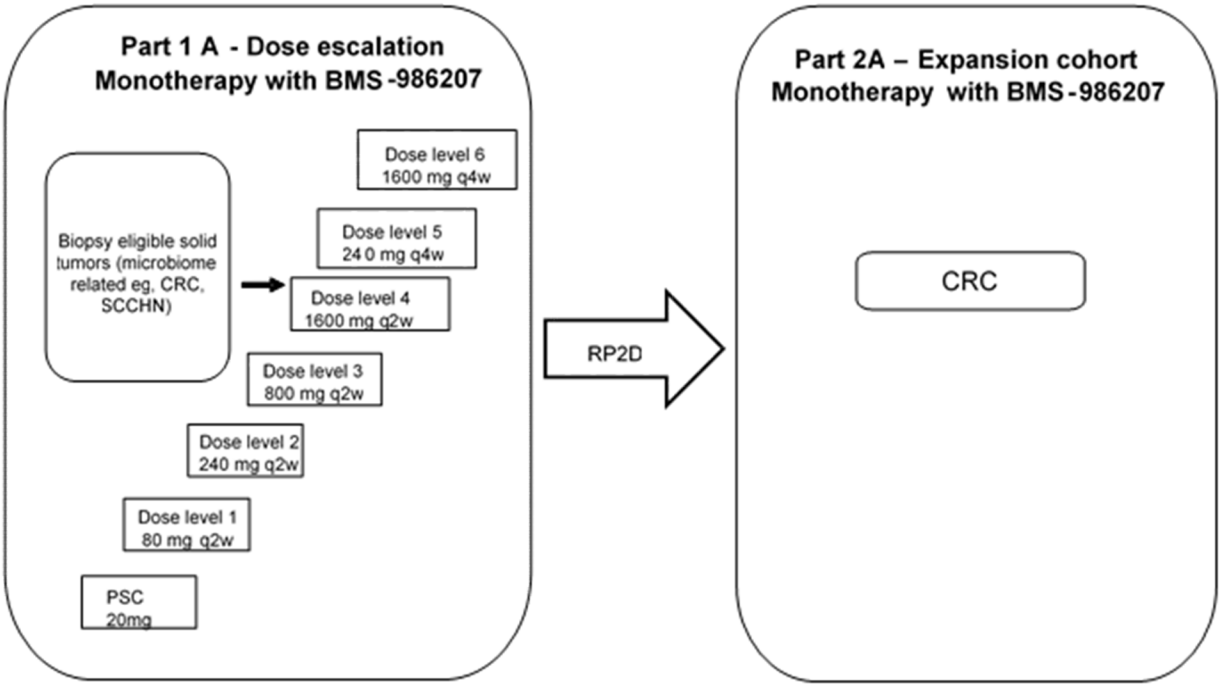
Sentinel Participant

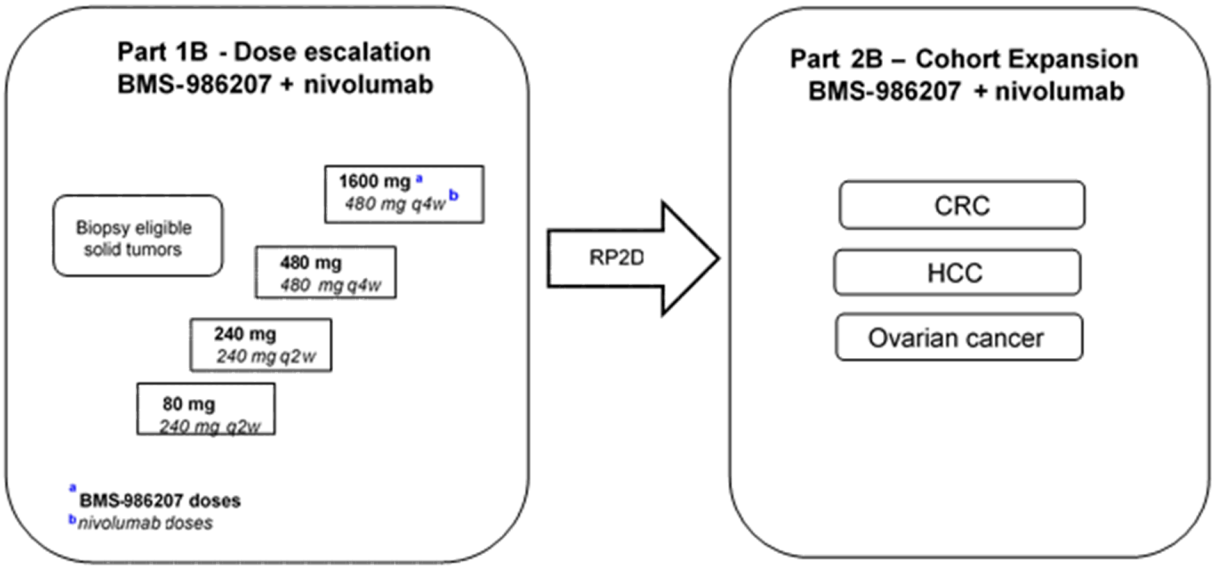
During the dose escalation phase, a staggered dosing (sentinel participant) approach will be used. The first participant in both Parts 1A and 1B will receive Cycle 1 Day1 dose of study drug(s), and be observed for 5 days, before additional participants (ie, Participant 2 onward in that cohort) receive study drugs. The first participants to be dosed in all subsequent dose level cohorts will also be subject to a 5-day sentinel period.

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 4-week dose-limiting toxicity (DLT) period is completed, an extra participant may be enrolled in each dose escalation cohort. Therefore, there will be a total of 4 participants (3 + 1) at the start of each cohort, provided that the fourth participant is able to start the first day of dosing within approximately 1 week of the third participant in the same dose escalation cohort.

Figure 5.1.2.3-1 illustrates the dose escalation phase of the study.

Figure 5.1.2.3-1: Schematic of the Dose Escalation and Cohort Expansion Phases of the Study





Abbreviations: CRC, colorectal cancer; HCC, hepatocellular carcinoma; PSC, preliminary safety cohort; RP2D, recommended Phase 2 dose; SCCHN, squamous cell carcinoma of the head and neck

5.1.2.4 Dose Escalation Decisions for Monotherapy and Combination (Parts 1A and 1B)

The dose escalation phase of the study will evaluate the safety and tolerability of BMS-986207, given alone or in combination with nivolumab, based on DLTs, using a BLRM model (for BMS-986207 as monotherapy) and a BLRM-copula model (for BMS-986207 in combination with nivolumab).

Combination dose escalation (Part 1B) will not begin until 3 dose cohorts (i.e., 20 mg, 80 mg and 240 mg) have been determined to be safe in monotherapy dose escalation (Part 1A) During the dose escalation phase, a set of approximately 3 participants will be treated at each specified dose level. Cohort tolerability assessment and subsequent dose recommendation will occur when at least 2 evaluable participants within a cohort have completed a 4-week DLT period. Any toxicities that occur beyond the 4-week DLT period will be accounted for in making dose level decisions and/or dose level modifications.

If the potential DLT occurring in the third evaluable participant regarding the specific dose level does not influence the dose recommendation by BLRM or the BLRM-Copula model, the next dose level may proceed without waiting for the third participant to complete the corresponding DLT observation period, after discussion and agreement between the Sponsor and Investigators. Continuous re-assessment of dose recommendation, by BLRM in the escalation phase and BLRM-Copula in the combination phase, will be carried out for each dose level. Planned dose levels for dose escalation are provided in Table 5.1.2.4-1. Planned dose levels may be modified, or intermediate dose levels added, based upon the BLRM analysis.

Table 5.1.2.4-1: Planned Doses During Part 1B (Combination Dose Escalation)

Dose Level/Cohort	BMS-986207	Nivolumab	Dose Schedule
1	80 mg	240 mg	q2w
2	240 mg	240 mg	q2w
3	480 mg	480 mg	q4w
4	1600 mg	480 mg	q4w

The RP2D dose of BMS-986207, alone and in combination with nivolumab, selected for cohort expansion will be based on evaluating the recommendation from BLRM and an overall assessment of all available safety, PK/[redacted] and efficacy data.

Once the safety (during DLT evaluation) of a dose level has been established (Part 1A and/or Part 1B), additional participants (up to a total of 15) may be added to that dose level, to better characterize the PK, safety [redacted] profiles[redacted] assessments.

5.1.2.5 Dose Limiting Toxicities in Dose Escalation Phases (Parts 1A and 1B)

For the purpose of guiding dose escalation, DLTs will be defined based on the incidence, intensity, and duration of AEs for which no clear alternative cause is identified. The DLT period will be 28 days (4 weeks) in Part 1A and 28 days (4 weeks) in Part 1B. Any toxicities that occur beyond the 4-week DLT period will be accounted for in making dose level decisions.

For the purpose of participant management, any AE that meets DLT criteria, regardless of the cycle in which it occurs, will lead to discontinuation of study drug. Participants who withdraw from the study during the DLT evaluation period for reasons other than a DLT may be replaced with a new participant at the same dose level. The incidence of DLT(s) during the DLT evaluation period will be used in dose escalation decisions and to define the MTD. AEs occurring after the 4-week DLT evaluation period will be considered for the purposes of defining the RP2D upon agreement between the Sponsor, Medical Monitor, and Investigators, if the AEs are determined to have no clear alternative cause and are not related to disease progression.

Participants experiencing a DLT will not be retreated with study drug and will enter the safety follow-up period of the study. AEs will be graded according to the NCI CTCAE v4.03.

5.1.2.6 Safety Evaluation Phase of Part 1C

Up to 18 participants per dose level tested will be treated in the Triplet Cohort. BMS-986207 will be administered at 600 mg and/or 360 mg q3w and nivolumab will be administered at 360 mg q3w. Ipilimumab, at a dose of 1 mg/kg, will be given q6w. The DLT period in Part 1C will be 42 days (6 weeks).

A dose of 1200 mg BMS-986207 administered every 3 weeks has been tested per Amendment 03 but due to the DLTs observed no additional participants will be tested at this dose (see Section 3.2.1.4).

The DLT safety monitoring during the dose evaluation phase, including the potential decision to de-escalate to a lower dose, will be based on the BOIN design framework with target toxicity (DLT) rate of 30% (24%, 36%), as presented in Table 5.1.2.6-1.[23,24] The BOIN design takes a very simple form, rendering it easy to implement in practice. It is more straightforward and transparent than other model-based and model-assisted methods. The decisions on dose tolerability guided by the design are based on comparing the observed DLT rate at the current dose with a pair of fixed dose escalation and de-escalation boundaries. This allows generation of a decision table that guides DLT assessment depending on the number of participants treated and observed DLTs. The performance of the design based on the operating characteristics is shown in Appendix 12.

As a dose escalation is not planned in Part 1C, a design recommendation to declare a dose as tolerable is based on meeting the same criteria needed to escalate. A minimum of 6 DLT evaluable participants will be required in Part 1C to declare a dose tolerable for initiation of Part 2C. In addition, to better estimate tolerability of the dose level in combination with nivolumab and ipilimumab, more participants will be treated even if a dose is declared tolerable with n=6, for up to a total of 18 treated. In contrast, a design recommendation "Stay" indicates that this dose level needs to be evaluated further for safety to declare this dose tolerable. In that case, additional cohorts of 3-4 or more participants (depending on the number of observed DLTs) will be treated up to a total of 18. If dose-de-escalation is recommended by the design based on the number of participants with DLTs observed during this dose evaluation phase (Table 5.1.2.6-1), then the next lower dose level will be used (360 mg BMS-986207 q3w) for the remaining participants as well as for those currently on treatment. In addition, other lower doses of BMS-986207 (200 mg q3w) than that seen as safe and tolerable may also be tested.

Initially, the first 3 to 4 participants treated in the Triplet Cohort will be evaluated for DLTs. If 0 or 1 DLT is observed during the 6-week DLT period, an additional 3-4 participants will be treated at the same BMS-986207 dose level. If ≤1 DLTs are observed out of the first 6 DLT-evaluable participants, the dose will be considered safe. If 2 DLTs are observed out of 6 DLT-evaluable participants, an additional 3-4 participants will be enrolled. If ≤3 DLTs are observed out of 9 DLT-evaluable participants, an additional 3 participants will be enrolled. If 2 DLTs are observed out of 12 DLT evaluable participants, the dose level will be considered safe.

If 3 or 4 DLTs are observed out of 12 DLT evaluable participants as shown in Table 5.1.2.6-1, the design recommends to stay at the same dose level, indicating that more participants may need to be evaluated to determine whether the dose level is safe. After considering additional information such as provided in Table 5.1.2.6-2 and the totality of available data including safety, PK/pharmacodynamics from all treated participants, a lower dose may be considered for evaluation, (eg, if 4 /12 DLTs) or the dose may be considered safe (eg, with 3/12 DLTs) based on discussion between the Investigator and Sponsor/Medical Monitor, and based on posterior probability of the DLT rate exceeding the target. Once a dose is declared safe based on at least 6 participants, an additional 6-12 participants may be treated up to a total of 18 to continue to confirm the safety of the selected dose. At the same time, enrollment in Part 2C may begin. In addition, another cohort up to 18 participants may be treated at the next lower dose of BMS-986207 to optimize dose selection. Participants who do not complete the DLT observation period for

reasons other than DLTs may be replaced. De-escalation may be considered if the safety and tolerability profile for the selected BMS-986207 dose is evaluated as not acceptable, after discussion between the Investigator (s) and the Sponsor/Medical Monitor.

Table 5.1.2.6-1: Triplet Safety Evaluation Guidance for DLT-Related Decisions by BOIN Design Framework

Actions based on number of DLT's	The number of DLT-evaluable participants treated at the current dose									
	3	4	5	6	7	8	9	10	11	12
Declare dose tolerable if # of DLT ≤[a]	0/NA	0/NA	1/NA	1	1	1	2	2	2	2
Stay if # of DLT=	1	1	NA	2	2	2	3	3	3	3,4
De-escalate if # of DLT ≥	2	2	2	3	3	3	4	4	4	5
Eliminate if # of DLT ≥	3	3	4	4	5	5	5	6	6	7

Abbreviations: BOIN, Bayesian optimal interval; DLT, dose-limiting toxicity

[a] The decision meets the same requirements as needed to "escalate" in standard design. NA indicates that decisions to declare a dose tolerable will not be made with fewer than 6 participants

In addition to the above guidance, the following posterior probability may be considered to guide the DLT tolerability decision. Assuming a 33% acceptable DLT rate in triplet, which corresponds to a Beta (1, 2) distribution, Table 5.1.2.6-2 shows the chance of confirming a BMS-986207 dose level as safe based on the observed DLTs and expressed as a posterior of DLT probability given the number of DLTs observed in the first 6, 9, or 12 participants during the triplet evaluation phase.

Table 5.1.2.6-2: Posterior Probability of DLT in Triplet Cohort Assuming Observed Data

Number of Participants at a Dose level	Number of Participants with an Observed DLT	Probability of DLT Rate>30%	Probability of DLT Rate>33%	Probability of DLT Rate>40.0%
6	1	0.26	0.2	0.11
6	2	0.55	0.47	0.32
9	2	0.31	0.24	0.12
9	3	0.57	0.48	0.30
12	2	0.16	0.11	0.04
12	3	0.36	0.27	0.12
12	4	0.58	0.48	0.28

Abbreviations: DLT, dose-limiting toxicity.

5.1.2.7 Cohort Expansion (Parts 2A, 2B, and 2C)

The purpose of cohort expansion is to gather additional safety, tolerability, preliminary efficacy, PK, [redacted] information regarding BMS-986207 alone and in combination with nivolumab. Continuous evaluation of toxicity events in the cohort expansions will be performed throughout enrollment in the expansion cohorts. If, at any time, the aggregate rate of treatment-related toxicities meeting DLT criteria exceeds 33% across all participants treated in cohort expansions 2A or 2B, the findings will be discussed and further enrollment will be interrupted. Depending on the nature and grade of the toxicity, and after assessing the risk/benefit ratio, a new dose for all cohorts may be initiated at a previously tested lower dose level or at a dose level intermediate to previously tested, lower dose levels.

In Part 2A, only CRC will be evaluated in cohort expansion with BMS-986207 as monotherapy. In Part 2B, the 3 disease-restricted populations, ovarian cancer, colorectal cancer (CRC) and HCC will be investigated in cohort expansions with BMS-986207 in combination with nivolumab. A Fleming 2-stage design framework will be used as a guide in cohort expansion.

During the cohort expansion phase, participants with CRC who have disease progression on BMS-986207 monotherapy will be able to cross over to combination treatment (BMS-986207 + nivolumab), once the CRC expansion arms (ie, monotherapy and combination therapy) are both enrolling. This cross-over option, for CRC participants only, is not applicable during the escalation phases.

The purpose of Part 2C is to gather preliminary efficacy information regarding BMS-986207 in combination with nivolumab and ipilimumab. Participants with advanced, treatment-naive NSCLC whose tumors express PD-L1 will be treated with BMS-986207 in combination with nivolumab and ipilimumab. BMS-986207 will be administered at 600 mg q3w (or tolerable dose as determined in Part 1C) and nivolumab will be administered at 360 mg q3w. Ipilimumab, at a dose of 1 mg/kg, will be given q6w.

Part 2C may begin once there is sufficient safety data from a minimum of 6 participants in Part 1C.

Part 2C will enroll a minimum of 20 participants per dose level of BMS-986207. One or two doses are planned to be evaluated and selected from the range of doses assessed as tolerable and not exceeding the maximum tolerated dose in Part 1C. If two doses will be tested at the Sponsor's discretion, participants will be randomized in a 1:2 ratio schema between the highest dose selected in Part 1C and the next lower dose, after at least 10 participants will have been tested at the dose found safe in Part 1C.

Continuous evaluation of toxicity events will also be performed in this part of the study. If, at any time, the aggregate rate of treatment-related toxicities meeting DLT criteria exceeds 33% in Parts 2A or 2B, the findings will be discussed and further enrollment may be interrupted. In addition, a more guided continuous safety monitoring will be implemented in Part 2C, 1L NSCLC expansion, using a Bayesian framework and specific criteria based on a posterior probability of a DLT rate exceeding 33% implemented starting with n=6 (Table 10.3.8-1). Depending on the nature and

grade of the toxicity, and after assessing the risk/benefit ratio, a new BMS-986207 dose for all participants, including those currently on treatment, may be initiated at a lower dose level.

Participants with an outcome of unconfirmed progressive disease, 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 number of cycles
- Confirmed PD (see 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

5.1.2.8 Treatment with Additional Cycles Beyond 24 Weeks (Parts 1A, 1B, 2A, and 2B)

All participants will be treated for up to 24 weeks (3 cycles) with monotherapy (Parts 1A and 2A) or combination therapy (Parts 1B and 2B), unless treatment discontinuation criteria are met earlier (Section 8.1). Participants with ongoing disease control (CR, PR or SD) or unconfirmed progressive disease, after completing approximately the initial 24 weeks of treatment, may be eligible for an **additional 3 cycles of study therapy** in both the monotherapy (Parts 1A and 2A) and combination therapy (Parts 1B and 2B). These participants will be selected on a case by case basis, after careful evaluation and discussion with the BMS Medical Monitor, to determine whether the risk/benefit ratio supports administration of further study therapy. Upon completion of 3 cycles of study therapy (or up to a maximum of 6 cycles if applicable), all participants will enter the safety follow-up period.

Individual participants with confirmed CR will be given the option to discontinue study treatment, on a case by case basis, after specific consultation and agreement between the Investigator and BMS Medical Monitor in settings where benefit/risk justify discontinuation of study therapy.

5.1.3 Follow-up

5.1.3.1 Safety Follow-up Period

For participants in Parts 1A, 1B, 2A and 2B, upon completion of 3 cycles of study therapy (or up to a maximum of 6 cycles if applicable), and once the decision is made to discontinue the participant from treatment, ie, at end of treatment (EOT), all participants will enter a safety follow-up period.

In Parts 1C and 2C, participants can receive study treatments up to a maximum of 2 years in the absence of disease progression or unacceptable toxicity. Once a decision is made to discontinue treatment, the participant will enter a safety follow-up period.

For participants who complete all scheduled cycles of therapy, the EOT visit will be the same visit as the last scheduled and completed on-treatment visit, and will be the start of the safety follow-

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

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

5.1.3.2 Response Follow-up Period (Parts 1A, 1B, 1C, 2A, 2B, and 2C)

Participants, with SD, PR, or CR, at the time of the EOT visit or at the time of study drug discontinuation, will continue to have radiologic and clinical tumor assessments every 12 weeks for the first year after discontinuation of study drug/EOT visit. Subsequently, they will continue to receive tumor assessment scans as per standard of care guidelines, or at a minimum of every 6 months up to 2 years following the last dose of study drug, or until disease progression/withdrawal of study consent. 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 following an initial course of study therapy will not be evaluated for response 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, participants in Parts 1A, 1B, 2A and 2B will start the survival follow-up period. Participants will be followed-up by telephone every 12 weeks (from EOT) for 2 years until death, loss to follow-up, withdrawal of consent, or conclusion of the study, whichever comes first. Participants with SD, PR or CR will have both the response follow-up period and survival follow-up period occur simultaneously during the 2-year follow-up period. The duration of this follow-up is up to 2 years following the last dose of study drug, although a longer follow-up period could be considered in selected cases if an efficacy signal is apparent. Tumor assessment scans, for participants who have ongoing clinical benefit beyond the 2 year period following last dose of study drug, may continue to be collected as part of standard-of-care treatment.

In Parts 1C and 2C, the survival follow-up period will continue for 2 years following the last dose of study drug or until death, lost to follow-up, withdrawal of consent, or conclusion of the study, whichever comes first. Survival follow-up visits will occur every 12 weeks (±7 days) until 2 years after the last dose of study drug. Study assessments are to be collected as outlined in Table 2-5.

5.1.3.4 Retreatment During Follow-up Periods (Parts 1A, 1B, 2A, and 2B)

Retreatment may be allowed for participants with disease progression during the safety, response or survival follow-up period. Participants completing approximately 3 cycles of study therapy (or up to a maximum of 6 cycles, if applicable), and entering the survival follow-up period with

ongoing disease control (CR, PR or SD), may be eligible for retreatment upon disease progression. Eligibility will be dependent upon participants having confirmed disease progression within 12 months after the last dose of study drug, and will considered on a case by case basis, after careful evaluation and discussion with the BMS Medical Monitor, to determine whether the risk/benefit ratio supports administration of further study therapy. Participants meeting criteria for retreatment will have to provide written consent prior to receiving any additional retreatments, by signing an ICF which describes any reasonably foreseeable risks or discomforts, or other alternative treatment options. Participants meeting criteria for, and consenting to, retreatment, will be treated with the originally assigned monotherapy or combination therapy regimen (eg, same dose and dose schedule as administered during the first 24 weeks), unless that dose and its schedule were subsequently found to exceed the MTD. In that case, the participant will be treated at the next lower or alternate dose and schedule. Alternatively, if the MTD has been determined at the time point when the participant is being retreated, that participant can be retreated at the MTD.

Participants entering retreatment will follow the same Time and Events schedule as outlined in Section 2. Samples for PK will be collected less frequently (only at predose of each treatment cycle). [redacted]

5.1.4 Treatment Beyond Progression

Treatment beyond progression may be allowed for a maximum treatment duration of up to 2 years in selected participants with initial RECIST v1.1 progressive disease, following discussion and agreement with the BMS Medical Monitor that the benefit-risk assessment favors continued administration of study treatment (eg, participants are continuing to experience clinical benefit, as assessed by the Investigator, tolerating treatment, and meeting other criteria).

A described in Section 5.4.6, accumulating evidence indicates a minority of participants treated with immunotherapy may derive clinical benefit despite initial evidence of progressive disease. Participants will be permitted to continue on study drug for treatment beyond initial RECIST v1.1-defined progressive disease as long as they meet the following criteria:

- Investigator-assessed clinical benefit and no rapid disease progression
- Participant is tolerating study treatment
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious
- complications of disease progression (eg, CNS metastases)
- Participant provides written informed consent prior to receiving additional BMS-986207, nivolumab, and ipilimumab treatment, using an ICF describing any reasonably foreseeable risks or discomforts, or other alternative treatment options.

The decision to continue treatment beyond initial Investigator-assessed progression should be discussed with the BMS Medical Monitor and documented in the study records. A follow-up scan should be performed within 4 to 6 weeks of original progressive disease to determine whether there has been a decrease in the tumor size or continued progression of disease. Subsequent scans should be performed every 12 weeks until further progression is determined. If the Investigator

feels that the participant continues to achieve clinical benefit by continuing treatment, the participant should remain on the trial and continue to receive monitoring according to the Schedule of Activities in Section 2. For participants who continue study therapy beyond progression, further progression is defined as an additional 10% increase in tumor burden from time of initial progressive disease. 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 progressive disease. Nivolumab, ipilimumab, and BMS-986207 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.

5.1.5 Data Monitoring Committee and Other External Committees

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 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 accumulated safety data. Within BMS, an SMT is established for investigational therapies under clinical development, and a member of WWPS chairs this team. In addition, safety signal detection is performed at least monthly and ad hoc throughout the study by the SMT composed, at a minimum, of the WPS medical safety assessment physician (Chair of the SMT) and WWPS single-case review physician, the study Medical Monitor, the study biostatistician, and epidemiologist, all of whom evaluate the safety data regularly. Furthermore, the SMT routinely monitors for actual or potential issues related to participant safety that could result in a change in the medical benefit-risk balance associated with the use of study treatment(s). For Part 2C, continuous safety monitoring based on a Bayesian framework is also planned in the NSCLC cohort for ongoing evaluation of the tolerability of the selected dose.

5.2 Number of Participants

The approximate number of evaluable participants will be approximately 241. Approximately 100 of these participants will be treated with monotherapy and combination therapy dose escalation (35 participants each for Part 1A and Part 1B and additional 30 participants for the substudy of

Part 1B), and approximately 36 participants treated (6 initial participants for safety evaluation followed by evaluation of approximately 12 additional participants per dose level) with BMS-986207, nivolumab, and ipilimumab in the Triplet Cohort (Part 1C). The remaining participants (up to 105) will be treated as part of dose expansion, with up to 24 participants in Part 2A and 41 participants in Part 2B, and 40 participants with NSCLC and [redacted] (pre-existing or prior PD-L1 IHC results from testing of tumor tissue) considered to be response-evaluable, in Part 2C. In the event more than 25% of the participants in Part 2C are found to have a PD-L1 tumor cell score of < 1%, based on central lab testing, additional participants may be enrolled in order to have at least 30 participants with a PD-L1 tumor cell score ≥ 1%.

5.3 End of Study Definition

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

5.4 Scientific Rationale for Study Design

BMS-986207 is being investigated in humans with advanced solid tumors; either as monotherapy and in combination with nivolumab and ipilimumab. The study design for Parts 1A, 1B, 2A, and 2B includes the following:

- 28-day screening period
- 24-week (3 cycles) treatment period, with the option of an additional 24 weeks (3 cycles) of treatment (granted on a case by case basis)
  - Dose escalation phase
  - Cohort expansion phase
- Safety follow-up period
- Response/Survival follow-up period, with the possibility for retreatment

The study design for Parts 1C and 2C, aligned with concurrent use of nivolumab and ipilimumab, includes the following:

- 28-day screening period
- Treatment period − up to a maximum of 2 years in the absence of disease progression or unacceptable toxicity
- Safety follow-up period (30, 60, and 100 days (± 7 days) after last dose or date of discontinuation)
- Survival follow-up period − 2 years following the last dose of study drug or until death, lost to follow-up, withdrawal of consent, or conclusion of the study, whichever comes first

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

5.4.1 Rationale for BMS-986207 Monotherapy in Colorectal Cancer Cancer and Other Cancers Associated with Fusobacterium Nucleatum

In CRC, bacteria such as *Fusobacterium nucleatum* (*F. nucleatum*) are abundant in the tumor microenvironment. The amount of *F. nucleatum* DNA in CRC tissue is associated with shorter survival, and may potentially serve as a prognostic [redacted] *F. nucleatum* is thought to facilitate a tumor's ability to evade immune cell attack through inhibition of the function of T lymphocytes and NK cells.[25] Tumor-infiltrating lymphocytes usually express TIGIT, thus T cell activities can be inhibited by *F. nucleatum* via Fap2, a protein unique to *F. nucleatum*. Given localization of Fap2 in the colon, it is anticipated that BMS-986207 monotherapy will be therapeutically effective for CRC. *F. nucleatum* may play a role in mediating tumor immune escape through interaction with TIGIT in other indications, such as SCCHN, in which the bacterium may be isolated from saliva samples.[26] In these other tumors, similarly to CRC, *F. nucleatum* activates lymphocyte apoptosis by Fap2 and RadD,[27] supporting the rationale for testing anti-TIGIT therapy in SCCHN and other tumor types associated with *F. nucleatum* infection.

In addition, microbiome data will be collected in other tumor types in expansion (HCC and ovarian cancer) to explore the hypothesis that the gut microbiome may condition the response to immunotherapy.[28]

5.4.2 Rationale for the Combination of BMS-986207 and Nivolumab

Therapeutic antibodies with the ability to block immune checkpoint receptors, or activate immunostimulatory receptors, have the potential to be effective for the treatment of cancer by modulating the participant's immune system. It has become apparent that tumors co-opt some specific immune-checkpoint pathways to engender immune resistance, particularly against T cells that are specific for tumor antigens.[29] Co-engagement of multiple immune receptors on activated T cells (combination immunotherapy) may result in better outcomes as compared to engagement of a single immune receptor. Nonclinical data, evaluating the combination of BMS-986207 and nivolumab in the CT26 mouse, support this hypothesis (Section 3.2.1.1). Combining the anti-TIGIT mAb, BMS-986207, with the anti-PD1 antibody, nivolumab, is an opportunity to evaluate the activity of therapeutic drugs targeting PD1 and TIGIT, given in combination, in humans.

5.4.3 Rationale for the Combination of BMS-986207, Nivolumab, and Ipilimumab

As discussed in Section 3.2.4, nivolumab and ipilimumab have demonstrated beneficial effects in multiple tumor types in multiple clinical trials. Several studies have shown benefit of combining TIGIT and PD-L1 inhibitors, particularly in NSCLC patient populations.[15,16] There are no studies, to date, which have examined the effects of both anti-TIGIT and anti-CTLA-4 in tumors in humans. TIGIT and CTLA-4 are members of the same family of immunoglobulin-related receptors that are responsible for various aspects of T cell immune regulation. Like PD-1 these receptors have inhibitory roles in T cell function. In BMS study BDX-1482-105, anti-mouse TIGIT combined with anti-mouse CTLA-4 showed superior antitumor activity and prolonged survival compared with antibodies administered as single agents in a CT26 mouse model.[30] In the present

CA020002 study, to evaluate whether a differentiated approach of using TIGIT inhibition and cancer immunotherapies can further enhance [redacted] immune activity, BMS-986207 in combination with nivolumab and ipilimumab will first be evaluated for safety and proper doses of each drug in participants with various solid tumors (Part 1C). This safety evaluation will then be followed by evaluation of the safety and efficacy of this triplet combination in 1L NSCLC patients with tumors having PD-L1 expression ≥1%.

The above data, together with the recent data shown for TIGIT inhibition and PD-L1 inhibitors in this tumor type, as well as that only limited participants (n=2) with NSCLC have been treated in the present CA020002 study [redacted], indicate that further evaluation is warranted for BMS-986207 in combination with nivolumab and ipilimumab in 1L NSCLC participants whose tumors have ≥ 1% PD-L1 expression.[31,32]

5.4.4 Rationale for the Combination of BMS-986207, Nivolumab and Ipilimumab in NSCLC

Recent reports in the literature have shown comparable efficacy with anti-TIGIT agents, vibostolimab or tiragolumab in combination with anti-PD-L1 agents, pembrolizumab and atezolizumab, respectively. Modest or no anti-tumor activity was seen when the anti-TIGIT agents were given as monotherapy in NSCLC, HNSCC, triple-negative breast cancer, or esophageal cancer populations. Best clinical responses were observed in these studies in 1L and previously treated NSCLC participants whose tumors expressed PD-L1.[15,16,17,31]

A randomized Phase 2 study comparing the anti-TIGIT agent tiragolumab plus atezolizumab versus placebo plus atezolizumab in PD-L1-positive 1L Stage IV NSCLC patients demonstrated improvement in the overall response rate (ORR; 37% vs. 21% with atezolizumab alone). The treatment regimen was well tolerated, with safety similar to that seen in the placebo plus atezolizumab treatment. In addition, recent data presented from a Phase 1 study (NCT02964013) of the anti-TIGIT antibody vibostolimab plus pembrolizumab in participants with anti-PD-(L)1-naive NSCLC demonstrated anti-tumor activity (ORR 29% in all patients and 46% in patients with PD-L1 ≥ 1% expression).[16,17] These data suggest that combining TIGIT blockade with anti-PD-(L)1 can be safe, tolerable, and have clinical benefits in PD-L1-positive 1L NSCLC.[16,32]

In the present CA020002 study, heterogeneous, refractory solid tumor participant populations primarily with tumors that are not anti-PD-1 responsive (eg, CRC, ovarian, post-PD-1 melanoma) have been enrolled and treated either with BMS-986207 monotherapy or BMS-986207 in combination with nivolumab. There was no opportunity to evaluate BMS-986207 in NSCLC patients in Cohorts 1A, 1B, 2A, and 2B. The first two participants with NSCLC were enrolled in Part 1C.

Data from BMS CheckMate 227, a randomized, open-label, phase 3 study in participants with treatment-naive PD-L1-positive NSCLC demonstrated that, among the patients with a PD-L1 tumor cell expression level of 1% or more, the combination of nivolumab plus ipilimumab was safe and tolerable and improved overall survival (OS) compared to chemotherapy alone (median

OS=17.1 versus 14.9 months, HR=0.79, 95% CI: 0.65-0.96).[33] The combination of nivolumab and ipilimumab without chemotherapy is approved, per the USPI, for adults with metastatic NSCLC expressing PD-L1 ≥ 1%.[34,35]

Based on these data and specific indications, the nivolumab and ipilimumab combination is an appropriate backbone therapy in PD-L1 positive 1L NSCLC for the addition of a novel anti-TIGIT agent BMS-986207. Using this triplet combination enables the use of a checkpoint inhibitors combination of proven efficacy (nivolumab + ipilimumab), along with the potential advantage of adding anti-TIGIT (BMS-986207) to a NSCLC population that appears to benefit from TIGIT inhibition based on recent studies.[16,17] Inclusion of 1L NSCLC patients with PD-L1 expression ≥ 1% will capture the potential benefit of an anti-TIGIT antibody in a larger population and promote enrollment. Recently published data support the use of anti-TIGIT antibodies in this population and, if proved to be effective, will fulfill the unmet need of treatment options that do not include chemotherapy.

5.4.5 Rationale for Treatment Duration

Despite recent advances in immunotherapies for the treatment of cancer, the ideal treatment duration to achieve and perpetuate good durable response is still an area of ongoing investigation. Current clinical data on the time to response suggest that, most patients who show a response, do so within the first 24 weeks on therapy. At the time of this study's initiation, treatment with BMS-986207, alone or in combination with nivolumab, was limited to 24 weeks (3 cycles), with an option of an additional 24 weeks (3 cycles) based on evaluation of individual risk/benefit on a case by case basis.

Accumulating evidence from different clinical trials in which participants with different tumor types were treated with nivolumab or nivolumab combined with ipilimumab indicates that most responses generally occur early, with a median time to response of 2 to 4 months including responses observed in patients with NSCLC. [36,37, 38] A recent analysis in a melanoma study suggests the majority of patients who discontinue nivolumab and/or ipilimumab for toxicity maintain disease control in the absence of further treatment. [39] For these reasons, treatments in Parts 1C and 2C will be given for up to 2 years in the absence of disease progression or unacceptable toxicity.

5.4.6 Rationale for Treatment Beyond Progression

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

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

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

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

5.4.7 Rationale for Tumor Selection

TIGIT is expressed by activated T cells, Tregs, and NK cells, and binds the adhesion molecules PVR (CD155) and Nectin-2 (CD112) with higher and lower affinity, respectively.[13] PVR and Nectin-2 also bind to TIGIT's co-stimulatory counterpart, DNAM-1 (CD226). DNAM-1 is an activating receptor expressed on NK cells, CD8+ T cells, and other immune cells. [40] Upon recognizing its ligands PVR and Nectin-2, DNAM-1 promotes NK cell–mediated elimination of damaged cells.

One can hypothesize that the tumors most likely to respond to anti-TIGIT therapy are those with the highest PVR/Nectin-2 expression, and those with moderate-to-high immune cell infiltration. Accordingly, the selected tumor types of HCC, CRC, ovarian cancer, and NSCLC and their respective rationale for selection, are given in Table 5.4.7-1.

Table 5.4.7-1: Rationale for Tumor Selection

	Rationale	Tumor Selection	Comments
1	• High ligand expression but low TILs • Aim to increase TILs and trigger anti-tumor activity • Potential for anti-TIGIT and nivolumab combination	HCC	
2	PD1 nonresponsive tumors with mechanistic rationale	CRC	TIGIT-mediated immune escape via microbiome. CRC, and other indications in which *F nucleatum* may play a role in the immune escape, will be evaluated in TIGIT monotherapy and TIGIT + nivolumab.

Table 5.4.7-1: Rationale for Tumor Selection

Rationale		Tumor Selection	Comments
3	Nectin-centric tumor to differentiate role of nectin-2 and PVR	Ovarian cancer	Nectin-2 in ovarian cancer is the key driver of TIGIT-mediated immune suppression.
4	• High ligand expression correlates with PD-L1 expression especially in TILs • Potential for anti-TIGIT and anti-PD-L1/PD-1 antibodies combination in PD-L1-positive NSCLC.	NSCLC	

Abbreviations: CRC, colorectal cancer; HCC, hepatocellular carcinoma; NSCLC, non-small cell lung cancer; PD-(L)1, anti-programmed cell death (ligand) 1; PVR, poliovirus receptor TIGIT, T cell Ig and ITIM domain; TIL, tumor infiltrating lymphocyte.

5.4.8 Rationale for Dose Escalation Phase Design

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 preclinical studies as well as historical clinical trials. The Escalation with Overdose Control (EWOC) principle limits the risk of exposing participants in the next cohort to an unsafe 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 with 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. After completing the monotherapy phases (Parts 1A and 1B), the drug-associated dose-toxicity profiles are characterized and incorporated as prior knowledge into the drug combination phase of the study (Parts 2A and 2B) or used in future studies.

For Part 1C where a single select dose level of BMS-986207 will be evaluated with potential for a lower dose (de-escalation), a simpler mode-assisted design framework will be used, the BOIN design, to evaluate tolerability based on incidence of DLTs.[23,24] Additional lower doses may be tested for dose optimization at the Sponsor's discretion.

5.5 Justification for Planned Dose Selection

5.5.1 The current study is a FIH study.

There is no previous clinical experience with BMS-986207.

5.5.1.1 Introduction

The FIH starting dose of BMS-986207 as an immune-mediated anti-cancer agent was determined using both toxicology- and pharmacology- (anti-tumor efficacy)-based approaches to ensure

participant safety while limiting the number of participants receiving nonpharmacologically active doses. The toxicology-based approach utilized the HNSTD determined from a 1-month repeat-dose toxicity study in cynomolgus monkeys. The pharmacology-based approach leveraged the pharmacology data (ie, anti-tumor efficacy) obtained from mouse surrogates to project the human effective dose, from which the FIH starting dose was selected. The starting doses determined from both approaches were integrated, and the lower dose (1 mg/kg or 80 mg assuming an average body weight of 80 kg in cancer patients) derived from the pharmacology data is recommended as the FIH starting dose for BMS-986207.

To further ensure a sufficient safety margin for the monotherapy starting dose, given the absence of previous clinical experience with BMS-986207, a Preliminary Safety Cohort (PSC) was added to the study. In the PSC, a single participant will receive BMS-986207 monotherapy starting at the 2 mg dose, with intra-participant dose escalation to 6 mg, and then to 20 mg. Following a 5-day safety observation period for this participant following the initial administration of the 20 mg dose, two additional participants will begin the study at the 20 mg BMS-986207 dose level. See Appendix 13 for complete detail on the Preliminary Safety Cohort.

5.5.1.2 Nonclinical Pharmacokinetics and Efficacy

Human starting dose selection is based on preclinical pharmacological activity. The anti-tumor efficacy of an anti-mouse TIGIT antibody surrogate (10A7-mIgG1 D265A, abbreviated as 10A7) was studied in a mouse CT26 colon adenocarcinoma model as a single agent and in combination with an anti-mouse PD-1 antibody (4H2-mIgG1 D265A, abbreviated as 4H2). In the study, 10A7 did not have single agent activities. When combined with 4H2, 10A7 exhibited dose-dependent anti-tumor efficacies, and with the dose increased from 0 to 0.3, 1, 3, and 10 mg/kg, the median tumor growth inhibition (TGI) increased from [redacted] respectively. Consistently, the number of tumor-free mice in each dose group [redacted] also increased in a dose-dependent manner. The effective dose of 10A7 in combination with 4H2 in the mouse CT26 model is considered to be [redacted] to achieve close to maximal efficacy ([redacted] TGI). At the effective dose level, the Cave.14d and Cmin.14d of 10A7 are estimated to be [redacted] µM, respectively. Because 10A7 and BMS-986207 exhibited similar binding affinities on the respective activated mouse and human CD8+ T cells [redacted] respectively), the human effective dose of BMS-986207 is projected to target the steady-state Cave and Cmin of [redacted], respectively.

To project the human effective dose, the human clearance [redacted] was allometrically scaled from the cynomolgus monkey data with a power exponent o[redacted] and the human volume of distribution ([redacted] was assumed to be equal to that in cynomolgus monkeys (Please refer to Table 5.5.1.2-1). Additionally, the following assumptions were made: 1) 2-compartment PK model; 2) dose-proportional PK; and 3) minimal impact of ADAs on PK. By achieving the same Cave and Cmin in humans at the steady state as the effective Cave.14d and Cmin.14d in mice, the human effective dose of BMS-986218, administered q2w, was projected to be 4 mg/kg (or 320 mg for a body weight of 80 kg). At the equivalent exposure of the clinical starting dose, the projected anti-tumor efficacy of its mouse surrogate 10A7 in combination with 4H2 is approximately [redacted] TGI in the CT26 tumor model.

Table 5.5.1.2-1: Exposure Multiples from Monkey GLP Toxicity Studies versus Proposed FIH Starting Dose of 1 mg/kg and Other Planned Clinical Doses

BMS-986207 Dose, mg/kg (Flat Dose)	Projected Human AUC(0-336h),ss (µg•h/mL)	Projected Human Cmax (µg/mL)	Safety Multiples[a] Based on AUCτ,ss	Safety Multiples[a] Based on Cmax,ss
[redacted]				

Abbreviations: AUC, area under the concentration-time curve; BMS, Bristol-Myers Squibb; FIH, first-in-human

[a] Based on BMS-986207 exposure [redacted] Cmax 4110 µg/mL) following repeat IV qw dosing in [redacted] at the NOAEL/HNSTD ([redacted]). [redacted]

5.5.1.3 Nonclinical Toxicity Data

The nonclinical safety of BMS-986207 was evaluated in vitro in a human tissue cross-reactivity study and cytokine release and lymphocyte activation assays with human cells, as well as in an in vivo 1-month intermittent repeat-dose IV toxicity study in cynomolgus monkeys. The cynomolgus monkey was selected as the toxicology species because BMS-986207 binds to TIGIT expressed on activated cynomolgus monkey T cells with a similar affinity as TIGIT expressed on activated human T cells [redacted] and is pharmacologically active in monkeys. BMS-986207 does not bind rodent TIGIT.

In a Good Laboratory Practice-compliant tissue cross-reactivity study in normal human tissues, fluoresceinated BMS-986207 produced membrane and cytoplasmic staining of mononuclear cells in human lymphoid tissues and select nonlymphoid tissues. This staining was expected based on TIGIT expression by mononuclear cell types, such as T cells and NK cells. No unexpected tissue cross-reactivity was observed. BMS-986207 did not induce cytokine release or increase the expression of activation [redacted] on human T, B, or NK cells in an in vitro human peripheral blood mononuclear cell cytokine release and cell activation assay, suggesting a low risk of BMS-986207-induced cytokine release syndrome.

In a 1-month pivotal toxicity study in monkeys, BMS-986207 was administered IV as a slow bolus at doses of 0, 10, 30, or 100 mg/kg (5 doses/week). BMS-986207 was clinically well tolerated by all monkeys at 30 and 100 mg/kg doses, while 3 out of 10 monkeys in the 10 mg/kg dose group exhibited signs of ADA mediated hypersensitivity reactions immediately after dosing. The clinical signs were transient, accompanied by increases in serum cytokine levels and complement activation, and no treatment was required for the affected monkeys. The timing, type of clinical observations, and correlative complement activation are consistent with the formation of

treatment-emergent ADAs, a common response by monkeys to a foreign protein. This immunogenicity is not considered to be predictive for ADA responses in humans (ICH S6). [redacted] responses in terms of NK cell activation, CD8+ T cell activation and proliferation, were observed at all doses, and were generally dose-independent. Based on the lack of directly BMS-986207-related adverse findings, the no-observed-adverse-effect level (NOAEL) was considered to be [redacted] In addition, for determination of the maximum recommended human starting dose, [redacted] was also considered the HNSTD. The HNSTD/NOAEL of [redacted] than the proposed starting dose in humans (1 mg/kg) with a corresponding plasma [redacted] the projected human AUC (0-336),ss at 1 mg/kg [redacted]

Overall, the nonclinical toxicology assessment of BMS-986207 has demonstrated an acceptable safety profile, supporting clinical use in oncology patients.

5.5.1.4 Rationale for Starting Dose in Humans

The selection of the BMS-986207 starting dose is based on the nonclinical CT26 mouse syngeneic tumor model (TGM1607), for combined BMS-986207 and nivolumab, and the pivotal repeat-dose IV toxicology study in monkeys.

In the pivotal repeat-dose (5 doses/week) IV toxicity study, the dose of [redacted]) was established as the HNSTD and NOAEL dose. Using a safety factor of 6, the maximum recommended starting dose (MRSD) of [redacted] was derived. This toxicity-based dose of [redacted] was considered an inappropriate starting dose given that dose level's relationship to the projected human effective dose.

Therefore, the projected human effective dose derived from CT26 mouse tumor model was used to determine the selection of the FIH starting dose. At the dose of 1 mg/kg for BMS-986207 (IV q2w), its TGI was projected as approximately [redacted] Additionally, the dose of 1 mg/kg was projected with AUC (0-336h),ss of [redacted] which has an approximate [redacted] fold safety margin relative to the AUC[0-168h],ss of HNSTD and NOAEL dose [redacted] from the weekly, repeat-dose monkey study, after normalization of the dosing interval.

Based on the projected [redacted] TGI and the corresponding [redacted]-fold safety margin, 1 mg/kg was selected as the FIH starting dose for BMS-986207 monotherapy, administered q2w. The recommended starting human dose of 1 mg/kg was converted to a flat dose of 80 mg by multiplying by a standard body weight assumption of 80 kg.

5.5.2 Rationale for Dosing Schedule

5.5.2.1 BMS-986207

In this study, the BMS-986207 dosing schedule of q2w was based on the projected human half-life, derived from a monkey single dose study [redacted]. The PK profiles of BMS-986207 in monkeys following a single IV dose of 1, 10, and 100 mg/kg were used to project the human PK

parameters. The projected half-life in humans is [redacted], which approximates 14 days (q2w), the selected dosing schedule.

The human effective dose of BMS-986207 administered in combination with nivolumab in cancer patients, was projected to target steady-state average plasma concentration (Cave) and minimum plasma concentration (Cmin) of [redacted], respectively, equivalent to 10A7-mIgG1 D265A Cave_14d and Cmin_14d at the efficacious dose in CT26 mouse tumor model. Based on the projected human PK of BMS-986207, the human effective is projected to be 4 mg/kg IV administered once every 2 weeks (q2w). A flat dose of BMS-986207 (mg) will be used in this study, given similar exposure variability of flat-dose as compared to body weight-based dosing for many therapeutic antibodies and practical advantages. [41]

The current protocol evaluates the q2w dosing regimen. A dosing regimen of q4w is being considered for the single-agent of BMS-986207, as well as with in combination with nivolumab. The q4w option will benefit the patients with less frequent visits and reduce the medical burden from the care givers and the cancer treatment institutions. The projected human PK profile of BMS-986207 is linear, and the dose for q4w dosing schedule will be based on q2w with linear extrapolation. The exposure, efficacy and safety, of BMS-986207 as a single agent and in combination with nivolumab, will be evaluated and compared with the q2w dosing schedule. Based on the totality of clinical data, the sponsor will consider to revise the dosing regimen, if appropriate.

BMS-986207 PK was evaluated in participants with advanced solid tumors receiving q2w (20, 80, 240, 800, or 1600 mg) and q4w (480 or 1600 mg) doses in Part 1A, 1B and 2A of CA020002. Preliminary PK results of BMS 986207 suggest the increase in exposure is proportional across the dose range evaluated, which is in agreement with preclinical predictions. The CLT appears consistent across doses. For participants who received combination treatment with nivolumab in Part 1B, the PK of BMS-986207 appears to be consistent with that reported for monotherapy in Part 1A and 2A.[19]

In the Triplet Cohort (Part 1C), the initial proposed BMS-986207 dose was 1200 mg q3w based on lower Cmax, similar Cavg and [redacted] as compared to 1600 mg q4w, a safe and tolerable dose evaluated in combination with nivolumab in Part 1B and the projected saturation of intratumoral TIGIT receptor occupancy at [redacted] level to provide optimal clinical benefit. Preliminary data as per 20-Oct-2021, revealed that 2 out of 4 DLT-evaluable participants experienced DLTs with the combination of BMS-986207 1200 mg Q3W, nivolumab 360 mg Q3W, and ipilimumab 1 mg/kg Q6W (see Section 3.2.1.4 for more details). BMS-986207 dose of 1200 mg Q3W was reduced to 600 mg per BOIN design. BMS-986207 dose of 600 mg Q3W is expected to provide half of the exposure as compared to 1200 mg Q3W, and a relatively high intratumoral TIGIT receptor occupancy at the [redacted] level. In addition, BMS-986207 dose of 360 mg Q3W may be explored to aid in RP2D dose selection and per BOIN design if de-escalation is needed.

The selection of an every-3-weeks regimen allows for aligning the schedule of BMS-986207 with combination of nivolumab q3w and ipilimumab q6w in 1L NSCLC (See Section 5.5.2.2 and

Section 5.5.2.3), since the primary efficacy evaluation in Part 2C will be in participants with 1L NSCLC.

5.5.2.2 Nivolumab

Nivolumab monotherapy has been extensively studied in multiple tumor types, including melanoma, NSCLC, RCC, cHL, SCCHN, and urothelial carcinoma, and has been safely administered at doses up to 10 mg/kg q2w. Nivolumab is currently approved for the treatment of various tumor types with monotherapy regimen of 480 mg q4w, 240 mg q2w, or 3 mg/kg q2w. When used in combination with ipilimumab and chemotherapy, nivolumab 360 mg q3w is approved for the treatment of 1L NSCLC.

Based on the clinical experience and quantitative clinical pharmacology understanding, nivolumab 480 mg q4w, 360 mg q3w, or 240 mg q2w infused over approximately 30 minutes were selected in this study as these doses are expected to provide similar nivolumab exposures (Cavg and Ctrough), and to allow the flexibility of aligning doses of nivolumab at the same dosing frequency of BMS-986207 for the combination treatment.

Specifically, in the Triplet Cohort (Part 1C) and Triplet NSCLC Expansion (Part 2C), participants will receive 360 mg q3w nivolumab in combination with ipilimumab 1 mg/kg q6w and BMS-986207 600 mg q3w.

5.5.2.3 Ipilimumab

Ipilimumab is approved as monotherapy for the treatment of advanced melanoma and adjuvant melanoma with 3 mg/kg q3w for 4 doses and 10 mg/kg q3w for 4 doses followed by maintenance dose, respectively. Ipilimumab is also approved in combination with nivolumab for the treatment of various cancers, including melanoma, RCC, CRC, and HCC with a dosing regimen of 1 mg/kg q3w or 3 mg/kg q3w for 4 doses, depending on tumor type.[22]

In addition, a less frequent but continuous ipilimumab regimen (1 mg/kg q6w) is being evaluated in combination with nivolumab or nivolumab plus chemotherapy in a number of pivotal studies, including 1L NSCLC studies CA209227 and CA2099LA, 1L SCCHN study CA209651, and 1L mesothelioma study CA209743. For instance, study CA2099LA, evaluating nivolumab 360 mg q3w plus ipilimumab 1 mg/kg q6w given concomitantly with 2 cycles of chemotherapy, demonstrated superior survival benefit to patients with 1L NSCLC as compared to SOC chemotherapy. The safety profile of this triple combination regimen was reflective of the known safety profiles of the immunotherapy and chemotherapy. Ipilimumab 1 mg/kg q6w is currently approved for the treatment of 1L NSCLC, in combination with nivolumab or with nivolumab and 2 cycles of chemotherapy, and is also approved for the treatment of 1L mesothelioma, in combination with nivolumab.[34]

Based on the clinical experience, low-dose ipilimumab 1 mg/kg q6w infused over approximately 30 minutes will be examined in combination with nivolumab and BMS-986207 in the Triplet Cohort (Part 1C) and Triplet NSCLC Expansion (Part 2C) of this study.

5.5.2.4 Rationale for Infusion Times

Long infusion times (greater than or equal to 60 minutes), especially when multiple agents are administered sequentially to an individual, place a burden on participants and treatment centers. Establishing that investigational agents, such as BMS-986207, can be safely administered using an infusion time of 60 minutes will diminish the burden, provided there is no change in the safety profile.

In addition, a 60-minute post infusion safety observation period is considered appropriate given BMS-986207 is a fully human monoclonal antibody that is an antagonist (not an agonist) and has a low likelihood of resulting in infusion reactions. For participants < 42 kg on the 1600 mg dose, the infusion time will be 90 minutes. Details of drug preparation are found in Pharmacy Manual, a document that will be provided separately to the site.

In Parts 1B and 2B, when both study drugs are given in combination, nivolumab will be given first, over a 30 minute infusion period, followed by BMS-986207 over a 60-minute infusion period, beginning at least 30 minutes after completion of the infusion of nivolumab.

Nivolumab has been administered safely over 60 minutes at doses ranging up to 10 mg/kg over long treatment duration. In Study CA209010 (a Phase 2, randomized, double-blinded, dose-ranging study of nivolumab in participants with advanced/metastatic clear cell RCC), a dose association was observed for infusion site reactions and hypersensitivity reactions (1.7% at 0.3 mg/kg, 3.7% at 2 mg/kg, and 18.5% at 10 mg/kg). All the events were Grade 1 to 2 and were manageable. An infusion duration of 30 minutes for 3 mg/kg nivolumab (30% of the dose provided at 10 mg/kg) is not expected to present any safety concerns compared to the prior experience at 10 mg/kg nivolumab dose infused over a 60 minute duration.

Similarly, ipilimumab, which will be given in Part 1C and Part 2C, was safely administered over 90 minutes at 10 mg/kg. In the CA184022 study, where ipilimumab was administered up to a dose of 10 mg/kg, on-study drug related hypersensitivity events (Grade 1-2) were reported in 1 (1.4%) participant in the 0.3 mg/kg group and in 2 (2.8%) participants in the 10 mg/kg group. There were no drug-related hypersensitivity events reported in the 3 mg/kg group. Across the 3 treatment groups, no Grade 3-4 drug-related hypersensitivity events were reported and there were no reports of infusion reactions. Ipilimumab 10 mg/kg monotherapy has also been safely administered as a 90 minute infusion in large phase 3 studies in prostate cancer (CA184043) and as adjuvant therapy for stage 3 melanoma (CA184029), with infusion reactions occurring in participants. Administering 1 mg/kg of ipilimumab represents one-tenth of the 10 mg/kg dose and will be administered over one-third the time, for a lower infusion rate.

Of note, CA209153, a Phase 3b/4 safety study of nivolumab in participants with metastatic NSCLC who have progressed during or after at least 1 prior systemic regimen, used a 30 minute infusion in a cohort of participants with no safety issues.

Overall, infusion reactions, including high-grade hypersensitivity reactions, have been uncommon with nivolumab or ipilimumab administration or the combination of nivolumab and ipilimumab. Overall, a change in safety profile is not anticipated with a 30-minute infusion of nivolumab or ipilimumab, infusion times that are consistent with the current USPIs for each drug.

For participants with a bodyweight of > 250 kg the dosing of BMS-986207 will occur the day after dosing of nivolumab and ipilimumab when these drugs are administered on the same day. Details of study drug preparation are found in the Pharmacy Manual, a document that will be provided separately to the site.

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 that 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 must sign the ICF prior to the performance of any study-related procedures that are not considered part of standard of care.
   b) The participant must sign the consent for pretreatment and on treatment [redacted] (See [redacted] for details).
2) Target Population
   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).
   b) Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 (Appendix 8)
   c) All solid tumor histologies will be permitted in Parts 1A, 1B, and 1C
   d) Parts 1A, 1B, and 1C, participants must have received, and then progressed or been intolerant to, at least 1 standard treatment regimen in the advanced or metastatic setting, if such a therapy exists.
   e) Part 1A, participants with tumor types where the microbiome has been hypothesized, based on preclinical or clinical data, to mediate TIGIT inhibition (such as, but not limited to, CRC and SCCHN), will be prioritized for enrollment
   f) Part 1B, participants with tumor types where PD1/PD-L1 inhibitors are indicated as front line treatment can be enrolled to this study treatment naïve
   g) Part 2 A, only participants with CRC
   h) Part 2 B, only participants with CRC, HCC and ovarian cancer,
   i) Participants with CRC must have received, and then progressed on 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).
   j) Participants with CRC, microsatellite instability (MSI), mismatch repair (MMR), V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS), and B-Raf proto-oncogene (BRAF) status, if known, should be documented. If unknown, participants must consent to allow their submitted archived tumor tissue sample (block or unstained slides) to be tested.

k) For Part 2B Participants with HCC must have advanced HCC not amenable to curative resection, ablation or liver transplant.

l) For participants with HCC who progressed after locoregional therapy, then locorgegional therapy must be completed at least 4 weeks prior to the baseline scan. All acute toxic effects of any prior local treatment must have resolved to NCI CTCAE v4.03 Grade ≤ 1 or been deemed irreversible

m) Participants with radiological diagnosis of HCC may be enrolled for screening in the study but histological confirmation of HCC is mandatory prior to initiation of study therapy.

n) For participants with HCC, previous progressive disease, or been intolerant to, at least 1 line of therapy or refused treatment with sorafenib

o) For participants with HCC A Child-Pugh Class A (6 points or less) (Appendix 11)

p) For participants with HCC Must have results of testing for hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody, hepatitis B DNA polymerase chain reaction (PCR), hepatitis C antibody and hepatitis C ribonucleic acid (RNA) PCR.

q) For HCC participants with hepatitis B infection, a hepatitis B DNA viral load < 100 IU/mL is required and the participant must be on anti-viral therapy per institutional guidelines

r) For participants with hepatitis B infection, there must be no co-infection with hepatitis C or hepatitis D (must obtain hepatitis D antibody testing)

s) For participants with hepatitis C infection (HCV), active HCV infection, as defined by any detectable HCV RNA and positive antibody, can be enrolled providing they are on anti-viral therapy. Resolved HCV infection, as evidenced by undetectable HCV RNA and positive antibody, can be enrolled. Participants on antiviral therapy for HCV are permitted to enroll in the study and should continue treatment during the study. Participants with active HCV who are not on antiviral therapy at screening cannot be enrolled in the study

t) For participants with ovarian cancer in Part 2B, histologically or cytologically documented epithelial ovarian cancer, primary peritoneal carcinoma, or fallopian tube cancer

u) For participants with ovarian cancer in Part 2B completed at least one platinum based therapy (PBT) regimen (carboplatin, cisplatin, or another organoplatinum compound)

v) For participants with ovarian cancer in Part 2B, with platinum refractory, resistant, sensitive, intolerance to PBT (inability to receive PBT due to hypersensitivity reactions to platinum) are eligible

w) Part 2C, only participants with NSCLC who are treatment naive with baseline tumor PD-L1 expression ≥1% are eligible
   i) Participants with NSCLC in Part 2C must have histologically confirmed NSCLC per the 8th International Association for the Study of Lung Cancer classification (IASLC) of squamous or non-squamous histology, with no prior systemic anti-cancer therapy

(including epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK)/ROS1 inhibitors) given as primary therapy for advanced or metastatic disease.

ii) Prior definitive chemoradiation for locally advanced disease is permitted as long as the last administration of chemotherapy or radiotherapy (which ever was given last) occurred at least 6 months prior to enrollment.

iii) Prior adjuvant or neoadjuvant chemotherapy is permitted as long as the last administration of the prior regimen occurred at least 6 months prior to enrollment.

iv) Measurable disease by CT or MRI per RECIST v1.1 criteria (Appendix 5); radiographic tumor assessment performed within 28 days before randomization

v) Target lesions may be located in a previously irradiated field if there is documented (radiographic) disease progression in that site after the completion of radiation therapy.

vi) A formalin-fixed, paraffin-embedded (FFPE) tumor tissue block (preferred) or a minimum of 20 unstained slides of tumor tissue from core biopsy, excisional or incisional biopsy obtained during screening or prior to enrollment (within 3 months of enrollment and with no intervening systemic anti-cancer treatment between time of acquisition and enrollment) must be sent to the central laboratory. Fine needle aspirates or other cytology samples are not acceptable. Biopsies of bone lesions that do not have a soft tissue component or decalcified bone tumor samples are also not acceptable.

vii) Participants must have pre-existing or prior PD-L1 immunohistochemistry (IHC) results within 3 months of enrollment from testing of tumor tissue. PD-L1 expression must be tumor cell positive ≥ 1% for a participant to be eligible for enrollment.

viii) Prior palliative radiotherapy to non-CNS lesions must have been completed at least 2 weeks prior to randomization. Participants with symptomatic tumor lesions at baseline that may require palliative radiotherapy within 4 weeks of randomization are strongly encouraged to receive palliative radiotherapy prior to treatment assignment.

3) Physical and Laboratory Test Findings

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

i) Neutrophils ≥ 1500/μL

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

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

iv) WBC >_2000/μL

b) Adequate hepatic function (except for HCC)

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)

iii) **Specifically for participants with HCC:**

(1) Prothrombin time-international normalized ratio (PT/INR) ≤ 2.3 or PT ≤ 6 seconds above control

(2) Adequate hepatic function as documented by:

(a) Serum albumin ≥ 2.8 g/dL

(b) Total bilirubin ≤ 3 mg/dL

(c) AST and ALT ≤ 5 x the institutional ULN

c) Clinically stable thyroid function 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 PD sample collection and required study follow-up periods

4) Age and Reproductive Status

a) Males and females, aged at least 18 years old or local age of majority.

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

i) If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

ii) Additional requirements for pregnancy testing during and after study intervention are located in Section 2, Schedule of Activities.

iii) The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

c) Women must not be breastfeeding

d) WOCBP must agree to follow instructions for method(s) of contraception defined in Appendix 4 and as described below (g) and included in the ICF.

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

f) Male participants should maintain their usual practice with regard to contraception (if any); however, no specific contraceptive measures are required.

g) Please see Appendix 4 for further information on contraception methods.

h) WOCBP are permitted to use hormonal contraception methods (as described in Appendix 4)

i) A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

(1) Is not a WOCBP

OR

(2) Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of < 1% per year), preferably, with low user dependency, as described in Appendix 4 during the intervention period and for at least 5 months and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction for the same time period

i) Female participants must have documented proof that they are not of childbearing potential.

j) Women who are not of childbearing potential are exempt from contraceptive requirements.

Investigators shall counsel WOCBP, and male participants who are sexually active with WOCBP, on the importance of pregnancy prevention and the implications of an unexpected pregnancy.

6.2 Exclusion Criteria

1) Target Disease Exclusions

a) Participants with primary CNS disease, or tumors with CNS metastases as the only site of disease, will be excluded. Participants with controlled brain metastases, however, will be allowed to enroll. Controlled brain metastases are defined as no radiographic progression for at least 4 weeks following radiation and/or surgical treatment (or 4 weeks of observation if no intervention is clinically indicated), and no longer taking steroids for at least 2 weeks prior to first dose of study drug, and with no new or progressive neurological signs and symptoms.

b) Participants in Part 2C with known EGFR mutations which are sensitive to available targeted inhibitor therapy (including, but not limited to, deletions in exon 19 and exon 21 [L858R] substitution mutations) are excluded. All participants with non-squamous histology must have been tested for EGFR mutation status; use of an FDA-approved test

is strongly encouraged. Participants with non-squamous histology and unknown or indeterminate EGFR status are excluded.

c) Participants in Part 2C with known ALK translocations which are sensitive to available targeted inhibitor therapy are excluded. If tested, use of an FDA-approved test is strongly encouraged.

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 Sponsor/Medical Monitor is mandatory
   c) Prior immune therapy 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
   d) Prior participation in an anti-TIGIT clinical study
3) Prior anti-cancer treatments such as chemotherapy, radiotherapy, hormonal, or immunotherapy (including anti-PD1/PD-L1) are permitted (except for NSCLC participants in Part 2C).
4) Medical History and Concurrent Diseases
   a) Participants with concomitant second malignancies (except adequately treated nonmelanomatous skin cancers or in situ bladder, breast, or cervical cancers) are excluded unless a complete remission was achieved at least 2 years prior to study entry, and no additional therapy is required or anticipated to be required during the study period
   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 either resolved, returned to baseline or Grade 1, or deemed irreversible
      i) Any active neuropathy > Grade 2 (NCI CTCAE v4.03)
   e) Participants with the following:
      i) Active, known, or suspected autoimmune disease
         – Participants with well controlled asthma and/or mild allergic rhinitis (seasonal allergies) are eligible
         – Participants with the following disease conditions are also eligible:
            • Vitiligo
            • Type 1 diabetes mellitus
            • Residual hypothyroidism due to autoimmune condition only requiring hormone replacement
            • 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 drug)

- 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 (eg, anti-CTLA-4 or anti-PD-1/PD-L1 treatment or any other antibody or drug specifically targeting T cell co-stimulation or immune checkpoint pathways) except those that are unlikely to re-occur with standard countermeasures (eg, hormone replacement after adrenal crisis).

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

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

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

- Myocardial infarction or stroke/transient ischemic attack within the past 6 months
- Uncontrolled angina within the past 3 months
- Any history of clinically significant arrhythmias (such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes)
- History of other clinically significant heart disease (eg, cardiomyopathy, congestive heart failure with New York Heart Association functional classification III to IV [Appendix 9] pericarditis or significant pericardial effusion)
- Cardiovascular disease-related requirement for daily supplemental oxygen therapy
- QT interval corrected for heart rate using Fridericia's formula (QTcF) prolongation > 480 msec, except for right bundle branch block
- History of myocarditis, regardless of etiology

v) History of chronic hepatitis (except for HCC) as evidenced by the following:

- Positive test for hepatitis B surface antigen
- Positive test for qualitative hepatitis C viral load by PCR
  - 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.
  - Additional testing or substitute testing per institutional guidelines to rule out infection is permitted.
- **Specific exclusions for participants with HCC:**
  - Active coinfection with both hepatitis B and C

- Hepatitis D infection in participants with hepatitis B
- Clinically significant ascites or clinically significant variceal bleeding

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

vii) Known history of testing positive for HIV or known acquired immunodeficiency syndrome
Note: Testing for HIV must be performed at sites where mandated by local requirements.

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

ix) Receipt of nononcology vaccines containing live virus for prevention of infectious diseases within 4 weeks prior to first dose of study drug

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

(2) Previous SARS-CoV-2 vaccine within 14 days of C1D1 is not permitted.

x) Receipt of packed red blood cells or platelet transfusion within 2 weeks of the first dose of study drug unless agreed by the medical monitor.

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

xii) 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

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

(3) 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.

f) WOCBP who are pregnant or breastfeeding

5) Allergies and Adverse Drug Reaction

a) History of allergy to study drug components

b) History of severe hypersensitivity reaction to any mAb

6) Other Exclusion Criteria
   a) Prisoners or participants who are involuntarily incarcerated. (Note: under certain specific circumstances a person who has been imprisoned may be included or permitted to continue as a participant. Strict conditions apply and Sponsor approval is required.
   b) Participants who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness

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

6.3 Lifestyle Restrictions

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

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized/entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements (Appendix 10), and to respond to queries from regulatory authorities. Minimal information includes date of consent, demography, screen failure details, eligibility criteria, and any SAEs.

6.4.1 Retesting During Screening or Lead-In Period

This study allows for the re-enrollment of a participant that has discontinued the study as a pretreatment failure. Retesting of laboratory parameters and/or other assessments during the extended screening period will be allowed.

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

Testing for asymptomatic SARS-CoV-2 infection by 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 (e.g. 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. TREATMENT

7.1 Treatments Administered

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

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

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

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

Table 7.1-1: Study Drugs

Product Description Class and Dose Form	Potency	Blinding	Packaging Appearance	Storage Conditions (per Label)
BMS-986207 for injection[a]	160 mg/vial (20 mg/mL)	None	Vial	2 to 8°C. Protect from light and freezing.
Nivolumab (BMS-936558) solution for injection[a]	100 mg/vial (10 mg/mL)	None	Vial	2 to 8°C. Protect from light and freezing.
Ipilimumab (BMS-734016) solution for injection[a]	200 mg (5 mg/mL)	None	Vial	2 to 8°C. Protect from light and freezing.

Abbreviation: BMS = Bristol-Myers Squibb; C = Celsius; IP = investigational product

[a] All study drugs are considered IPs

For Parts 1A, 1B, 2A and 2B, the initial treatment period is up to 24 weeks (3 cycles) of dosing. Following each treatment cycle, the decision to treat a participant with the next cycle of study therapy, up to a maximum of 48 weeks (6 cycles) of treatment, will be based on risk/benefit

analysis and tumor assessment. For Parts 1C and 2C, the treatment period is up to a maximum of 2 years in the absence of disease progression or unacceptable toxicity.

Upon completion of treatment, participants will enter a safety follow-up period. Details of the dose escalation and cohort expansion phases in this study are given as part of the study design in Section 5. The selection and timing of dose for each participant are as shown in Table 7.1-2.

Table 7.1-2: Selection and Timing of Dose

Study Treatment	Participant Weight	Dosage formulation Frequency of Administration	Route of Administration	Infusion Time (min)
BMS-986207[a]				
80 mg	Any	Infusion q2w	IV	60
200 mg	Any	Infusion q3w	IV	60
240 mg	Any	Infusion q2w	IV	60
360 mg	Any	Infusion q3w	IV	60
480 mg	Any	Infusion q4w	IV	60
600 mg	Any	Infusion q3w	IV	60
600 mg	Any	Infusion q4w	IV	60
800 mg	Any	Infusion q2w	IV	60
1200 mg	< 38 kg	Infusion q3w	IV	90
1200 mg	≥ 38 kg	Infusion q3w	IV	60
1600 mg	< 42 kg	Infusion q2w and q4w	IV	90
1600 mg	≥ 42 kg	Infusion q2w and q4w	IV	60
Nivolumab				
240 mg	Any	Infusion q2w	IV	30
360 mg	Any	Infusion q3w	IV	30
480 mg	Any	Infusion q4w	IV	30
Ipilimumab				
1 mg/kg	Any	Infusion q6w	IV	30

Abbreviations: IV, intravenous; q2w, every 2 weeks, q3w, every 3 weeks; q4w, every 4 weeks; q6w, every 6 weeks.

[a] If dose-de-escalation is recommended by the design based on the number of participants with DLTs observed during this dose evaluation phase (Table 5.1.2.6-1), then the next lower dose level will be used (360 mg BMS-986207 q3w) for the remaining participants. In addition, other lower doses of BMS-986207 (200 mg q3w) than that seen as safe and tolerable may also be tested.

For participants < 42 kg on the 1600 mg dose, the infusion time will be 90 minutes. Details of study drug preparation are found in the Pharmacy Manual, a document that will be provided separately to the site.

For participants on combination treatment, a 30-minute infusion of nivolumab will be followed by a 30-minute observation period, followed by a 60-minute infusion of BMS-986207 and a 60-minute observation period after all infusions in Cycle 1 for each participant. A 60-minute post-infusion safety observation period is considered appropriate given BMS-986207 is fully human

antibody that is an antagonist antibody (not an agonist antibody) and has a low likelihood of resulting in infusion reactions. For participants in the Triplet Cohort (Part 1C) and Triplet NSCLC Expansion (Part 2C), a 30-minute infusion of nivolumab will be followed by a 30-minute observation period, followed by a 30-minute infusion of ipilimumab, a 30-minute observation period, followed by a 60-minute infusion of BMS-986207.

For participants < 38 kg on the 1200 mg dose, the infusion time will be 90 minutes. For participants with a bodyweight of > 250 kg the dosing of BMS-986207 will occur the day after dosing of nivolumab and ipilimumab when these drugs are administered on the same day. Details of study drug preparation are found in the Pharmacy Manual.

7.2 Method of Treatment Assignment

In this open-label study, enrolled participants, including those not dosed, will be assigned via IRT sequential participant numbers starting with [redacted] (eg, [redacted]). Those enrolled participants meeting the inclusion criteria, and none of the exclusion criteria, will be eligible to be dosed. Sequential numbering may restart at [redacted] for each participating site as the distinct participant identification number will ultimately comprise of the site number and participant number, (eg, [redacted]). In the expansion phase only, participants with CRC will be randomized in a 1:1 manner to either BMS-986207 monotherapy, or combination therapy with BMS-986207 and nivolumab, to eliminate the possibility of enrollment bias.

Participants in Part 2C with 1L NSCLC and tumor cell PD-L1 expression of ≥ 1% based on pre-existing lab results will be enrolled to receive combination therapy with BMS-986207, nivolumab, and ipilimumab. If more than 25% of the participants have a PD-L1 score < 1% as determined by the central lab, additional participants may be enrolled in order to have at least 30 participants with a tumor cell score of ≥ 1%.

Participants will not be replaced if they are discontinued from the study secondary to an AE unless the AE can be determined to be unrelated to treatment. If a participant is replaced after dosing, then the replacement participant will be assigned the original participant's number plus [redacted] The replacement participant will receive the same treatment as the participant being replaced but a new participant number will be assigned to him or her. For example, Participant [redacted] would be replaced by Participant [redacted]

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

7.3 Blinding

This is a non-randomized, open-label study and blinding procedures are not applicable.

7.4 Dosage Modification

For Parts 1A, 1B, 2A, and 2B intra-participant dose escalation/reduction of BMS-986207, nivolumab, or ipilimumab is not permitted in this study in order to allow better evaluation of the safety and efficacy at individual dose levels and schedules except as described for the Preliminary

Safety Cohort (see Section 5.1.2.3). For intra-participant dose reduction of BMS-986207 in Part 1C and 2C, see Section 5.1.2.6 and Section 5.1.2.7, respectively.

7.4.1 Dose Limiting Toxicities

For the purpose of guiding dose escalation, DLTs will be defined based on the incidence, intensity, and duration of AEs for which no clear alternative cause is identified. The DLT period will be 28 days (4 weeks) in Parts 1A and 1B. The DLT period for Part 1C will be 42 days (6 weeks).

For the purpose of participant management, any AE that meets DLT criteria, regardless of the cycle in which it occurs, will lead to discontinuation of study drug unless the Investigator determines that only 1 of the agents must be discontinued due to toxicity attributed to that agent alone. Participants who withdraw from the study during the 4-week DLT evaluation period (6-week DLT evaluation period for Parts 1C and 2C) for reasons other than a DLT may be replaced with a new participant at the same dose level. The incidence of DLTs during the 4-week DLT evaluation period (6-week DLT evaluation period for Parts 1C and 2C) will be used in dose escalation decisions and to define the MTD. AEs occurring after the 4-week DLT period (6-week DLT evaluation period for Parts 1C and 2C) will be considered for the purposes of defining the RP2D upon agreement between the Sponsor, Medical Monitor, and Investigators.

Participants experiencing a DLT will not be retreated with study drug, and will enter the safety follow-up period of the study. DLTs occurring after the 4-week (or 6-week period for Parts 1C and 2C) DLT observation period will be accounted for in determining the RP2D for expansion.

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

7.4.1.1 Hepatic Dose-Limiting Toxicity

Any one of the following study drug-related events will be considered a hepatic DLT (except for HCC participants):

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

Hepatic DLT for HCC participants

- AST or ALT > 10 × ULN for > 2 weeks
- AST or ALT > 15 × ULN, irrespective of duration

- Total bilirubin > 8 × ULN, irrespective of duration for participants with elevated total bilirubin at study entry, or > 5 × ULN for those with normal total bilirubin at entry
- Concurrent ALT ≥ 10 × ULN **AND** total bilirubin ≥ 2 × ULN or baseline value (if elevated bilirubin at study entry), **AND** no other immediately apparent possible causes of ALT elevation and hyperbilirubinemia. (For definition of p-DILI, see Section 9.2.7).

7.4.1.2 Hematologic Dose-Limiting Toxicity

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

7.4.1.3 Dermatologic Dose-Limiting Toxicity

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

7.4.1.4 Other Dose-Limiting Toxicities

Any of the following events will be considered a DLT:

- Grade 2 drug-related uveitis, episcleritis, iritis eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Grade 3 drug-related uveitis, episcleritis, iritis, pneumonitis, bronchospasm or neurologic toxicity
- Grade ≥ 4 hypersensitivity reaction or Grade 3 that does not resolve to Grade 1 in < 6 hours
- Other ≥ Grade 3 study drug-related toxicity will be considered a DLT. However, the following Grade 3 or 4 events will **not** be considered DLTs:
    - Grade 3 or Grade 4 electrolyte abnormalities that are not complicated by associated clinical adverse experiences, last less than 48 hours and either resolve spontaneously or respond to conventional medical intervention
    - Grade 3 nausea, vomiting, or diarrhea that lasts less than 48 hours, and either resolves spontaneously or responds to conventional medical intervention
    - Grade 3 or grade 4 elevation of amylase or lipase not associated with clinical or radiographic evidence of pancreatitis
    - Grade 3 fever not associated with hemodynamic compromise (eg, hypotension, clinical or laboratory evidence of impaired end-organ perfusion)
- Grade 3 endocrinopathy that is well controlled by hormone replacement

- Grade 3 tumor flare (defined as pain, irritation, or rash that localizes to sites of known or suspected tumor)
- Grade 3 fatigue
- Grade 3 infusion reaction that returns to Grade 1 in < 6 hours

7.4.2 Management Algorithms for Immuno-Oncology Agents

Immuno-oncology agents are associated with immune-related AEs that can differ in severity and duration from AEs caused by other therapeutic classes. BMS-986207 and nivolumab are considered I-O agents in this protocol. Early recognition and management of immune-related AEs associated with I-O agents may mitigate severe toxicity. Management algorithms have been developed from extensive experience with nivolumab to assist Investigators in assessing and managing the following groups of immune-related AEs:

- Gastrointestinal
- Renal
- Pulmonary
- Hepatic
- Endocrinopathies
- Skin
- Neurological
- Myocarditis

The clinical nature of AEs events noted with BMS-986207 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 immune-related AEs in this protocol are in Appendix 6.

7.4.3 Dose Delays Due To Toxicity

Participants who experience the following must have all study drug(s) withheld:

- Potential DLTs, until DLT relatedness is defined.
- Select AEs and laboratory abnormalities:
  - ≥ Grade 1 pneumonitis
  - ≥ Grade 2 abnormality in AST, ALT or total bilirubin
  - ≥ Grade 2 creatinine
  - ≥ Grade 2 diarrhea or colitis
  - ≥ Grade 2 neurological AE
  - AE, laboratory abnormality, or concurrent illness that, in the judgment of the Investigator, warrants delaying study drug administration.
- Confirmed SARS-CoV-2 infection.

Criteria for participants who are required to permanently discontinue both study drugs is listed in Section 8.2. Participants not meeting guidelines for permanent discontinuation will be permitted to resume therapy based on the criteria specified below in Section 7.4.3.3. Participants eligible to resume study therapy will resume study therapy at the nominal treatment visit following their last received study medication dose.

The end of cycle tumor assessments, such as computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET), will continue on a q8w schedule relative to the participant's first dose, regardless of any treatment delay incurred.

7.4.3.1 Criteria for Dose Delay Secondary to Changes in AST or ALT for Participants with HCC

Participants with HCC who experience the following must have the study drug delayed:

1) If a participant has a baseline AST or ALT that is within normal limits, delay dosing for drug-related ≥ Grade 2 toxicity (2 grade shift)
2) If a participant has baseline AST or ALT within the Grade 1 toxicity range, delay dosing for drug-related ≥ Grade 3 toxicity (2 grade shift)
3) If a participant has baseline AST or ALT within the Grade 2 toxicity range, delay dosing for a 2-fold drug-related increase in AST or ALT **or** for AST or ALT values 8 × ULN (whichever is lower)
4) Hepatic DLT as defined in Section 7.4.1.1

It is recommended to monitor elevations in AST or ALT approximately every 3 days until levels peak and begin to decline. BMS-986207 dosing can be resumed where criteria to resume treatment are met (Section 7.4.3.3)

7.4.3.2 Protocol-Specific Recommendation for Management of Hepatic Events in HCC Participants

The algorithms recommended for the management of immune-related AEs in this protocol are in Appendix 6. Protocol-specific recommendation for the management of hepatic events in HCC participants are as follows:

- Dose delay criteria for hepatic events are outlined in Section 7.4.3.1. If AST or ALT levels do not improve with a dose delay of 3 to 5 days, or if the levels worsen, steroid therapy should be initiated at 0.5 to 2 mg/kg/day methylprednisolone or oral equivalent
- For ALT or AST levels > 8 x ULN, steroid therapy should be initiated promptly at 1 to 2 mg/kg/day methylprednisolone IV, intramuscularly, or oral equivalent
- For all participants receiving steroid treatment for hepatic events, the BMS Medical Monitor should be consulted within 24 hours after initiation of steroids. Gastroenterology consult is recommended
- If AST or ALT levels do not improve within 3 to 5 days after the start of steroid therapy, or the levels worsen after the start of steroid therapy, discussion with the BMS Medical Monitor regarding the possibility of adding mycophenolate mofetil 1 g twice daily should occur

- Tapering of steroids can start once AST or ALT levels have declined by 1 CTCAE grade. Steroids should be tapered slowly, over no less than 1 month

As outlined in Section 7.4.3.3, study therapy may resume when AST or ALT have returned to Grade 1 or baseline unless the AE meets the criteria for permanent discontinuation (Section 7.4.4). The BMS Medical Monitor must be consulted prior to resuming nivolumab for all participants who required steroid intervention.

7.4.3.3 Criteria to Resume Treatment

Subsequent dosing with study therapy may resume once drug-related nonDLT AEs resolve to Grade 1 or baseline.

Participants experiencing AEs not meeting criteria for permanent discontinuation as outlined in Section 7.4.4 may resume treatment with study medication under the following criteria:

- Participants may resume treatment with study drug when the drug-related AE(s) resolve to Grade ≤ 1 or baseline value, with the following exceptions:
  - Participants may resume treatment in the presence of Grade 2 fatigue
  - Participants who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
  - Participants with Grade 2 uveitis, episcleritis, iritis, eye pain or blurred vision not meeting DLT criteria (Section 8.2) must resolve to baseline prior to resuming study therapy
- For participants with Grade 2 AST, ALT, or total bilirubin elevations, dosing may resume when laboratory values return to baseline, and management with corticosteroids (if needed), is complete
- Participants with combined Grade 2 AST/ALT **and** total bilirubin values meeting DLT criteria (Section 7.4.1.1) should have treatment permanently discontinued
- 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.

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

  - Participants who require dose delays for drug-related increased AST, ALT, or bilirubin may resume treatment when hepatic parameters are at baseline or Grade 1, and after discussion with the BMS Medical Monitor
  - Participants with AST, ALT or bilirubin values meeting permanent discontinuation parameters (Section 7.4.4) should have treatment permanently discontinued
- Drug-related pulmonary toxicity, diarrhea, or colitis, must have resolved to baseline before treatment is resumed. Participants with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month, may be eligible for retreatment if discussed with, and approved by, the BMS Medical Monitor
- Participants with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement, may resume treatment

If the criteria to resume treatment are met, the participant should restart treatment at the next nominally scheduled timepoint per protocol.

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, to determine the risks and benefits of continuing on therapy following resolution versus discontinuing therapy permanently.

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 unless the Investigator determines that only 1 of the agents must be discontinued due to toxicity attributed to that agent alone, **with the exception of the following**:

- Grade 3 diarrhea, nausea, vomiting, or abdominal pain that returns to Grade 1 or baseline within 3 days with medical intervention
- Grade 3 pruritus or rash that returns to Grade 1 or baseline within 7 days with medical intervention
- Isolated Grade 3 or 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 3 days of their onset
- Grade 4 neutropenia < 7 days in duration
- Grade 4 lymphopenia or leukopenia
- Grade 3 or 4 increase in amylase or lipase that is not associated with clinical or radiographic evidence of pancreatitis
- Grade 3 infusion reactions that return to Grade 1 in < 6 hours
- Grade 3 fever not associated with hemodynamic compromise (eg, hypotension, clinical, or laboratory evidence of impaired end-organ perfusion)

- Grade 3 tumor flare (defined as pain, irritation, or rash that localizes to sites of known or suspected tumor)
- Grade 3 fatigue
- Grade 3 or 4 drug-related endocrinopathy AEs, such as adrenal insufficiency, adrenocorticotropic hormone, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS Medical Monitor
- Any event that leads to delay in dosing, lasting > 6 weeks from the previous dose, requires discontinuation, with the exception of the following:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related AEs are allowed. Prior to re-initiating treatment in a participant with a dosing delay lasting > 6 weeks from the previous dose, the BMS Medical Monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks, or more frequently if clinically indicated, during such dosing delays.
  - Dosing delays lasting > 6 weeks from the previous dose that occur for non drug-related reasons may not require discontinuation, if approved by the BMS Medical Monitor. Prior to re-initiating treatment in a participant with a dosing delay lasting > 6 weeks, the BMS Medical Monitor must be consulted.
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the participant with continued nivolumab dosing.

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

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

7.4.5 Management of Drug-related Infusion Reactions

Since BMS-986207 and nivolumab contain only human Ig protein sequences, they are unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgia, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the BMS Medical Monitor and reported as an SAE. Infusion reactions should be graded according to NCI CTCAE v4.03 guidelines.

Treatment recommendations for infusion reactions are provided below and may be modified based on local treatment standards and guidelines, as appropriate.

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

- 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 1000 mg at least 30 minutes before study drug administrations.

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

- Stop the study drug 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 1000 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, the rate may be increased to 100% of the original infusion rate. Monitor participant closely. If symptoms recur, then no further BMS-986207 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 1000 mg should be administered at least 30 minutes before study drug infusions. If necessary, corticosteroids (up to 25 mg of hydrocortisone or equivalent) may be used.

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

- Immediately discontinue infusion of study drug. Begin an IV infusion of normal saline and treat the participant as follows: recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Participant should be monitored until the Investigator is comfortable that the symptoms will not recur. Study drug will be permanently discontinued except for a Grade 3 infusion reaction that returns to Grade 1 in less than 6 hours. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor participant until recovery of the symptoms.

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

7.4.6 Discontinuation Due to Hypersensitivity

Any single grade 5 hypersensitivity related event, or two grade 4 hypersensitivity related events (according to the NCI CTCAE v4.03) will require permanent discontinuation of drug administration for these participants and further enrollment in the study will be halted until a full safety assessment can be completed.

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.

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

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

Refer to the current version of the IB and/or Pharmacy Manual for complete storage, handling, and dispensing information.

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

7.5.1 Retained Samples for Bioavailability / Bioequivalence

Not Applicable.

7.6 Treatment Compliance

Study treatment compliance will be periodically monitored by Drug Accountability Concomitant Therapy.

7.6.1 Prohibited and/or Restricted Treatments

Prohibited and/or restricted medications taken prior to the first dose of study drug in the study are described below. Medications taken within 4 weeks prior to the first dose of study drug must be recorded on the CRF.

- Prior exposure to anti-TIGIT therapy
- Exposure to any investigational drug within 4 weeks of the first dose of study drug

- Any live/attenuated vaccine (eg varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella) during treatment and until 100 days post-last dose
- Administration of investigational SARS-CoV-2 vaccines is not allowed during the study. Participants may receive approved SARS-CoV-2 vaccines while continuing on study treatment at the discretion of the Investigator. Non-live SARS-CoV-2 vaccination is considered a simple concomitant medication within 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.

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 anti-neoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive, nonpalliative radiation therapy, or standard or investigational agents).

7.7 Treatment After the End of the Study

At the conclusion of the study, participants who continue to demonstrate clinical benefit may be eligible to receive BMS-supplied study treatment. Study treatment may 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).

7.7.1 Permitted Therapy

Participants are permitted the use of the following treatments:

- Topical, ocular, intra-articular, intra-nasal, and inhalational corticosteroids
- Adrenal replacement steroid doses ≥ 10 mg daily prednisone equivalent
- A brief (less than 3 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of nonautoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen)

8. DISCONTINUATION CRITERIA

8.1 Discontinuation from Study Treatment

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 the BMS-986207 is terminated for other reasons, including, but not limited, to lack of efficacy and/or not meeting the study objectives; c) the participant can obtain the study medications from a government sponsored or private health program. In all cases, BMS will follow local regulations.

- Participants MUST discontinue the IP (and nonIP at the discretion of the Investigator) 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
- Protocol-defined reasons for permanent discontinuation (Section 7.4.4)
- Any drug-related AE occurring at any time that meets DLT criteria as outlined in Section 7.4.1 will require permanent discontinuation unless the Investigator determines that only 1 of the agents must be discontinued due to toxicity attributed to that agent alone. Exceptions to permanent discontinuation are listed in Section 7.4.4.
- Participant requests to stop study treatment and/or participation in the study
- 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, 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 in settings where benefit/risk justifies discontinuation of study therapy.

Discontinuation of the study treatment for abnormal liver tests should be considered by the Investigator when a participant meets one of the conditions outlined in Section 9.2.7 (p-DILI) or if the Investigator believes that it is in best interest of the participant.

Refer to the Schedule of Activities for data to be collected at the time of treatment discontinuation and required 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.

8.1.1 Discontinuation Due to Further Progression (Confirmed Progression)

A radiographic assessment should be performed at each scheduled tumor assessment, 4 to 6 weeks following initial disease progression, to determine whether there has been continued progressive disease or not. Participants should discontinue study therapy upon evidence of further progression, defined as an additional 10% or greater increase in tumor burden volume from time of initial progression (including all target lesions and new measurable lesions).

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

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

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

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

8.1.2 Assessment Schedule for Participants with Post-progression Treatment

Participants should continue to receive monitoring according to the on-treatment assessments in Section 2. Radiographic assessment, by CT (preferred) or MRI described in Section 9.4.5, is required when participants continue post-progression treatment. For participants that discontinue post progression treatment with study therapy, no additional radiographic assessments will be required.

8.1.3 Post study Treatment Study Follow-up

In this study, safety is a primary endpoint. 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-up for collection of outcome and/or survival follow-up data as required and in line with Section 5.1.3.3.

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 3 documented phone calls, faxes, or emails as well as lack of response by participant to 1 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 a 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. Protocol waivers or exemptions are not allowed. Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.
- Study governance considerations in terms of compliance and reporting of AEs are available in Appendices 2 and 3.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before enrollment. 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.
- All immediate safety concerns must be discussed with BMS immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment

9.1 Efficacy Assessments

Efficacy assessments for the [redacted] activity of BMS-986207, alone, in combination with nivolumab, or in combination with nivolumab and ipilimumab will be based on tumor measurements, using RECIST v1.1, with CT and/or MRI, as appropriate. In Parts 1A, 1B, 2A, and 2B, assessments will be performed at baseline, q8w (± 1 week) during the treatment period, and q12w for the first year after discontinuation of study drug/EOT visit. Subsequently, they will continue to receive tumor assessment scans as per standard of care guidelines, or at a minimum of every 6 months up to 2 years following the last dose of study drug, or until disease progression/withdrawal of study consent. In Parts 1C and 2C, contrast-enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease should occur every 6 weeks starting from date of first dose (± 7 days) for the first 12 months (week 48), then every 12 weeks (± 7 days) until the end of year 2, then every 12 weeks (± 14 days) thereafter until disease progression or treatment discontinuation, whichever occurs later. The same imaging modality must be used for all assessments, per RECIST v1.1 (Appendix 5). Tumor assessment should be performed prior to initiating next cycle of treatment. Unconfirmed PR/CR must be confirmed at least 4 weeks after initial assessment finding.

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.

9.2 Adverse Events

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

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

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

Contacts for SAE reporting are specified in Appendix 3.

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

The collection of nonserious AE information should begin at initiation of study treatment until the follow-up contact, at the time points specified in the Schedule of Activities (Section 2). Nonserious AE information should also be collected from the start of an observational period intended to establish a baseline status for the participants.

Sections 5.6.1 and 5.6.2 in the BMS-986207 IB represent the Reference Safety Information to determine expectedness of SAEs for expedited reporting.[19] Following the participant's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures.

All SAEs must be collected that occur during the screening period and within 100 days of discontinuation of dosing. 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. Please note the following adverse event reporting requirements:

- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the appropriate section of the eCRF section.
- All SAEs will be recorded and reported to the Sponsor or Designee within 24 hours.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of this being available.

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

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

9.2.2 Method of Detecting AEs and SAEs

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

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 (Section 9.2).
- 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.
- All SAEs and AEs (including non-serious 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 9.2.3) or for suspected cases, until SARS-CoV-2 infection is ruled-out.

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

9.2.4 Regulatory Reporting Requirements for SAEs

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

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

9.2.5 Pregnancy

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

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

9.2.6 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE electronic Report Form, 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 the laboratory term would be used by the reporting Investigator (eg, anemia versus low hemoglobin value).

9.2.7 Potential Drug-induced Liver Injury (p-DILI)

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

Potential drug induced liver injury is defined as:

- ALT or AST elevation > 3 x ULN

  AND

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

  AND

- No other immediately apparent possible causes of aminotransaminases 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.

Specifically for HCC: p-DILI is defined as:

- Concurrent ALT ≥ 10 × ULN AND total bilirubin ≥ 2 × ULN or baseline value (if elevated bilirubin at study entry), AND
- No other immediately apparent possible causes of ALT elevation and hyperbilirubinemia, including, but not limited to, tumor progression, acute viral hepatitis, cholestasis, pre-existing hepatic disease or the administration of other drug(s), herbal medications and substances known to be hepatotoxic.

This is the standard drug-induced liver injury definition across the BMS HCC program.

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: (iii) Timely evaluation and triaging of p-DILI cases, (iv) Expedited reporting of p-DILI cases and (v) 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 drug 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, nonexhaustively and by way of example only: infectious diseases (such as active hepatitis A, B and C), congenital diseases (such as Gilbert's syndrome), neoplastic diseases (such as HCC), 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.

9.2.8 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, including electrocardiogram (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

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

For this study, any dose of BMS-986207 greater than the assigned dose, and considered excessive and medically important by the Investigator, will be considered an overdose.

All intentional overdose taken with possible suicidal/self-harming intent must be reported as SAEs (see Section 9.2).

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

- Contact the Medical Monitor immediately
- Closely monitor the participant for AEs/SAEs and laboratory abnormalities until BMS-986207 can no longer be detected systemically
- Obtain a plasma sample for PK if requested by the Medical Monitor (determined on a case by case basis)
- 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 based on the clinical evaluation of the participant.

9.4 Safety

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

9.4.1 Physical Examinations

Refer to Schedule of Activities for timing of assessments in Table 2-1, Table 2-2, Table 2-3, Table 2-4, Table 2-5, and Table 2-6.

9.4.2 Vital Signs

Refer to Schedule of Activities for timing of assessments in Table 2-1, Table 2-2, Table 2-3, Table 2-4, Table 2-5, and Table 2-6.

9.4.3 Electrocardiograms

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

The effect of BMS-986207 on the [redacted] will be evaluated by a central reader using ECG data collected in triplicates and conducted during the monotherapy and combination dose escalation only (Part 1A and Part 1B) (eg, 1 ECG test equals 3 consecutive individual 12-lead ECGs performed 5 minutes apart). For the purposes of monitoring participant safety, the Investigators will review the 12-lead ECGs using their site's standard ECG machines throughout the study. The [redacted] will be applied to each ECG reading.

9.4.4 Clinical Safety Laboratory Assessments

Investigators must document their review of each laboratory safety report.

A local laboratory will perform the analyses and will provide reference ranges for these tests. Results of clinical laboratory tests performed on Day -1 must be available prior to dosing.

The laboratory tests that will be performed for study participants are shown in Table 9.4.4-1.

Results of all laboratory tests required by this protocol must be provided to the Sponsor, recorded either on the laboratory pages of the CRF or by another mechanism as agreed upon between the Investigator and BMS (eg, provided electronically). If the units of a test result differ from those printed on the CRF, the recorded laboratory values must specify the correct units. Any abnormal

laboratory test result considered clinically significant by the Investigator must be recorded on the appropriate AE page of the CRF.

Table 9.4.4-1: Clinical Laboratory Assessments

Hematology	
Hemoglobin and hematocrit	
Total leukocyte count, including differential	
Platelet count	
Prothrombin time (PT), activated partial thromboplastin time (aPTT) and international normalized ratio (INR) (at screening and D0 for Retreatment eligible participants only)	
Serum Chemistry	
Aspartate aminotransferase	Total protein
Alanine aminotransferase	Albumin
Total bilirubin	Sodium
Direct bilirubin (reflex only if total bilirubin is elevated)	Potassium
	Chloride
Alkaline phosphatase	Calcium
Lactate dehydrogenase	Phosphorus
Creatinine	Magnesium
Blood urea nitrogen	Creatinine clearance (Cockcroft-Gault method) (screening only D0 for Retreatment eligible participants)
Uric acid	
Glucose	
Lipase	
Amylase	
Gamma glutamyl transferase (reflex only when AST, ALT are outside of normal range)	
Thyroid stimulating hormone	
Free T3 and T4 (screening and reflex only when TSH is outside of normal range)	
Urinalysis screening and D0 for Retreatment eligible participants only, unless clinically indicated	
Protein	
Glucose	
Blood	
Leukocyte esterase	
Specific gravity	
pH	
Microscopic examination of the sediment if blood, protein or leukocytes esterase are positive on the dipstick	
Serology	
Serum for hepatitis C antibody, hepatitis B surface antigen, HIV-1 and HIV-2 antibody (screening, and as mandated by local requirement), and hepatitis C RNA (reflex only for positive serology results)	
For HCC participants: hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody, hepatitis B DNA PCR, hepatitis C antibody and hepatitis C RNA PCR, and hepatitis D antibody testing for those with concurrent hepatitis B infection	
Other Analyses	
Pregnancy test (WOCBP only: screening, predose, discharge).	
Follicle stimulating hormone (FSH) (screening only and women only)	

Abbreviations: DNA, deoxyribonucleic acid FSH, follicle stimulating hormone; HCC, hepatocellular carcinoma; HIV, human immunodeficiency virus; PCR, polymerase chain reaction; PT, prothrombin time; RNA, ribonucleic acid; WOCBP, Women of childbearing potential

9.4.5 Imaging Assessment for the Study

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.

Central assessments are not planned for this study, however copies of all scans will be stored for possible future central analysis, if determined to be necessary by BMS. At the Sponsor's discretion, scans may be collected centrally to be reviewed by independent radiologists.

Computer Tomography/Magnetic Resonance Imaging

Contrast-enhanced CT scans acquired on dedicated CT equipment is preferred for this study. CT with contrast of the chest, abdomen, and pelvis are to be performed for tumor assessments. CT scans should be acquired with 5 mm slices with no intervening gap (contiguous).

Should a participant have a contraindication for CT IV contrast, a noncontrast CT of the chest and a contrast enhanced MRI of the abdomen and pelvis may be obtained. MRIs should be acquired with slice thickness of < 5 mm with no gap (contiguous).

Every attempt should be made to image each participant using an identical acquisition protocol on the same scanner for all imaging timepoints.

Use of CT component of a PET/CT scanner:

Combined modality scanning such as with fluorodeoxyglucose (FDG)-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 FDG-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 measurements. However, if a site can document that the CT performed as part of a FDG-PET/CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the FDG-PET/CT can be used for RECIST 1.1 measurements. Note, however, that the FDG-PET portion of the CT introduces additional data which may bias an Investigator if it is not routinely or serially performed.

MRI Brain

A MRI of the brain is required at screening if a participant is symptomatic or has a history of brain metastasis. Participants with a history of brain metastasis should have surveillance MRI approximately every 12 weeks, or sooner if clinically indicated.

MRI brain scans during on-study treatment and follow-up periods are required **only** if there is a prior history of lesions present at screening, or as clinically indicated for new signs and symptoms that suggest CNS involvement.

Bone Scan

Bone scans can be used to evaluate the presence of metastatic disease, and should not be used as modality for assessment of measurable metastatic disease.

9.5 Pharmacokinetics and Immunogenicity

The PK of BMS-986207 will be derived from serum concentration versus time data when appropriate. The PK parameters that will be assessed, following the intensive PK collection, are shown in Table 9.5-1.

Table 9.5-1: Pharmacokinetic Parameters

Parameters	Definition
Cmax	Maximum observed serum concentration
Tmax	Time of maximum observed serum concentration
AUC(0-T)	Area under the serum concentration-time curve from time zero to time of last quantifiable concentration
AUC(TAU)	Area under the concentration-time curve in one dosing interval
Parameters that may potentially be assessed following the dose administration in Cycle 2 Day 1	
Ctau	Observed concentration at the end of a dosing interval
CLT	Total body clearance
Css-avg	Average concentration over a dosing interval (AUC[TAU]/tau)
AI_TAU	Ratio of an exposure measure at steady state to that after the first dose (exposure measure includes AUC[TAU])
T-HALFeff	Effective elimination half-life that explains the degree of accumulation observed for a specific exposure measure (exposure measure includes AUC[TAU])
Parameter to be reported separately	
[redacted]	[redacted]

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

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 and immunogenicity. Further details of blood collection and processing will be provided to the site in the Laboratory Manual.

All predose samples should preferably be taken within 30 minutes before the start of any dose infusion. In Part 1C and 2C, as shown in Table 9.5-4 end-of-infusion (EOI) PK samples for BMS-986207, nivolumab, and ipilimumab should be taken immediately following the last drug infusion (preferably within 5 minutes after end of the infusion) on the contralateral arm (ie, the arm not used for the infusion). Since the EOI PK sample is drawn with the intent of accurately estimating the maximum concentration (Cmax) of the drug, draw the EOI-PK after all the study drug has been

infused. If the site infuses drug without a flush, then collect the EOI-PK sample within approximately 5 minutes after end of infusion. 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 5 minutes after the end of the flush. If the end of infusion is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly. On-treatment PK samples are intended to be drawn relative to actual dosing days. For Part 1A, 1B, 2A, and 2B, EOI PK samples for BMS-986207 or nivolumab should be taken following the instructions noted in Table 9.5-2 and Table 9.5-3.

If a dose occurs on a different day within the cycle due to delays or minor schedule adjustments, PK and ADA 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, an additional predose sample should be collected. ‘Event Kit - Dose Delay’ should be used in the event that a predose PK sample was obtained and the participant is not dosed on that same day. Following consensus of the Investigator and the BMS Medical Monitor, an additional PK and/or ADA sample may be taken following a SAE or important medical event using an ‘Event Kit - AE’. Further details of sample collection, processing, and shipment will be provided in the Laboratory Manual.

Table 9.5-2: Pharmacokinetic and Immunogenicity Sampling Schedule for BMS-986207 [redacted] in q2w Dose Panels in Part 1A, 1B, 2A, and 2B

Study Day of Sample Collection (1 cycle = 8 weeks)	Event	Time (Relative to Start of Infusion) Hour: Min	BMS-986207 Blood Sample (All Participants)	[redacted]	BMS-986207 ADA Samples (All participants)	[redacted]
C1D1	Predose	00.00	X		X	
	EOI[b]	30 to 60 min	X			
		4:00	X			
C1D2		24:00	X			
C1D5[c]		96:00	X			
C1D8[d]		168:00	X			
C1D15	Predose[a]	00: 00	X		X	
	EOI[b]	30 to 60 min	X			
		4:00	X			
C1D29	Predose[a]	00: 00	X		X	
	EOI[b]	30 to 60 min	X			
C2D1	Predose[a]	00: 00	X			
	EOI[b]	30 to 60 min	X			
		4:00	X			
C2D2		24:00	X			
C2D5[c]		96:00	X			
C2D8[d]		168:00	X			
C2D15	Predose[a]	00: 00	X			
C2D29	Predose[a]	00: 00	X		X	

Table 9.5-2: Pharmacokinetic and Immunogenicity Sampling Schedule for BMS-986207 [redacted] in q2w Dose Panels in Part 1A, 1B, 2A, and 2B

Study Day of Sample Collection (1 cycle = 8 weeks)	Event	Time (Relative to Start of Infusion) Hour: Min	BMS-986207 Blood Sample (All Participants)	[redacted]	BMS-986207 ADA Samples (All participants)	[redacted]
C3D1	Predose[a]	00: 00	X		X	
C3D29	Predose[a]	00: 00	X			
C4D1	Predose[a]	00: 00	X		X	
C5D1	Predose[a]	00: 00	X		X	
EOT			X		X	
30-day follow-up			X		X	
60-day follow-up			X		X	
PK SAE event	'PK EVENT Kit - AE' should be used when PK and/or ADA sample is taken following a SAE or important medical					
PK dose delay	'PK DELAY Kit - Dose Delay' should be used to collect an additional predose sample if a predose sample was already collected for the same visit but the dose was subsequently delayed					
Retreatment	PK/ADA sampling to be done predose on Day 1 of all cycles; @ EOT and 30 and 60 day followup visits. No dose delay PK sampling to be done in Retreatment					

Abbreviations: ADA, anti-drug antibody, BMS, Bristol-Myers Squibb; EOI, end of infusion, EOT, end of treatment

[a] Predose: All predose samples for [redacted] BMS-986207 should be taken prior to the start of the [redacted] infusion. If the predose sample has been taken, however, the unscheduled, missing, or delayed dose occurs, an additional predose sample shall be taken.

[b] EOI samples for both [redacted] BMS-986207 should be collected immediately following the infusion (preferably within 2 minutes of stopping the infusion). If the end of infusion is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.

[c] The 96:00 hour sample may be taken between 72:00 and 120:00 hours post dose

[d] The 168:00 hour sample may be taken between 144:00 and 192:00 hours post dose

Table 9.5-3: Pharmacokinetic and Immunogenicity Sampling Schedule for BMS-986207 [redacted] in q4w Dose Panels in Parts 1A, 1B, 2A, and 2B

Study Day of Sample Collection (1 cycle = 8 weeks)	Event	Time (Relative to Start of Infusion) Hour: Min	BMS-986207 Blood Sample (All Participants)	[redacted]	BMS-986207 ADA Samples (All participants)	[redacted]
C1D1	Predose	00.00	X		X	
	EOI[b]	30 to 60 min	X			
		4:00	X			
C1D2		24:00	X			
C1D5 [c]		96:00	X			
C1D8 [d]		168:00	X			
C1D15		336.00	X			
C1D22		504.00	X			
C1D29	Predose[a]	00: 00	X			
	EOI[b]	30 to 60 min	X			
C2D1	Predose[a]	00: 00	X		X	
	EOI[b]	30 to 60 min	X			
C2D29	Predose[a]	00:00	X			
	EOI	30 to 60 min	X			
C3D1	Predose[a]	00: 00	X		X	
	EOI[b]	30 to 60 min	X			
		4:00	X			
C3D2		24:00	X			
C3D5 [c]		96:00	X			

Table 9.5-3: Pharmacokinetic and Immunogenicity Sampling Schedule for BMS-986207 [redacted] in q4w Dose Panels in Parts 1A, 1B, 2A, and 2B

Study Day of Sample Collection (1 cycle = 8 weeks)	Event	Time (Relative to Start of Infusion) Hour: Min	BMS-986207 Blood Sample (All Participants)	[redacted]	BMS-986207 ADA Samples (All participants)	[redacted]
C3D8 [d]		168:00	X			
C3D15		336: 00	X			
C3D22		504: 00	X			
C3D29	Predose[a]	00: 00	X			
C4D1	Predose[a]	00: 00	X		X	
C5D1	Predose[a]	00: 00	X		X	
EOT			X		X	
30-day follow-up			X		X	
60-day follow-up			X		X	
PK SAE Event	‘PK EVENT Kit - AE’ should be used when PK and/or ADA sample is taken following a SAE or important medical					
PK Dose Delay	‘PK DELAY Kit - Dose Delay’ should be used to collect an additional predose sample if a predose sample was already collected for the same visit but the dose was subsequently delayed					
Retreatment	PK/ADA sampling to be done predose on Day 1 of all cycles; @ EOT and 30 and 60 day followup visits. No dose delay PK sampling to be done in Retreatment					

Abbreviations: ADA, anti-drug antibody, BMS, Bristol-Myers Squibb; EOI, end of infusion, EOT, end of treatment

[a] Predose: All predose samples for [redacted] BMS-986207 should be taken prior to the start of the [redacted] infusion. If the predose sample has been taken, however, the unscheduled, missing, or delayed dose occurs, an additional predose sample shall be taken.

[b] EOI samples for both [redacted] BMS-986207 should be collected immediately following the infusion (preferably within 2 minutes of stopping the infusion). If the end of infusion is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.

[c] The 96:00 hour sample may be taken between 72:00 and 120:00 hours post dose

[d] The 168:00 hour sample may be taken between 144:00 and 192:00 hours post dose

Table 9.5-4: Pharmacokinetic and Immunogenicity Sampling Schedule for BMS-986207, [redacted] in Parts 1C and 2C

Study Day of Sample Collection (1 cycle = 6 weeks)	Event	Time Relative to [redacted] Dose Hour: Min	BMS-986207 PK Serum Sample	[redacted]	BMS-986207 (ADA) Serum Samples	[redacted]
C1D1	Predose[a]	00.00	X		X	
	EOI[b]		X			
		4:00	X			
C1D2		24:00	X			
C1D5 [c]		96:00	X			
C1D8 [d]		168:00	X			
C1D15		336.00	X			
C1D22	Predose[a]	00: 00	X			
C1D29[e]		168:00	X			
C2D1	Predose[a]	00: 00	X		X	
C2D22	Predose[a]	00:00	X			
C3D1	Predose[a]	00: 00	X		X	
	EOI[b]		X			
		4:00	X			
C3D2		24:00	X			
C3D5		96:00	X			
C3D8		168:00	X			
C3D15		336: 00	X			

Table 9.5-4: Pharmacokinetic and Immunogenicity Sampling Schedule for BMS-986207, [redacted] in Parts 1C and 2C

Study Day of Sample Collection (1 cycle = 6 weeks)	Event	Time Relative to [redacted] Dose Hour: Min	BMS-986207 PK Serum Sample	[redacted]	BMS-986207 (ADA) Serum Samples	[redacted]
C3D22	Predose[a]	00: 00	X			
C4D1	Predose[a]	00: 00	X		X	
Every 4 cycles starting at Cycle 5 Day 1 until Cycle 17 (C5D1; C9D1; C13D1; C17D1)	Predose[a]	00: 00	X		X	

Abbreviations: ADA, anti-drug antibody, BMS, Bristol-Myers Squibb; C, cycle; D, day; EOI, end of infusion; PK, pharmacokinetics.

[a] Predose: All predose samples for [redacted] BMS-986207 should be taken prior to the start of the [redacted] infusion. If the predose sample has been taken, however, the unscheduled, missing, or delayed dose occurs, no additional predose sample shall be taken.

[b] EOI samples for [redacted] BMS-986207 should be collected immediately following the last drug infusion (preferably within 5 minutes of after end of infusion) on the contralateral arm (i.e. the arm not for the infusion). Since the EOI PK sample is drawn with the intent of accurately estimating the maximum concentration (Cmax) of the drug, draw the EOI-PK when all the study drug has been infused. If the site infuses drug without a flush, then collect the EOI-PK sample within approximately 5 minutes after end of infusion. 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 5 minutes after end of the flush. If the end of infusion is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.

[c] The 96:00 hour sample may be taken between 72:00 and 120:00 hours post dose

[d] The 168:00 hour sample may be taken between 144:00 and 192:00 hours post dose

[e] PK sample collection for C1D29 is strongly recommended to be synchronized (collected on the day) with biopsy collection for C1D29.

The serum samples will be analyzed for BMS-986207 [redacted] ADA (anti-BMS-986207 antibodies [redacted]).

9.5.1 Pharmacokinetic Sample Analyses

Validated immunoassays will be used to measure concentrations of BMS-986207, [redacted] in serum.

9.5.2 Immunogenicity Sample Analysis

Validated immunoassays will be used to assay samples for the presence of, and measure titers of anti-BMS-986207, [redacted] antibodies in serum.

[redacted]

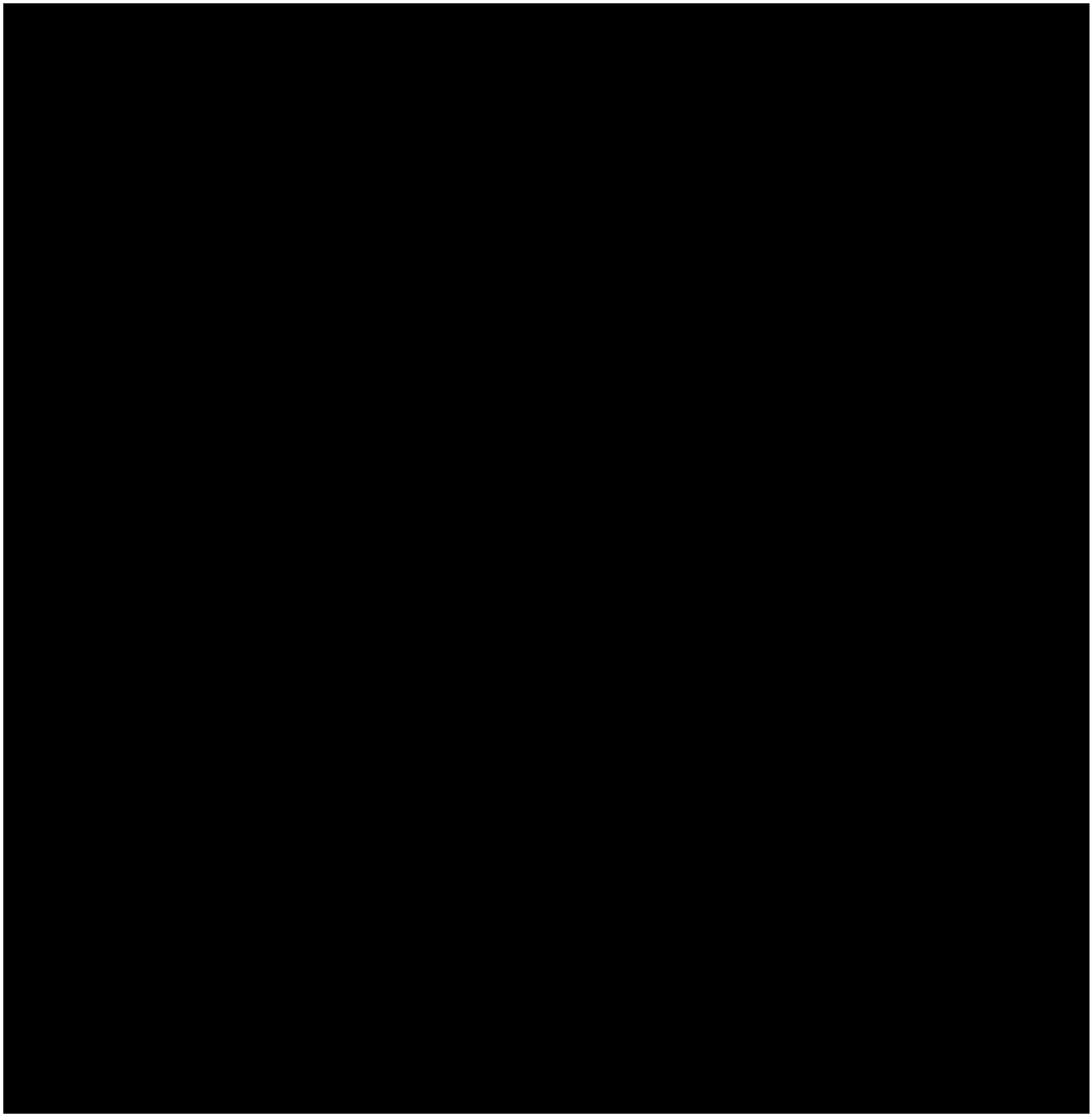
9.7 Pharmacogenomics

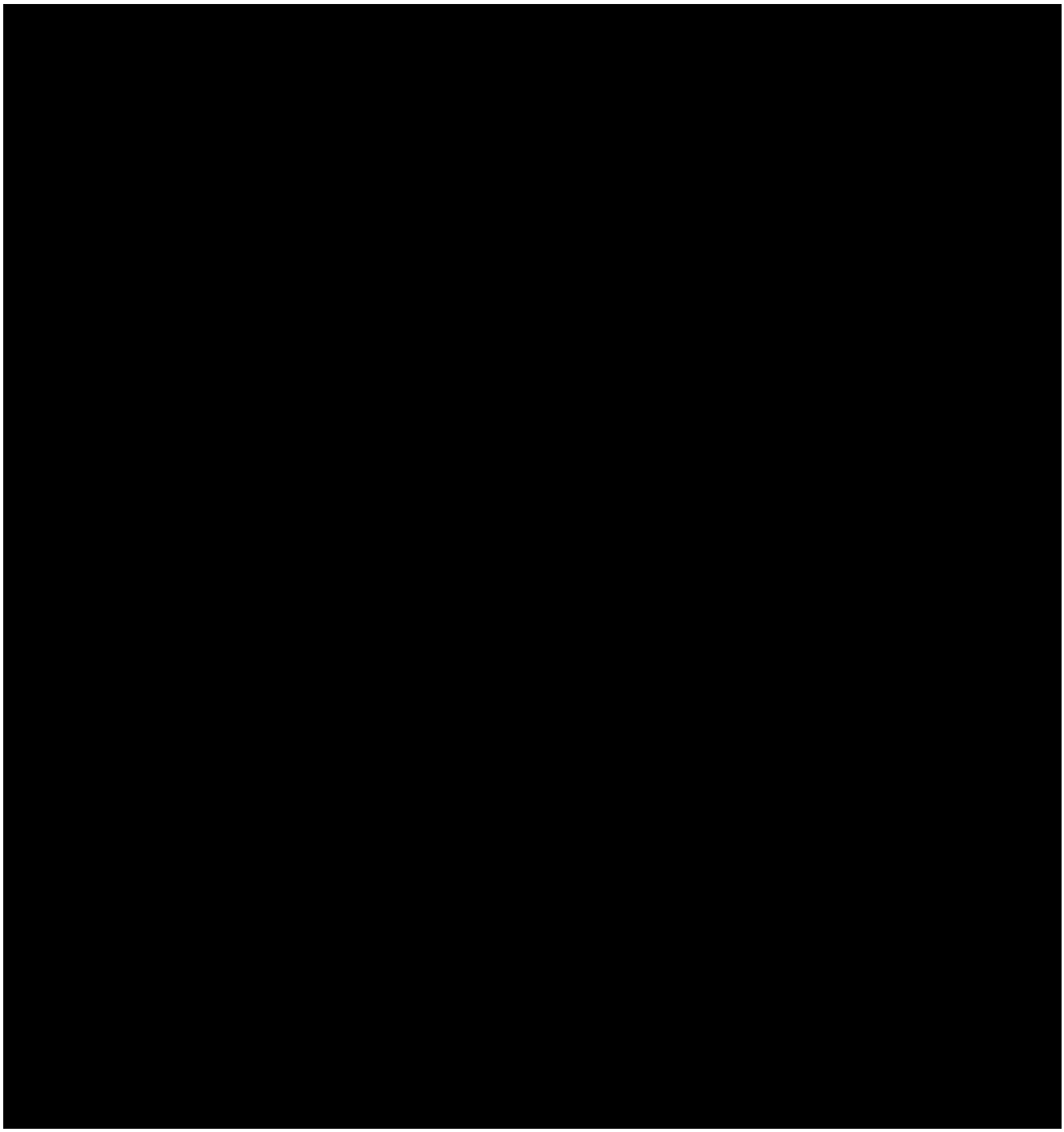
Circulation tumor DNA (ctDNA) and T cell Repertoire analysis may be performed to assess the association of these tumor-specific genetic features with clinical outcome. More details about these assays are described [redacted]

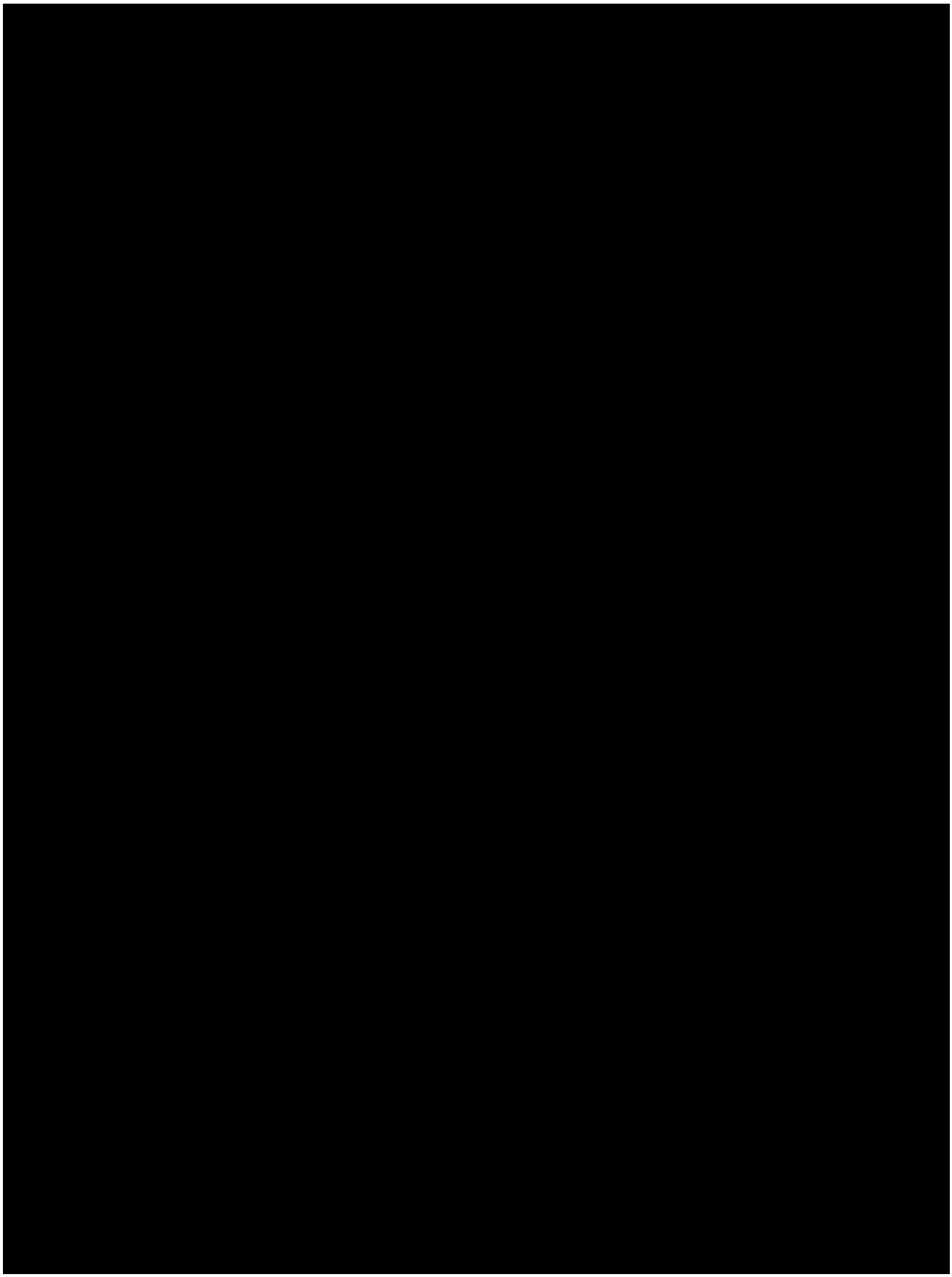
9.7.1 ADME Sampling

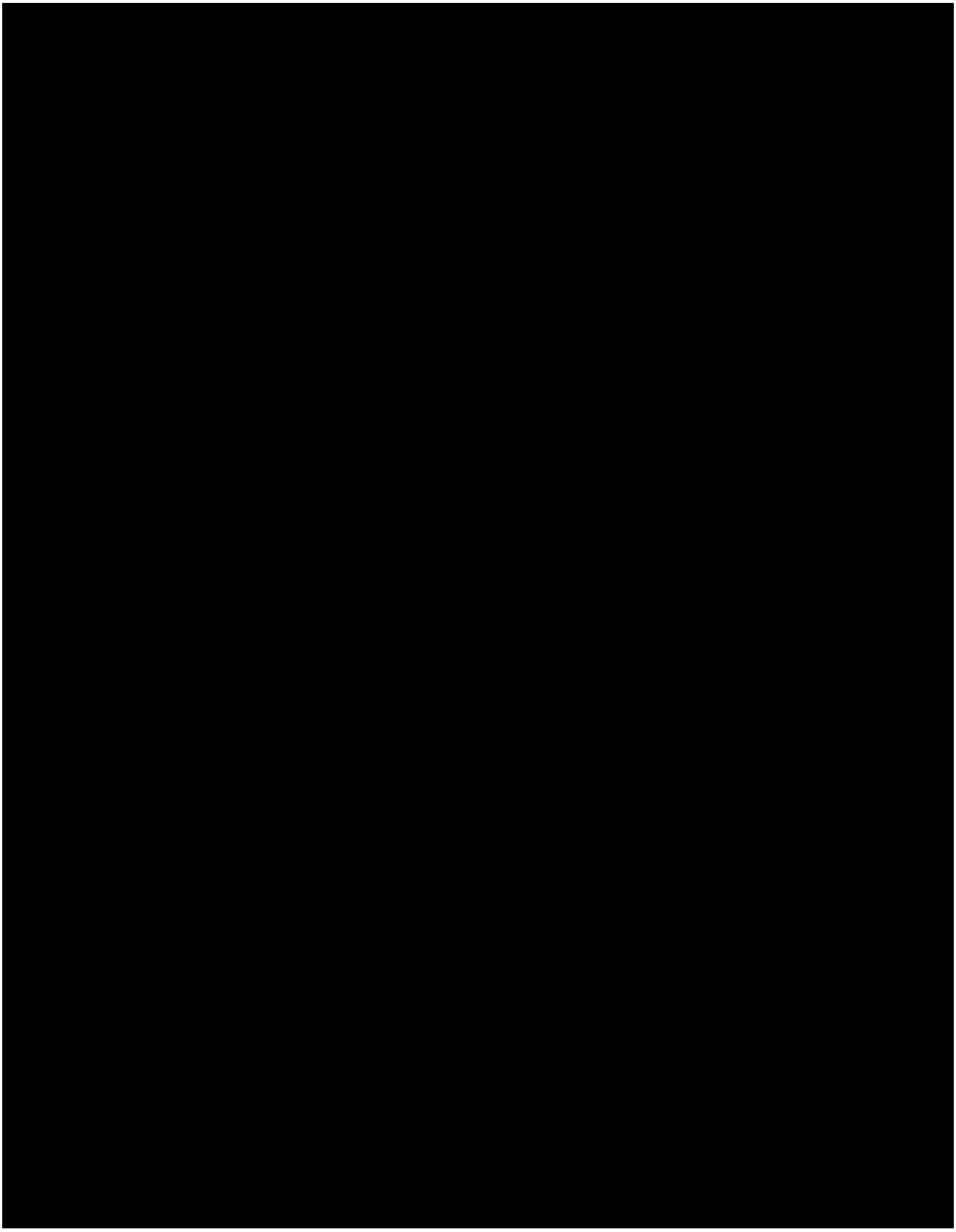
A whole blood sample will be drawn at baseline (Day 1) for potential analysis of DNA variants in absorption, distribution, metabolism and excretion (ADME)-related genes (Table 2-2, Appendix 7). Paxgene sampling will be performed in accordance with the Laboratory Manual. Further details of blood collection and processing will also be provided to the site in the Laboratory Manual.

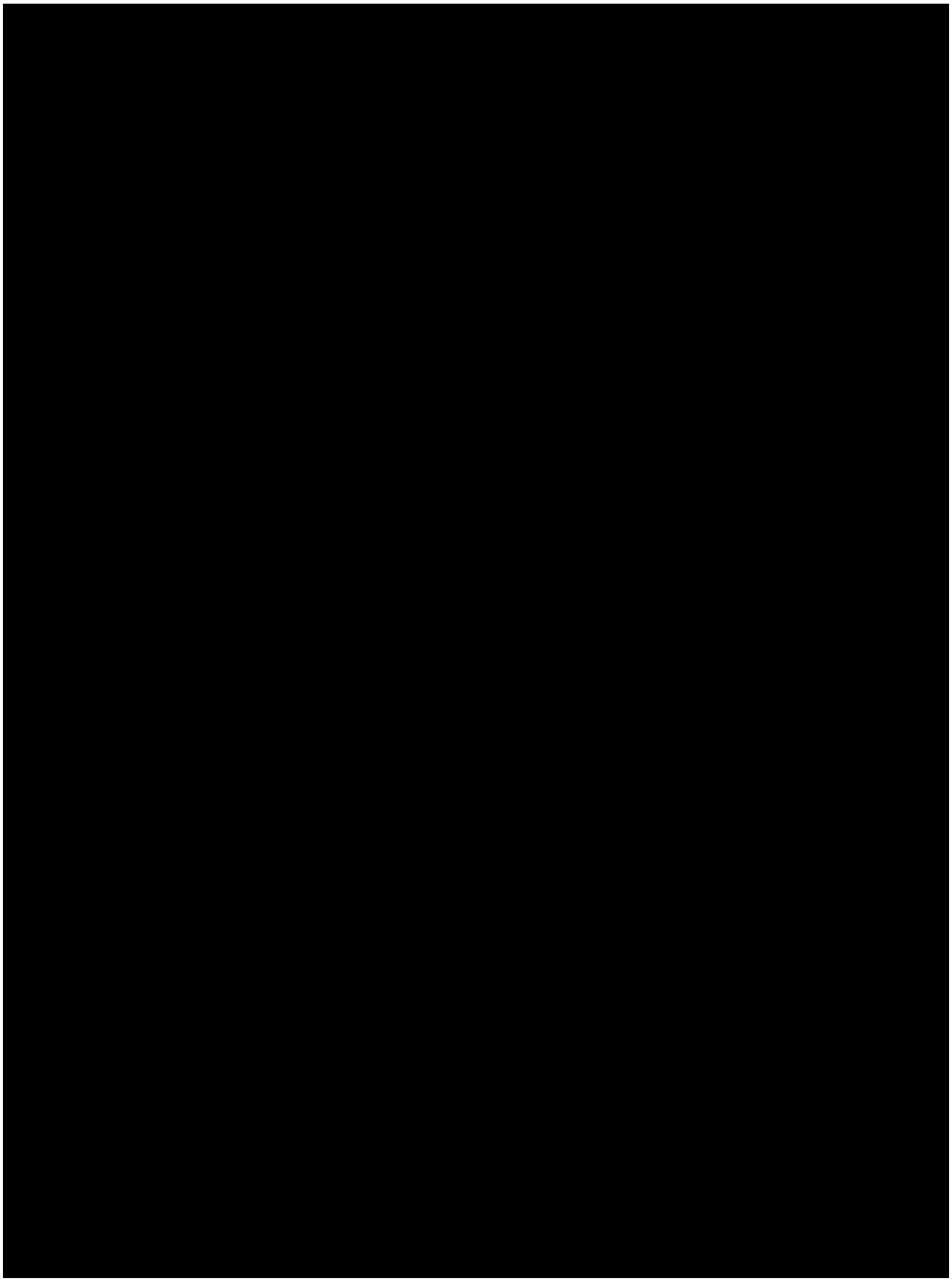
[redacted]

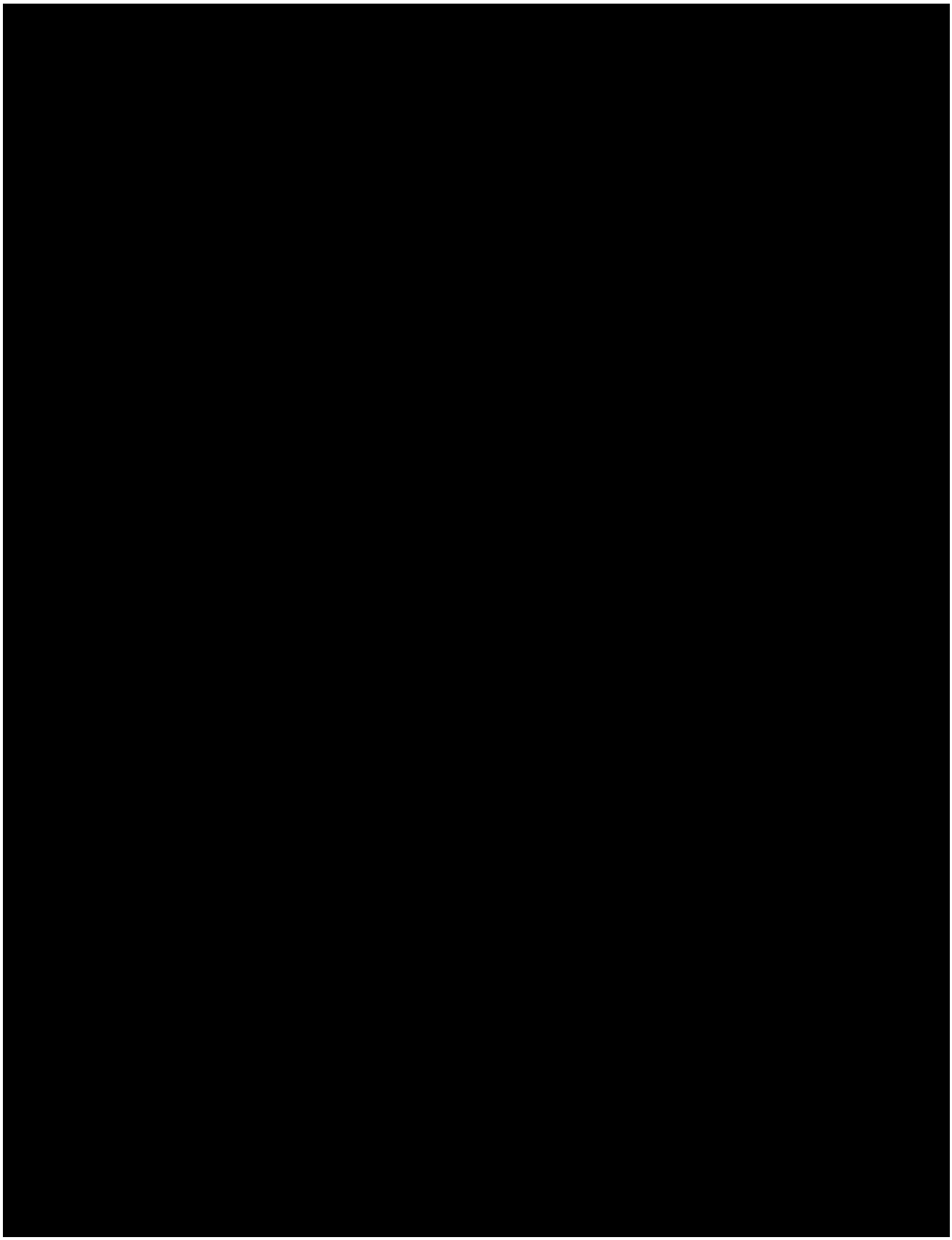












10. STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

10.1.1 Dose Escalation

During the dose escalation phase, an adaptive dose escalation scheme (BLRM for monotherapy and BLRM-copula for combination therapy) employing the escalation with overdose control (EWOC) principle will be used. The 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. 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 unsafe dose by ensuring the posterior probability of the DLT rate exceeding 33% at any dose is capped at 30%.

The maximum number of participants treated will be 35 for each dose escalation part (BMS-986207 monotherapy [Part 1A], BMS-986207 in combination with nivolumab [Part 1B]). However, simulation studies with various scenarios show that the expected number of DLT-evaluable participants is no more than approximately 20. (Appendix 12).

Approximately 3 participants will be treated at the starting dose levels of BMS-986207 or BMS-986207 in combination with nivolumab. While the BLRM/BLRM-copula will use DLT information from the DLT period only, clinical assessment will take into consideration of the totality of available data including PK/[redacted] from all treated participants encompassing monotherapy and combination therapy, in assigning a dose level for the next cohort of 3 participants. At least

6 DLT-evaluable participants will be treated at the MTD. At most 12 DLT-evaluable participants will be treated at each dose level. Additional participants (up to a total of 15) may be treated at or any dose level below the estimated MTD for further evaluation of safety, PK, [redacted] parameters as required.

The model-recommended MTD is the dose that satisfies the following three conditions:

1) The empirical posterior probability that the "DLT rate of 16% - <33%" is greater than a pre-specified value (i.e., 50%);
2) This probability needs to be the largest amongst the dose levels that satisfy the EWOC condition (i.e., the probability that the "DLT rate $\geq$ 33%" must be less than 30%);
3) Minimum number of participants (i.e., 6) were treated at this dose level.

The final recommended MTD/RP2D will be based on the recommendation from the BLRM/BLRM-copula and overall clinical assessment of all available safety, PK, [redacted] and efficacy data. Lower doses of BMS-986207 may be tested if none of the planned doses are found to be tolerable as monotherapy or in combination with nivolumab. Such decisions will be made after discussion and agreement between the Investigators and the BMS Medical Monitor.

10.1.2 Safety Evaluation Phase (Part 1C)

The safety of triplet therapy will be evaluated across the tumor types in up to approximately 18 treated participants per dose level who receive triplet therapy based on the number of DLTs observed. Assuming a DLT target of 30% (24%, 36%) the BOIN design framework will be used to guide decisions in this setting, including potential de-escalation to a lower dose of BMS-986207 in combination with both nivolumab and ipilimumab, if warranted by the observed results (see Table 5.1.2.6-1). In addition, calculations related to the risk of a BMS-986207 dose level selected as tolerable are shown expressed as a posterior probability of toxicity in Section 5.1.2.2 (Table 5.1.2.6-2).

10.1.3 Cohort Expansion

The purpose of cohort expansion is to gather additional safety, tolerability, preliminary efficacy, PK, [redacted] information regarding BMS-986207 alone or in combination with nivolumab. However, the sample size is strictly based on efficacy, specifically on the target ORR relative to historic response rate.

10.1.3.1 Cohort Expansion in Part 2A and Part 2B

Part 2A will be an expansion phase of the BMS-986207 monotherapy in participants with CRC at 1 dose level. Part 2B will be an expansion phase for BMS-986207 in combination with nivolumab in participants with CRC, HCC, and ovarian cancer. Each disease cohort expansion will be handled independently and there will be no multiplicity adjustment.

The Fleming 2-stage design framework will be used as a guide for the expansion cohorts in Parts 2A and 2B.[42,43] The total sample size for each expansion cohort will be calculated to provide a reasonable false-positive rate (FPR) <10% and false-negative rate (FNR) < 10% based on

assumptions of true (target) and historic ORR for each indication. The assumed historic and target response rates may change over time and may need to be adjusted by the time when the response data from this study are available. The sample size and operational characteristics of using a 2-stage design, as an example, are provided in Table 10.1.3.1-1, although this is not used for statistical hypothesis testing. Using a 2-stage design provides an option to stop early for futility, as well as a signal of preliminary [redacted] activity for strong-go, early on. Enrollment may continue into Stage 2, while the planned number of participants for Stage 1 are followed for efficacy evaluable tumor assessments. There will be no stopping of a disease cohort for efficacy, although an early plan for the next stage of clinical development may be initiated. Sample sizes may need to be increased in order to explore differential responses between [redacted] expressed and nonexpressed groups.

Guided by Table 10.1.3.1-1, approximately 11 CRC participants will be treated with BMS-986207 monotherapy in Stage 1. Assuming the true response rate is 20% in this population when treated with BMS-986207 monotherapy, if there are 2 or more responses in 11 participants, it may trigger an expansion of the clinical development plan after careful evaluation of all available data including duration of response and safety profile. The probability to observe such a favorable response is approximately 68% if in fact the treatment is efficacious. If there is no response in 11 treated participants, the cohort may be stopped for futility. The probability of early stopping for futility is approximately 80% if in fact the treatment is inefficacious, eg, 2%. If there is 1 response, an additional 13 participants may be treated to collect more data. At the end of Stage 2, if there is 1 or no response, further clinical development may not be warranted. If there are 2 or more responses, it may show evidence of treatment efficacy.

Table 10.1.3.1-1: Example of a 2-stage Design Characteristics

Treatment	Indication	Historic/ Target Rate (%)	Stage	Cum Sample Size	Conclude Inefficacy if R[a]	Conclude Efficacy if R[a]	PET[b] for Futility (%)	PEE[c] for Efficacy (%)
BMS-986207	CRC (nonMSI-H)	2/20	1	11	0	≥ 2	80	68
			2	24	≤ 1	≥ 2		
BMS-986207 and nivolumab	HCC, ovarian cancer	10/30	1	15	≤ 1	≥ 4	55	70
			2	26	≤ 5	≥ 6		
	CRC (nonMSI-H)	2/30	1	7	0	≥ 2	87	67
			2	15	≤ 1	≥ 2		

Abbreviations: BMS = Bristol-Myers Squibb, CRC, colorectal cancer; FNR, false-negative rate; FPR, false-positive rate; HCC, hepatocellular carcinoma; nonMSI-H, nonmicrosatellite instability-high; PEE, probability of early efficacy; PET, probability of early termination

[a] R is the cumulative number of responses at the end of stage; all FPRs and FNRs < 10%

[b] Probability of early termination if the historic rate is true

[c] Probability of early efficacy signal if the target rate is true

10.1.3.2 Cohort Expansion in Part 2C

Part 2C will be an expansion phase of the BMS-986207 in combination with nivolumab and ipilimumab in participants with advanced treatment-naive NSCLC whose tumor cells express ≥ 1% PD-L1.

The sample size for Part 2C is based on assessing an initial [redacted] activity signal as estimated by the ORR following treatment in the triplet combination arm and to provide additional information for the safety profile in the 1L NSCLC population.

One or two doses are planned to be evaluated in Part 2C and a minimum of 20 participants are enrolled per dose level of BMS-986207. So approximately 40 evaluable participants in total with 1L NSCLC with tumor cell PD-L1 expression of ≥ 1% will be treated with BMS-986207 in combination with nivolumab and ipilimumab.

In the event pre-existing PD-L1 results are not confirmed by the central lab test, additional participants (up to 20%) will be enrolled to achieve a sample size of 40 evaluable participants.

The following Bayesian posterior probability (PP) criteria will be used to assess signal of anti-tumor activity with benchmark of 36% as unfavorable ORR and 56% as desirable ORR:[44,45]

- An [redacted] activity signal is based on ORR satisfying the dual criteria: PP (ORR ≥ 0.56) ≥ 40% and PP (ORR ≥ 0.36) ≥ 80%
- A lack of activity signal is based on ORR meeting the criterion: PP (ORR ≥ 0.36) < 20%

A beta prior distribution beta (1, 1) for ORR and Binomial Bin (n, ORR) likelihood for number of responders were used.

Based on the above criteria, for each dose level a total of 20 evaluable participants in Part 2C will provide approximately 6.5% chance to show [redacted] activity when a true ORR is 36%, and at least 63% chance of showing activity signal if the true ORR is 56% or more (see Table 10.1.3.2-1)

The ORR thresholds for efficacy signal (responders ≥ 11/20) and lack of efficacy (≤ 6/20) and the operating characteristics of the posterior probability criteria are shown in Table 10.1.3.2-1.

Table 10.1.3.2-1: Operating characteristics of criteria for antitumor activity by ORR

Sample Size	True ORR	PP (Activity)	PP (No Activity)	PP(Inconclusive)	Responder Cutoff Activity/ No Activity
20	0.3	0.017	0.416	0.566	11/6
20	0.36	0.065	0.217	0.718	11/6
20	0.5	0.412	0.021	0.567	11/6
20	0.56	0.626	0.005	0.369	11/6
20	0.6	0.755	0.002	0.243	11/6
22	0.3	0.014	0.313	0.673	12/6
22	0.36	0.058	0.14	0.801	12/6
22	0.5	0.416	0.008	0.576	12/6
22	0.56	0.64	0.002	0.358	12/6
22	0.6	0.772	0	0.228	12/6
24	0.3	0.012	0.389	0.6	13/7
24	0.36	0.053	0.182	0.765	13/7
24	0.5	0.419	0.011	0.569	13/7
24	0.56	0.653	0.002	0.345	13/7
24	0.6	0.787	0.001	0.212	13/7
26	0.3	0.009	0.46	0.53	14/8/
26	0.36	0.048	0.226	0.726	14/8
26	0.5	0.423	0.014	0.563	14/8
26	0.56	0.664	0.003	0.333	14/8
26	0.6	0.801	0.001	0.199	14/8

ORR, objective response rate; PP: posterior probability

In addition, to the above, Table 10.1.3.2-2 summarizes the 80% exact CI for various ORRs for combination therapy with sample sizes of 20, 22, 24, and 26. For example, 11 responders will need to be observed in 20 evaluable participants respectively, (an observed ORR ≥ 55%) for the lower bound of the 80% CI to exclude a 36% ORR.

Table 10.1.3.2-2: Potential ORR in 1L NSCLC (≥ 1% PD-L1) and Exact 80% CI

Sample size	Number of Responders	ORR	80% Exact CI
20	10	0.5	[0.34, 0.66]
	11	0.55	[0.38, 0.71]
	13	0.65	[0.48, 0.79]
	14	0.7	[0.53, 0.83]
22	11	0.5	[0.35, 0.65]
	12	0.55	[0.39, 0.70]
	14	0.64	[0.48, 0.78]
	16	0.73	[0.57, 0.85]
24	12	0.5	[0.35, 0.65]
	13	0.54	[0.39, 0.69]
	15	0.63	[0.47, 0.75]
	17	0.71	[0.56, 0.83]
26	13	0.5	[0.36, 0.64]
	14	0.54	[0.40, 0.68]
	16	0.62	[0.47, 0.75]
	18	0.69	[0.55, 0.81]

Abbreviations: 1L NSCLC, first-line non-small cell lung cancer; CI, confidence interval; ORR, objective response rate; PD-L1, programmed cell death ligand 1.

10.2 Populations for Analyses

For purposes of analysis, the populations in are defined in Table 10.2-1.

Table 10.2-1: Population for Analyses

Population	Description
Enrolled	All participants who sign informed consent and are registered into the IRT
NSCLC efficacy	All treated participants in Part 2C with PD-L1 ≥ 1% by central lab
Treated	All participants who take at least 1 dose of study treatment.
Response-evaluable	All treated participants with measurable disease at baseline and one of the following: (a) at least 1 post baseline tumor assessment, (b) clinical progression, (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
[redacted]	[redacted]

Abbreviations: IRT, Interactive Response Technology.

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.

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 response-evaluable 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, [redacted] will be described in the Statistical Analysis Plan.

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 per RECIST v1.1 BOR for a participant will be assessed per RECIST v1.1 by Investigator	Estimate of ORR and corresponding 2-sided exact 95% CI using the Clopper-Pearson method by treatment for each tumor type (Parts 2A and 2B). Estimate of ORR and corresponding 2-sided exact 80% CI using the Clopper-Pearson method by treatment for 1L NSCLC with PD-L1 expression ≥ 1% by central lab (Part 2C).
Median DOR DOR for a participant with a BOR of CR or PR is defined as the time between the date of first response and the date of the first objectively documented tumor progression per RECIST v1.1 or death, whichever occurs first.	Median duration of response using 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 and treatment (Parts 1A, 2B, and 2C)
PFSR at 24 weeks PFS for a participant is defined as the time from the first dosing date (Part 1, Part 2A, and Part 2B)/randomization date (Part 2C) 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 95% CI will be derived based on Greenwood formula by treatment for each tumor type.

Abbreviations: BOR, best overall response; CI, confidence interval; CR, complete response; DOR, duration of response; ORR, overall response rate; PFS, progression free survival; PFSR, progression free survival rate; PR partial response; RECIST, Response Evaluation Criteria In Solid Tumors

10.3.2 Safety Analyses

All safety analyses will be performed on the treated population.

Endpoint	Statistical Analysis Methods
Incidence of DLTs, AEs, SAEs, AEs leading to discontinuation, and death AEs will be graded according to CTCAE v4.03	DLT rate by dose level, frequency distribution of treated participants with AE using the worst CTC grade. Participants will 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 v4.03.	Laboratory shift table using the worst CTC grade on treatment per participant

Abbreviations: AE, adverse event; CTC, common terminology criteria; CTCAE, common terminology criteria for adverse events; DLTs, dose-limiting toxicities; PT, preferred term; SAE, serious adverse event.

In addition, continuous safety monitoring for toxicity will be conducted in the NSCLC Expansion Phase 2C as described in Section 10.3.8.

10.3.3 Pharmacokinetic Analyses for BMS-986207, Nivolumab, and Ipilimumab

Endpoint	Statistical Analysis Methods
BMS-986207	
Cmax, AUC(0-T), AUC(TAU), Ctau, CLT, Css-avg, AI_AUC, and T-HALFeff_AUC	Summary statistics: geometric means and coefficients of variation
Cmax, AUC(0-T), AUC	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
[redacted]	
Nivolumab and Ipilimumab	
[redacted]	

Abbreviations: AI_AUC, accumulation index ratio of AUC at steady state to that after the first dose; 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; CI, confidence interval; CLT, total body clearance; Cmax, maximum observed concentration; Css-avg, average concentration over a dosing interval (AUC(TAU)/tau); Ctau, observed concentration at the end of a dosing interval; [redacted]
T-HALFeff, effective elimination half-life that explains the degree of accumulation observed for a specific exposure measure; Tmax, time of maximum observed concentration.

PK time-concentration data may be pooled with data from other studies for population PK analysis, which will be presented in a separate report.

10.3.4 Immunogenicity

Endpoint	Statistical Analysis Methods
Incidence of ADA to BMS-986207, [redacted] Baseline ADA-positive participant is defined as a participant who has an ADA-detected sample at baselinea ADA-positive participant is a participant with at least 1 ADA-positive sample relative to baseline after initiation of the treatment	Frequency distribution of baseline ADA-positive participants and ADA-positive participants after initiation of the treatment for each of BMS-986207, [redacted].

Abbreviations: ADA, anti-drug antibody.
[a] Baseline sample is the last sample before initiation of the treatment.

[redacted]

10.3.6 ECG Analyses

All ECG data analyses including summaries of each ECG parameter, frequency distribution of participants' maximum values/changes, and scatter plots will be performed following the current practice of ECG data analysis. Concentration-response analysis may be performed using mixed effect model, if appropriate (Part 1A). The details of ECG data analysis will be provided in the SAP.

10.3.7 Other Analyses

[redacted] analyses will be described in detail in the statistical analysis plan finalized before database lock. [redacted] at 1 year will be analyzed similarly to PFSR. The population PK [redacted] analysis may be presented separately from the main clinical study report.

10.3.8 Interim Analyses for Parts 2A, 2B, and 2C

The expansion phase of this study (Part 2A and Part 2B) employs a 2-stage design framework. Therefore, there will be an interim analysis as planned when an adequate number of participants have response-evaluable data. Additional interim analyses may also be performed for administrative purposes or publications. No formal inferences requiring any adjustment to statistical significance level will be performed.

For Part 2C, interim analyses may also be performed for administrative purposes or publications prior to the final database lock. No formal inferences requiring any adjustment to statistical significance level will be performed. Continuous safety monitoring will be implemented in Part

2C to further evaluate the safety of the triplet combination in the NSCLC population, in addition to that in Part 1C, as described below.

A Bayesian framework will be utilized for continuous monitoring of toxicity in Part 2C based on AEs meeting DLT criteria.[46] Observed incidence rates of treatment-related toxicities meeting DLT criteria (defined in Section 7.4.1) will be evaluated relative to a boundary (number of DLTs) associated with higher chance of the true DLT rate exceeding 33%.

Bayesian safety monitoring boundaries are established using a non-informative 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 2C participants and *n* is the subset of these *m* participants who experience treatment-related toxicities meeting DLT criteria. All treated Part 2C participants are considered evaluable. The criterion for excess toxicity is based on a posterior probability (PP) of treated Part 2C participants with toxicities meeting DLT criteria > 33% | cumulative data exceeding 80%. If the criterion is met during continuous monitoring in Part 2C, there is greater than 80% PP that the DLT rate exceeds 33%; based on the observed data, the dose level may be re-evaluated and, based on the totality of data, a lower dose may be administered to the remaining participants. The cutoff number of participants with DLT needed to meet the criterion depends on the number of evaluable participants, with a final boundary of 14 participants with a DLT out of 37 or more.

Table 10.3.8-1: Safety Monitoring Boundaries for AEs Meeting DLT Criteria in Part 2C

Number of evaluable participants	Minimum Number of participants with AE meting DLT criteria
4 -6	3
7-8	4
9-11	5
12-14	6
15-17	7
18-19	8
20-23	9
24-26	10
27-29	11
30-32	12
33-36	13
37-39	14

Abbreviations: AE = adverse event; DLT, dose limiting toxicity.

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12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
1L	first-line
AD-NSCLC	nonsmall cell lung adenocarcinoma
ADA	anti-drug antibody
ADME	absorption, distribution, metabolism and excretion
AE	adverse event
AI	accumulation index
AI_AUC	AUC accumulation index
AI_Cmax	Cmax accumulation index
AI_Ctau	Ctau accumulation index
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
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
BLRM	Bayesian Logistic Regression Model
BMS	Bristol-Myers Squibb
BOIN	Bayesian optimal interval
BRAF	B-Raf proto-oncogene
C	celsius
C1D1	cycle 1 day 1
Cave	steady-state average plasma concentration
CD155	adhesion molecules PVR
cHL	Classical Hodgkin Lymphoma
CHO	Chinese hamster ovary
CI	confidence interval
CLcr	creatinine clearance
CLR	renal clearance

Term	Definition
CLT	total body clearance
CLT/F	apparent total body clearance
CLT/F/fu or CLT/fu	apparent clearance of free drug or clearance of free if (if IV)
Cmax	maximum observed concentration
Cmin	minimum observed concentration
CNS	central nervous system
CONSORT	consolidated standards of reporting trials
CR	complete response
CRC	colorectal cancer
CrCl	creatinine clearance
CRF	case report form, paper or electronic
CRO	contract research organization
CRS	cytokine release syndrome
Css-avg	average concentration over a dosing interval (AUC(TAU)/tau)
CT	computed tomography
CTAg	Clinical Trial Agreement
Ctau	concentration in a dosing interval (eg, concentration at 24 hours, concentration at 12 hours, etc.)
CTC	common terminology criteria
CTCAE	common terminology criteria for adverse events
CTDNA	circulation tumor DNA
CTLA	cytotoxic T lymphocyte-associated protein
Ctrough	trough observed plasma concentration
DLT	dose limiting toxicity
DNA	deoxyribonucleic acid
DNAM-1	DNAX accessory molecule 1, also called CD226
DOR	duration of response
EC	Ethics Committee
EC50	half-maximal effective concentration
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group

Term	Definition
eCRF	electronic case report form
eg	exempli gratia (for example)
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EOI	end-of-infusion
EOT	end of treatment
EU	endotoxin unit
EWOC	Escalation with Overdose Control
Fc	fragment crystallizable
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
FIH	first-in-human
FNR	false-negative rate
FPR	false-positive rate
FSH	follicle stimulating hormone
fu	fraction of unbound drug
GGT	gamma glutamyl transferase
GLP	Good Laboratory Practice
GPVE	Global Pharmacovigilance and Epidemiology
h	hour
HBsAg	hepatitis B surface antigen
HCC	hepatocellular carcinoma
hCG	human chorionic gonadotropin
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HNSTD	highest non-severely toxic dose
HR	hazard ratio
IB	investigator brochure
ICF	informed consent form

Term	Definition
ICH	International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ie	id est (that is)
Ig	immunoglobulin
IgG4	kappa
IHC	immunohistochemistry
IMP	investigational medicinal products
IND	investigational new drug
INR	international normalized ratio
I-O	immuno-oncology
IP	investigational product
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITIM	immunoreceptor tyrosine-based inhibitory motif
IV	intravenous
kg	kilogram
KO	knockout
KRAS	V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
L	liter
LAG-3	lymphocyte-activation gene 3
LDH	lactate dehydrogenase
LFT	liver function test
mAb	monoclonal antibody
MRSD	maximum recommended starting dose
MAD	maximum administered dose
mDOR	median duration of response
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mL	milliliter
MMR	mismatch repair

Term	Definition
MRI	magnetic resonance imaging
MSI	microsatellite instability
MTD	maximum tolerated dose
NCI	National Cancer Institute
NK	natural killer
NOAEL	no-observed-adverse-effect level
Non-MSI-H	nonmicrosatellite instability-high
NSCLC	nonsmall cell lung cancer
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cells
PBT	platinum based therapy
PCR	polymerase chain reaction
PD1	programmed cell death 1
PD-L1	programmed death-ligand 1
pDILI	potential drug-induced liver injury
PE	physical examination
PET	positron emission tomography
PFS	progression free survival
PFSR	progression free survival rate
PI	product information
PK	pharmacokinetics
PP	posterior probability
PR	partial response
PSC	preliminary safety cohort
PT	prothrombin time
PVR-2	poliovirus receptor-2
qd	once daily

Term	Definition
qw	once weekly
q2w	every 2 weeks
q3w	every 3 weeks
q4w	every 4 weeks
q8w	every 8 weeks
QTcf	QT correction method, Fridericia's
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RO	receptor occupancy
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCCHN	squamous cell carcinoma of the head and neck
SCLC	small-cell lung cancer
SD	stable disease
SmPC	Summary of Product Characteristics
SMT	Safety Management Team
SOC	standard of care
SQ-NSCLC	squamous nonsmall cell lung carcinoma
SUSAR	suspected, unexpected serious adverse reaction
TFT	thyroid function test
TGI	tumor growth inhibition
TIL	tumor infiltrating lymphocyte
T-HALF	half life
T-HALFeff_AUC	effective elimination half-life that explains the degree of AUC accumulation observed
T-HALFeff_Cmax	effective elimination half-life that explains the degree of Cmax accumulation observed)
TIGIT	T cell immunoglobin and ITIM domain
Tmax	time of maximum observed concentration

Term	Definition
Tregs	regulatory T cells
TSH	thyroid stimulating hormone
ULN	upper limit of normal
USPI	US Prescribing Information
Vss	apparent volume of distribution at steady state
WOCBP	women of childbearing potential
WWPS	Worldwide Patient Safety

APPENDIX 2 STUDY GOVERANCE 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 Guidelines Good Clinical Practice (GCP)
- As defined by the International Council on Harmonisation (ICH)
- In accordance with the ethical principles underlying European Union Directive 2001/20/EC
- United States Code of Federal Regulations, Title 21, Part 50 (21CFR50)
- Applicable local requirements.

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

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

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

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

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

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

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

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion of an amendment from the IRB/IEC (and if applicable, also by local health authority) except where necessary to eliminate an immediate hazard(s) to study subjects.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining relevant approval/favorable opinion(s) the deviation or change will be submitted, as soon as possible to:

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

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

If an amendment substantially alters the study design or increases the potential risk to the participant: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

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

FINANCIAL DISCLOSURE

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

INFORMED CONSENT PROCESS

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

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

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

Investigators must:

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

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

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

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

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

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

SOURCE DOCUMENTS

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

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

STUDY TREATMENT RECORDS

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

If	Then
Supplied by BMS (or its vendors):	Records or logs must comply with applicable regulations and guidelines and should include: • amount received and placed in storage area • amount currently in storage area • label identification number or batch number • amount dispensed to and returned by each participant, including unique participant identifiers • amount transferred to another area/site for dispensing or storage • nonstudy disposition (e.g., lost, wasted) • amount destroyed at study site, if applicable • amount returned to BMS • retain samples for bioavailability/bioequivalence, if applicable • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.
Sourced by site, and not supplied by BMS or its vendors (examples include IP sourced from the sites stock or commercial supply, or a specialty pharmacy)	The investigator or designee accepts responsibility for documenting traceability and study drug integrity in accordance with requirements applicable under law and the SOPs/standards of the sourcing pharmacy. These records should include: • label identification number or batch number • amount dispensed to and returned by each participant, including unique participant identifiers • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

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

CASE REPORT FORMS

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

For sites using the Sponsor or designee electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the electronic SAE form and Pregnancy Surveillance form, respectively. If electronic SAE form is not available, a paper SAE form can be used. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by Sponsor or designee.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form. Subinvestigators in Japan may not be delegated the CRF approval task For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

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

MONITORING

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

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable. Certain CRF pages and/or electronic files may serve as the source documents:

In addition, the study may be evaluated by Sponsor or designee internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to Sponsor or designee.

RECORDS RETENTION

The investigator (or head of the study site in Japan) must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS or designee, whichever is longer. The investigator (or head of the study site in Japan) must contact BMS prior to destroying any records associated with the study.

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

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

RETURN OF STUDY TREATMENT

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

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

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

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.

- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, i.e., incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

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

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

CLINICAL STUDY REPORT AND PUBLICATIONS

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

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

- Study Steering Committee chair or their designee

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

APPENDIX 3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW UP AND REPORTING

ADVERSE EVENTS

Adverse Event Definition:

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study treatment and that does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not considered related to the study treatment.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or results from other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Note that abnormal lab tests or other safety assessments should only be reported as AEs if the final diagnosis is not available. Once the final diagnosis is known, the reported term should be updated to be the diagnosis.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose, as a verbatim term (as reported by the investigator), should not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae and should specify "intentional overdose" as the verbatim term.

Events NOT Meeting the AE Definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).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 (eg, routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)
- admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)

Results in persistent or significant disability/incapacity

Is a congenital anomaly/birth defect

Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 9.2.7 for the definition of potential DILI.)

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

EVALUATING AES AND SAES

Assessment of Causality

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

Follow-up of AEs and SAEs

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

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

All SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

- SAEs, whether related or not related to study drug, 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 collection 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

Appendix 4 provides general information and definitions related to Woman of Childbearing Potential and methods of contraception that can be applied to most clinical trials. For information specific to this study regarding acceptable contraception requirements for female and male participants, refer to Section 6.1 of the protocol. Only the contraception methods as described in Section 6.1 are acceptable for this study.

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal 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. Suggested guidelines for the duration of the washout periods for HRT types are presented below. 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.

METHODS OF CONTRACEPTION

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

Highly Effective Contraceptive Methods That Are <u>User Dependent</u> *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. (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol.)[b] – Oral (birth control pills) – Intravaginal (rings) – Transdermal • Combined (estrogen-and progestogen-containing) hormonal contraception must begin at least 30 days prior to initiation of study therapy.
• Progestogen-only hormonal contraception associated with inhibition of ovulation. (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol.)[b] – Oral – Injectable • Progestogen-only hormonal contraception must begin at least 30 days prior to initiation of study therapy.
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation and/or implantation. (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol.)[b] • Intrauterine device.

• Intrauterine hormone-releasing system (IUS). (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol.)[b,c] • Bilateral tubal occlusion.
• Vasectomized partner Having 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. A vasectomy is a highly effective contraception method provided that the participant 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 participant chooses to forego complete abstinence. • Periodic abstinence (including, but not limited to, calendar, symptothermal, postovulation 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 7.6.1 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 7.6.1 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, postovulation methods).
- Withdrawal (coitus interruptus).
- Spermicide only.
- LAM.

CONTRACEPTION GUIDANCE FOR MALE PARTICIPANTS

Male participants should maintain their usual practice with regard to contraception (if any); however, no specific contraceptive measures are required.

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.

APPENDIX 5 RECIST 1.1 CRITERIA

1 ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

To assess objective response or future progression, it is necessary to estimate the *overall tumor burden at baseline* and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least 1 measurable tumor lesion. When computed tomographic (CT) scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

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

1.1 Measurable Lesions

Measurable lesions must be accurately measured in at least 1 dimension (longest diameter in the plane of the measurement to be recorded) with a minimum size of:

- 10 mm by CT/magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness no greater than 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray
- Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be □ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness is recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

1.2 Non-Measurable Lesions

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

1.3 Special Considerations Regarding Lesion Measurability

1.3.1 Bone Lesions

- Bone scan, positron emission tomography (PET) scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components that can be evaluated by cross sectional imaging techniques such as CT or MRI, can be considered

as measurable lesions if the soft tissue component meets the definition of measurability described above.

- Blastic bone lesions are non-measurable.

1.3.2 Cystic Lesions

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

1.3.3 Lesions with Prior Local Treatment

Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

1.4 Specifications by Methods of Measurements

1.4.1 Measurement of Lesions

All measurements should be recorded in metric notation (mm). All baseline evaluations should be performed as close as possible to the treatment start and never more than 30 days before the beginning of the treatment.

1.4.2 Method of Assessment

The **same method of assessment and the same technique should be used** to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical examination.

1.4.2.1 CT/MRI Scan

CT/MRI is the best currently available and reproducible method to measure lesions selected for response assessment. Measurability of lesions on CT/MRI scan is based on the assumption that CT/MRI slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

1.4.2.2 Chest X-ray

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

1.4.2.3 Clinical Lesions

Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers. For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As previously noted, when lesions can be evaluated by both clinical examination and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

1.4.2.4 Ultrasound

Ultrasound is ***not*** useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

1.4.2.5 Endoscopy, Laparoscopy

The utilization of these techniques for objective tumor evaluation is ***not*** advised.

2 BASELINE DOCUMENTATION OF 'TARGET' AND 'NON-TARGET' LESIONS

2.1 Target Lesions

When more than 1 measurable lesion is present at baseline all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as *target lesions* and will be recorded and measured at baseline.

Target lesions should be selected on the basis of their **size** (lesions with the longest diameter), should be representative of all involved organs, and should lend themselves to ***reproducible repeated measurements***.

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

2.1.1 Lymph Nodes

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. Pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a **short axis of ≥ 15 mm by CT scan**. Only the *short* axis of these nodes will contribute to the baseline sum. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

2.2 Non-Target Lesions

All other lesions (or sites of disease) including pathological lymph nodes should be identified as *non-target lesions* and should also be recorded at baseline. Measurements are not required and these lesions should be followed as **'present'**, **'absent'**, or in rare cases **'unequivocal**

progression'. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

3 TUMOR RESPONSE EVALUATION

3.1 Evaluation of Target Lesions

Complete Response (CR): **Disappearance of all target lesions.** Any pathological lymph nodes (whether target or non-target) must 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 1 or more new lesions is also considered progression.)

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

3.1.1 Special Notes on the Assessment of Target Lesions

3.1.1.1 Lymph Nodes

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. Pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a **short axis of ≥ 15 mm by CT scan**. Only the *short* axis of these nodes will contribute to the baseline sum. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

3.1.1.2 Target Lesions That Become 'Too Small to Measure'

All lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). If the radiologist is able to provide an actual measurement, that should be recorded, even if it is below 5 mm.

However, when such a lesion becomes difficult to assign an exact measure to then:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (note: in case of a lymph node believed to be present and faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5-mm CT slice thickness (but should not be changed with varying CT slice thickness).

3.1.1.3 Target Lesions That Split or Coalesce on Treatment

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

3.2 Evaluation of Non-Target Lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-CR/Non-PD: Persistence of 1 or more non-target lesion(s) above the normal limits.

Progressive Disease (PD): *Unequivocal progression* of existing non-target lesions. (*Note:* The appearance of 1 or more new lesions is also considered progression.)

3.2.1 Special Notes on Assessment of Non-Target Lesions

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

3.2.1.1 When the Subject Also Has Measurable Disease

- To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.
- A modest 'increase' in the size of 1 or more non-target lesions is usually not sufficient to quality for unequivocal progression status.

3.2.1.2 When the Subject Has Only Non-Measurable Disease

- To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening such that the overall tumor burden has increased sufficiently to merit discontinuation of therapy.
- A modest 'increase' in the size of 1 or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.
- Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are non-measurable), a useful test that can be applied when assessing subjects for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: that is, an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large'

or an increase in lymphangitic disease from localized to widespread or may be described in protocols as 'sufficient to require a change in therapy'.

- If 'unequivocal progression' is seen, the subject should be considered to have had overall PD at that point.

[redacted]

3.3 New Lesions

The appearance of new malignant lesions denotes disease progression. The finding of a new lesion should be unequivocal: that is, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (eg, some 'new' bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the subject's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was *not* scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the subject who has visceral disease at baseline and while on study has a CT or MRI brain scan ordered that reveals metastases. The subject's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. *If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.*

3.3.1 FDG-PET Evaluation

While [^{18}F] fluorodeoxyglucose (FDG)-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of the qualitative assessment of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up:
  - If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
  - If the positive FDG-PET at follow-up is not confirmed as a new site of disease 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 positive FDG-PET scan).

– If the positive FDG-PET at follow-up corresponds to a preexisting site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

4 RESPONSE CRITERIA

4.1 Timepoint Response

A response assessment should occur at each timepoint specified in the protocol.

For subjects who have **measurable disease** at baseline Table 4.1-1 provides a summary of the overall response status calculation at each timepoint.

Table 4.1-1: Timepoint Response: Subjects with Target (+/– Non-Target) Disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	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

Abbreviations: CR = complete response; NE =not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

Missing Assessments and Not Evaluable Designation

When no imaging/measurement is done at all at a particular timepoint, the subject is **not evaluable (NE)** at that timepoint. If only a subset of lesion measurements are made at an assessment, the case is also considered NE at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not have changed the assigned timepoint response.

4.1.1 Confirmation Scans

- Verification of Response: Confirmation of PR and CR is required at least 4 weeks following initial assessment to ensure responses identified are not the result of measurement error.

4.2 Best Overall Response: All Timepoints

The *best overall response* is determined once all the data for the subject are known. It is the best response recorded from the start of the study treatment until the date of objectively documented progression based on RECIST v1.1, taking into account any requirement for confirmation, or the date of subsequent anti-cancer therapy, whichever occurs first in the study. The subject's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

Best response is defined as the best response across all timepoints with subsequent confirmation. Complete or partial responses may be claimed only if the criteria for each are met at a subsequent timepoint as specified in the protocol (generally 4 weeks later).

In this circumstance, the best overall response can be interpreted as specified in Table 4.2-1. When SD is believed to be best response, it must meet the protocol specified minimum time from baseline. Measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6 to 8 weeks) that is defined in the study protocol.

Table 4.2-1: Best Overall Response When Confirmation of CR and PR Is Required

Overall Response First Timepoint	Overall Response Subsequent Timepoint	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD

Table 4.2-1: Best Overall Response When Confirmation of CR and PR Is Required

Overall Response First Timepoint	Overall Response Subsequent Timepoint	Best Overall Response
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

Abbreviations: CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

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

4.3 Duration of Response

4.3.1 Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

4.3.2 Duration of Stable Disease

Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

APPENDIX 6 MANAGEMENT ALGORITHMS FOR IMMUNO-ONCOLOGY 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 therapeutic procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

GI Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea:< 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hrs; not interfering with ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recur: • 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as grade 3/4
Grade 3-4 Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with ADL Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation	• Discontinue I-O therapy per protocol • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

27-Jun-2019

Renal Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

Grade of Creatinine Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 Creatinine > ULN and > than baseline but ≤ 1.5x baseline	• Continue I-O therapy per protocol • Monitor creatinine weekly	If returns to baseline: •Resume routine creatinine monitoring per protocol If worsens: •Treat as Grade 2 or 3/4
Grade 2-3 Creatinine > 1.5x baseline to ≤ 6x ULN	• Delay I-O therapy per protocol • Monitor creatinine every 2-3 days • 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent • Consider renal biopsy with nephrology consult	If returns to Grade 1: •Taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy and routine creatinine monitoring per protocol If elevations persist > 7 days or worsen: •Treat as Grade 4
Grade 4 Creatinine > 6x ULN	• Discontinue I-O therapy per protocol • Monitor creatinine daily • 1.0-2.0 mg/kg/day methylprednisolone IV or IV equivalent • Consult nephrologist • Consider renal biopsy	If returns to Grade 1 : Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

27-Jun-2019

Pulmonary Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.

Grade of Pneumonitis (NCI CTCAE v4)	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 • 1.0 mg/kg/day methyl-prednisolone IV or oral equivalent • Consider bronchoscopy , lung biopsy	• Re-image every 1-3 days If improves: - When symptoms return to near baseline, taper steroids over at least 1 month and then resume I-O therapy per protocol and consider prophylactic antibiotics If not improving after 2 weeks or worsening: - 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 methylprednisolone 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 (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids

27-Jun-2019

Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.

Grade of Liver Test Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 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	• Continue LFT monitoring per protocol If worsens: • Treat as Grade 2 or 3-4
Grade 2 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 LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol
Grade 3-4 AST or ALT > 5 x ULN or T.bili >3 x ULN	• Discontinue I-O therapy* • Increase frequency of monitoring to every 1-2 days • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent* • Add prophylactic antibiotics for opportunistic infections • Consult gastroenterologist	If returns to grade 2: • 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 other immunosuppressants per local guidelines

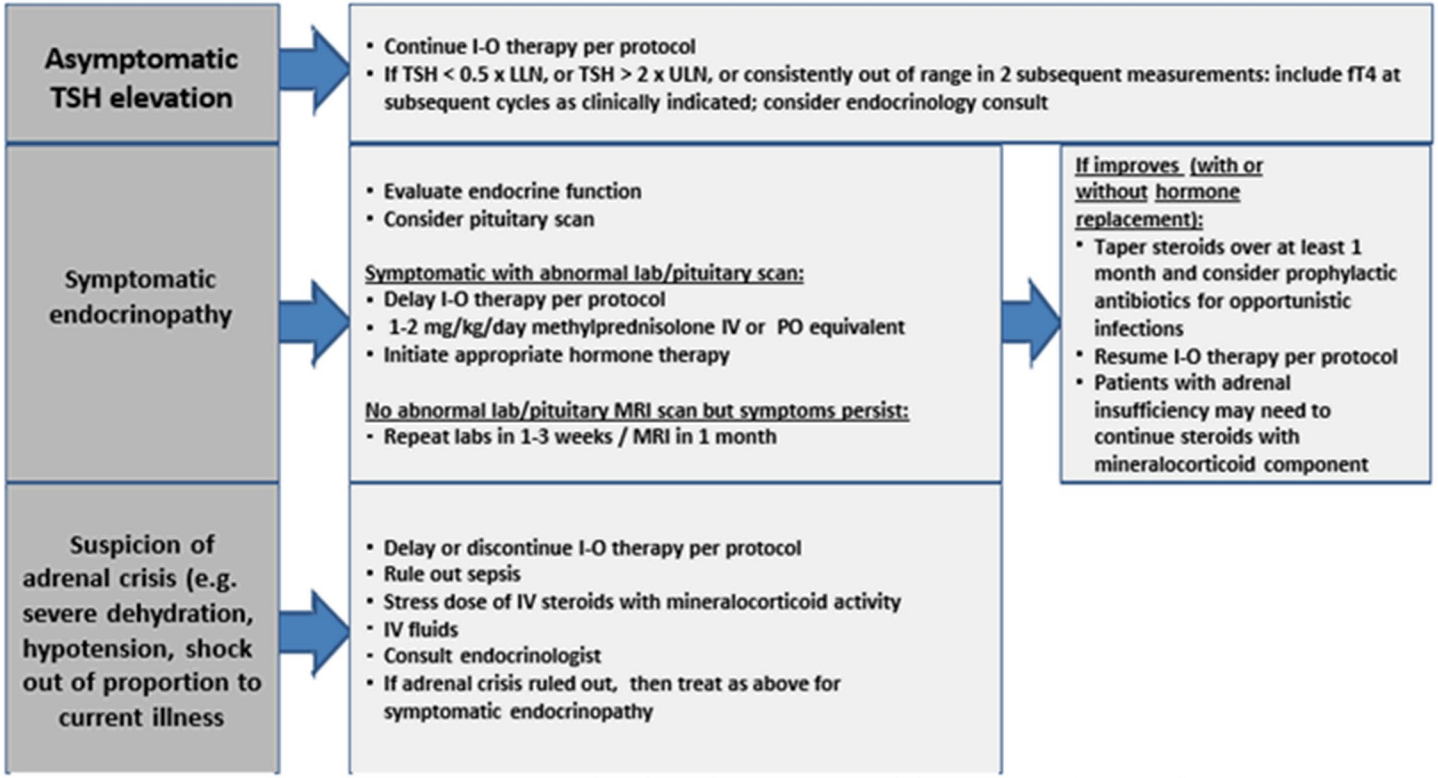
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

*The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

27-Jun-2019

Endocrinopathy Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.

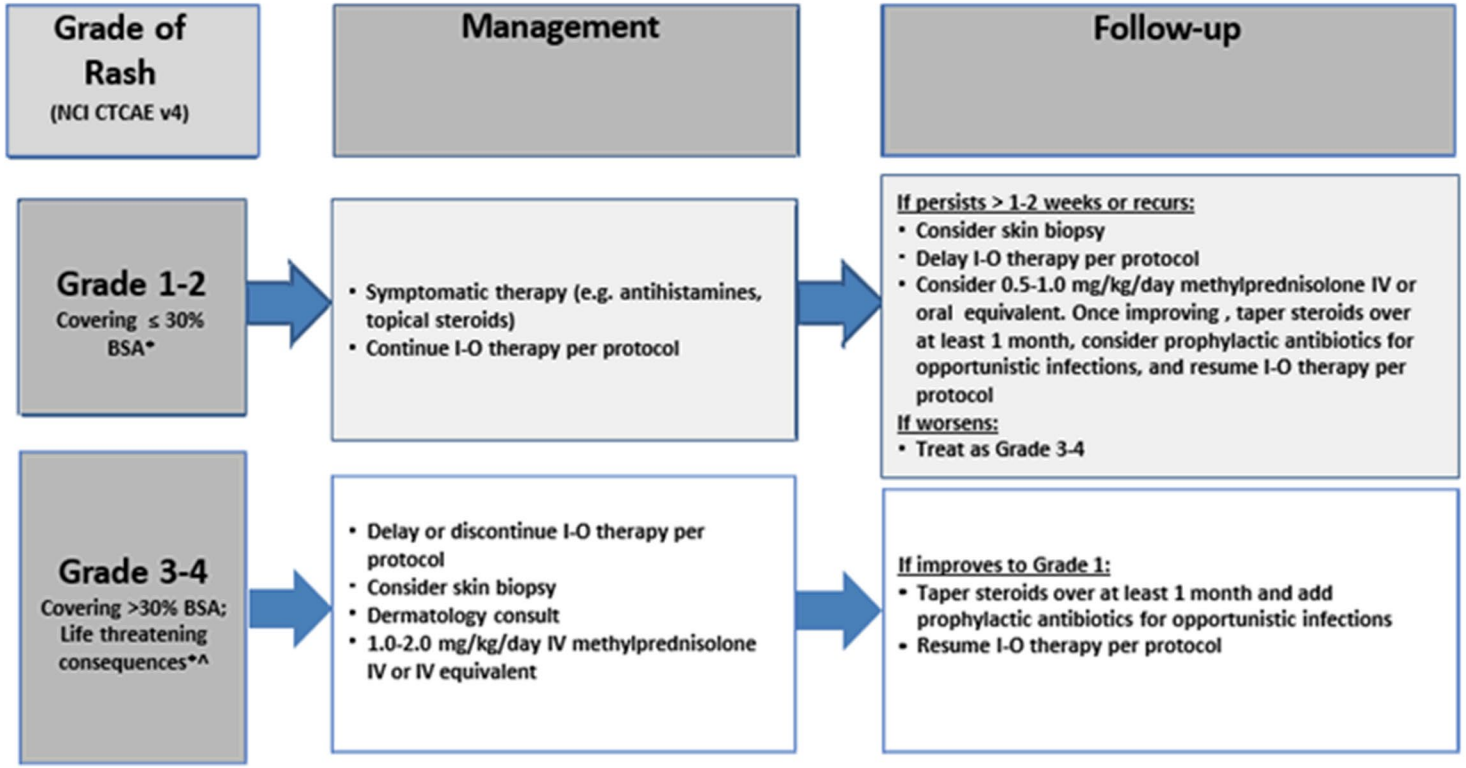


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

27-Jun-2019

Skin Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

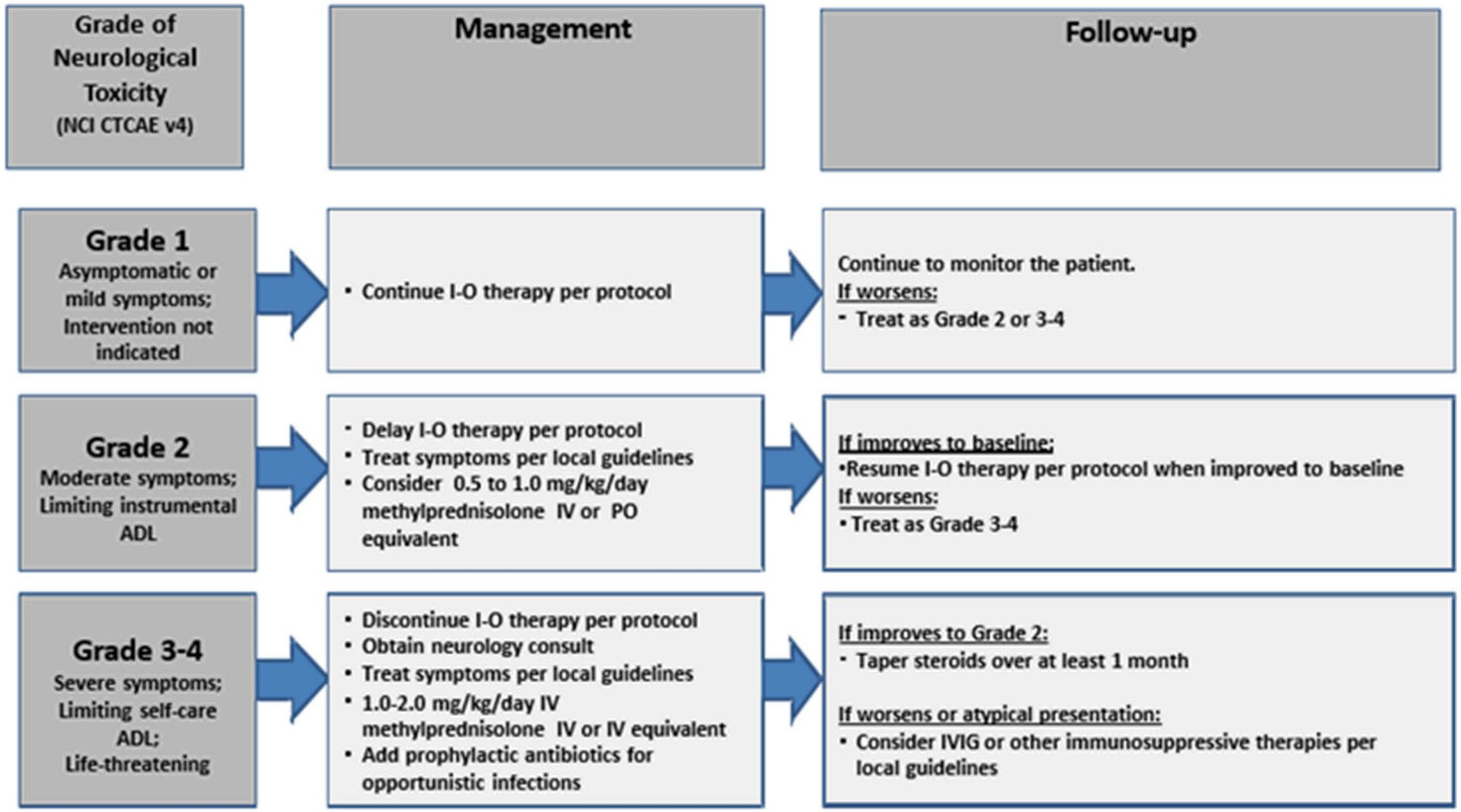
*Refer to NCI CTCAE v4 for term-specific grading criteria.

^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

27-Jun-2019

Neurological Adverse Event Management Algorithm

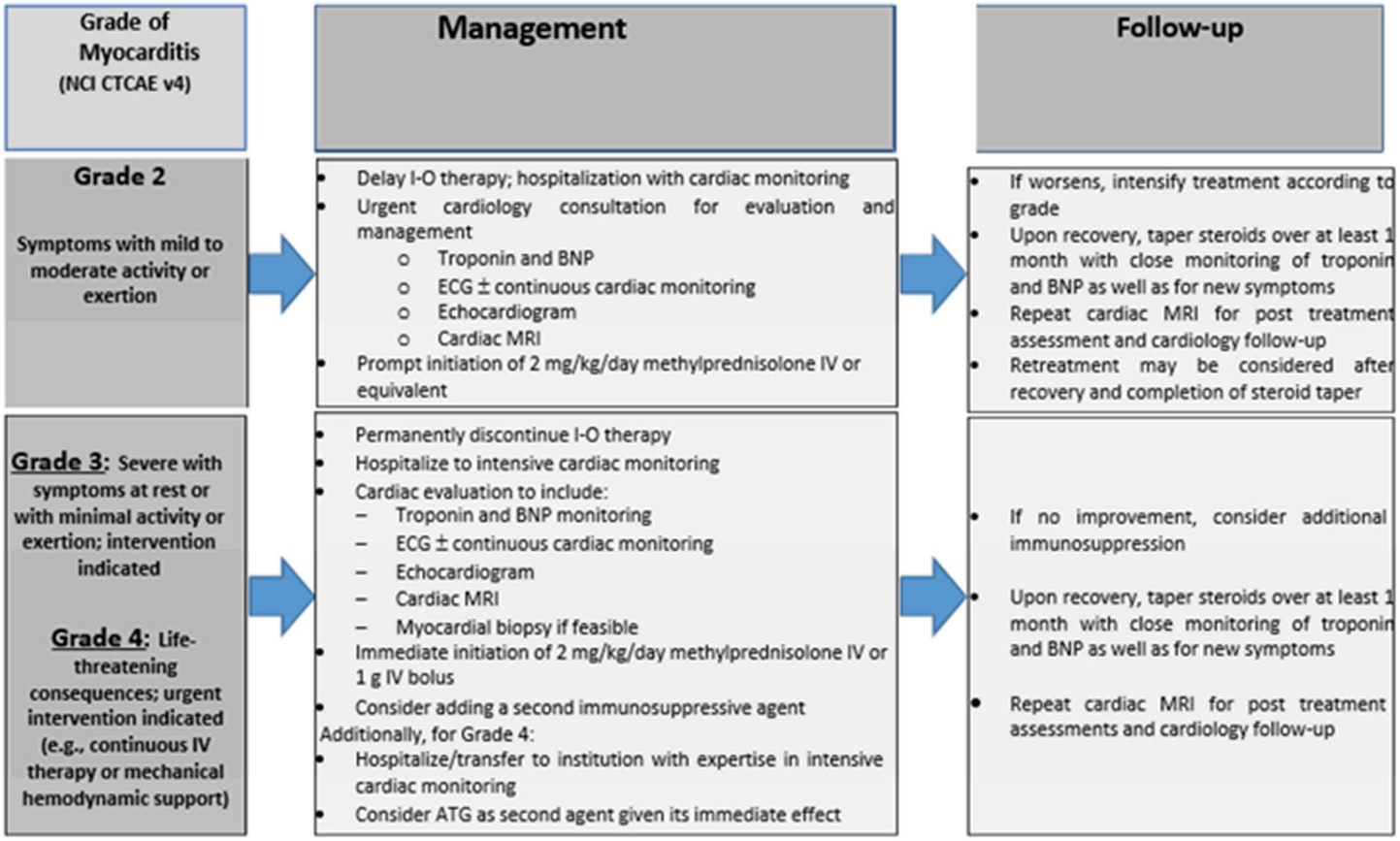
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

27-Jun-2019

Myocarditis Adverse Event Management Algorithm



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.

ATG = anti-thymocyte globulin; BNP = B-type natriuretic peptide; ECG = electrocardiogram; IV = intravenous; MRI = magnetic resonance imaging

27-Jun-2019

APPENDIX 7 ADME RELATED GENES

http://pharmaadme.org

Core ADME Gene List

Gene Symbol	Full Gene Name	Class
ABCB1	ATP-binding cassette, sub-family B (MDR/TAP), member 1	Transporter
ABCC2	ATP-binding cassette, sub-family C (CFTR/MRP), member 2	Transporter
ABCG2	ATP-binding cassette, sub-family G (WHITE), member 2	Transporter
CYP1A1	cytochrome P450, family 1, subfamily A, polypeptide 1	Phase I
CYP1A2	cytochrome P450, family 1, subfamily A, polypeptide 2	Phase I
CYP2A6	cytochrome P450, family 2, subfamily A, polypeptide 6	Phase I
CYP2B6	cytochrome P450, family 2, subfamily B, polypeptide 6	Phase I
CYP2C19	cytochrome P450, family 2, subfamily C, polypeptide 19	Phase I
CYP2C8	cytochrome P450, family 2, subfamily C, polypeptide 8	Phase I
CYP2C9	cytochrome P450, family 2, subfamily C, polypeptide 9	Phase I
CYP2D6	cytochrome P450, family 2, subfamily D, polypeptide 6	Phase I
CYP2E1	cytochrome P450, family 2, subfamily E, polypeptide 1	Phase I
CYP3A4	cytochrome P450, family 3, subfamily A, polypeptide 4	Phase I
CYP3A5	cytochrome P450, family 3, subfamily A, polypeptide 5	Phase I
DPYD	dihydropyrimidine dehydrogenase	Phase I
GSTM1	glutathione S-transferase M1	Phase II
GSTP1	glutathione S-transferase pi	Phase II
GSTT1	glutathione S-transferase theta 1	Phase II
NAT1	N-acetyltransferase 1 (arylamine N-acetyltransferase)	Phase II
NAT2	N-acetyltransferase 2 (arylamine N-acetyltransferase)	Phase II
SLC15A2	solute carrier family 15 (H+/peptide transporter), member 2	Transporter
SLC22A1	solute carrier family 22 (organic cation transporter), member 1	Transporter
SLC22A2	solute carrier family 22 (organic cation transporter), member 2	Transporter
SLC22A6	solute carrier family 22 (organic anion transporter), member 6	Transporter
SLCO1B1	solute carrier organic anion transporter family, member 1B1	Transporter
SLCO1B3	solute carrier organic anion transporter family, member 1B3	Transporter
SULT1A1	sulfotransferase family, cytosolic, 1A, phenol-preferring, member 1	Phase II
TPMT	thiopurine S-methyltransferase,	Phase II
UGT1A1	UDP glucuronosyltransferase 1 family, polypeptide A1	Phase II
UGT2B15	UDP glucuronosyltransferase 2 family, polypeptide B15	Phase II
UGT2B17	UDP glucuronosyltransferase 2 family, polypeptide B17	Phase II

Gene Symbol	Full Gene Name	Class
UGT2B7	UDP glucuronosyltransferase 2 family, polypeptide B7	Phase II

Extended ADME Gene List

Rank	Gene Symbol	Full Gene Name	Class
7	ABCB8	ATP-binding cassette, sub-family B (MDR/TAP), member 8	Transporter
7	ABCC12	ATP-binding cassette, sub-family C (CFTR/MRP), member 12	Transporter
7	ABCC3	ATP-binding cassette, sub-family C (CFTR/MRP), member 3	Transporter
7	ABCC4	ATP-binding cassette, sub-family C (CFTR/MRP), member 4	Transporter
7	AHR	aryl hydrocarbon receptor	Modifier
7	ALDH4A1	aldehyde dehydrogenase 4 family, member A1	Phase I
7	ALDH5A1	aldehyde dehydrogenase 5 family, member A1	Phase I
7	ALDH6A1	aldehyde dehydrogenase 6 family, member A1	Phase I
7	CES1	carboxylesterase 1 (monocyte/macrophage serine esterase 1)	Phase I
7	CES2	carboxylesterase 2 (intestine, liver)	Phase I
7	CYP7A1	cytochrome P450, family 7, subfamily A, polypeptide 1	Phase I
7	EPHX1	epoxide hydrolase 1, microsomal (xenobiotic)	Phase I
7	FMO3	flavin containing monooxygenase 3	Phase I
7	GSTA1	glutathione S-transferase A1	Phase II
7	GSTA2	glutathione S-transferase A2	Phase II
7	GSTA3	glutathione S-transferase A3	Phase II
7	GSTA4	glutathione S-transferase A4	Phase II
7	GSTA5	glutathione S-transferase A5	Phase II
7	GSTM2	glutathione S-transferase M2 (muscle),glutathione S-transferase M4	Phase II
7	GSTM3	glutathione S-transferase M3 (brain)	Phase II
7	GSTM4	glutathione S-transferase M4	Phase II
7	GSTO1	glutathione S-transferase omega 1,glutathione S-transferase omega 2	Phase II
7	GSTO2	glutathione S-transferase omega 2	Phase II
7	GSTT2	glutathione S-transferase theta 2	Phase II
7	SLC10A1	solute carrier family 10 (sodium/bile acid cotransporter family), member 1	Transporter
7	SLC15A1	solute carrier family 15 (oligopeptide transporter), member 1	Transporter
7	SLC22A11	solute carrier family 22 (organic anion/cation transporter), member 11	Transporter
7	SLC22A8	solute carrier family 22 (organic anion transporter), member 8	Transporter
7	SLC7A5	solute carrier family 7 (cationic amino acid transporter, y+ system), member 5	Transporter

Rank	Gene Symbol	Full Gene Name	Class
7	SLCO1A2	solute carrier organic anion transporter family, member 1A2	Transporter
7	SLCO2B1	solute carrier organic anion transporter family, member 2B1	Transporter
7	SULT1A2	sulfotransferase family, cytosolic, 1A, phenol-preferring, member 2	Phase II
7	SULT1A3	sulfotransferase family, cytosolic, 1A, phenol-preferring, member 3	Phase II
7	SULT1B1	sulfotransferase family, cytosolic, 1B, member 1	Phase II
7	UGT1A3	UDP glucuronosyltransferase 1 family, polypeptide A3	Phase II
7	UGT1A6	UDP glucuronosyltransferase 1 family, polypeptide A6	Phase II
7	UGT1A7	UDP glucuronosyltransferase 1 family, polypeptide A7	Phase II
7	UGT1A8	UDP glucuronosyltransferase 1 family, polypeptide A8	Phase II
7	UGT1A9	UDP glucuronosyltransferase 1 family, polypeptide A9	Phase II
7	UGT2A1	UDP glucuronosyltransferase 2 family, polypeptide A1	Phase II
7	UGT2B11	UDP glucuronosyltransferase 2 family, polypeptide B11	Phase II
7	UGT2B28	UDP glucuronosyltransferase 2 family, polypeptide B28	Phase II
7	UGT2B4	UDP glucuronosyltransferase 2 family, polypeptide B4	Phase II
6	ABCA1	ATP-binding cassette, sub-family A (ABC1), member 1	Transporter
6	ABCA4	ATP-binding cassette, sub-family A (ABC1), member 4	Transporter
6	ABCB11	ATP-binding cassette, sub-family B (MDR/TAP), member 11	Transporter
6	ABCB4	ATP-binding cassette, sub-family B (MDR/TAP), member 4	Transporter
6	ABCB5	ATP-binding cassette, sub-family B (MDR/TAP), member 5	Transporter
6	ABCB6	ATP-binding cassette, sub-family B (MDR/TAP), member 6	Transporter
6	ABCB7	ATP-binding cassette, sub-family B (MDR/TAP), member 7	Transporter
6	ABCC1	ATP-binding cassette, sub-family C (CFTR/MRP), member 1	Transporter
6	ABCC10	ATP-binding cassette, sub-family C (CFTR/MRP), member 10	Transporter
6	ABCC11	ATP-binding cassette, sub-family C (CFTR/MRP), member 11	Transporter
6	ABCC5	ATP-binding cassette, sub-family C (CFTR/MRP), member 5	Transporter
6	ABCC6	ATP-binding cassette, sub-family C (CFTR/MRP), member 6	Transporter
6	ABCC8	ATP-binding cassette, sub-family C (CFTR/MRP), member 8	Transporter
6	ABCC9	ATP-binding cassette, sub-family C (CFTR/MRP), member 9	Transporter
6	ABCG1	ATP-binding cassette, sub-family G (WHITE), member 1	Transporter
6	ADH1A	alcohol dehydrogenase 1A (class I), alpha polypeptide	Phase I
6	ADH1B	alcohol dehydrogenase IB (class I), beta polypeptide	Phase I
6	ADH1C	alcohol dehydrogenase 1C (class I), gamma polypeptide	Phase I
6	ADH4	alcohol dehydrogenase 4 (class II), pi polypeptide	Phase I
6	ADH5	alcohol dehydrogenase 5 (class III), chi polypeptide,methionyl aminopeptidase 1	Phase I
6	ADH6	alcohol dehydrogenase 6 (class V)	Phase I

Rank	Gene Symbol	Full Gene Name	Class
6	ADH7	alcohol dehydrogenase 7 (class IV), mu or sigma polypeptide	Phase I
6	ALDH1A1	aldehyde dehydrogenase 1 family, member A1	Phase I
6	ALDH1A2	aldehyde dehydrogenase 1 family, member A2	Phase I
6	ALDH1A3	aldehyde dehydrogenase 1 family, member A3	Phase I
6	ALDH1B1	aldehyde dehydrogenase 1 family, member B1	Phase I
6	ALDH2	aldehyde dehydrogenase 2 family (mitochondrial)	Phase I
6	ALDH3A1	aldehyde dehydrogenase 3 family, memberA1	Phase I
6	ALDH3A2	aldehyde dehydrogenase 3 family, member A2	Phase I
6	ALDH3B1	aldehyde dehydrogenase 3 family, member B1	Phase I
6	ALDH3B2	aldehyde dehydrogenase 3 family, member B2	Phase I
6	ALDH7A1	aldehyde dehydrogenase 7 family, member A1	Phase I
6	ALDH8A1	aldehyde dehydrogenase 8 family, member A1	Phase I
6	ALDH9A1	aldehyde dehydrogenase 9 family, member A1	Phase I
6	AOX1	aldehyde oxidase 1	Phase I
6	ARNT	aryl hydrocarbon receptor nuclear translocator	Modifier
6	CBR1	carbonyl reductase 1	Phase I
6	CBR3	carbonyl reductase 3	Phase I
6	CDA	cytidine deaminase	Modifier
6	CYB5R3	cytochrome b5 reductase 3	Phase I
6	CYP11A1	cytochrome P450, family 11, subfamily A, polypeptide 1	Phase I
6	CYP11B1	cytochrome P450, family 11, subfamily B, polypeptide 1	Phase I
6	CYP11B2	cytochrome P450, family 11, subfamily B, polypeptide 2	Phase I
6	CYP17A1	cytochrome P450, family 17, subfamily A, polypeptide 1	Phase I
6	CYP1B1	cytochrome P450, family 1, subfamily B, polypeptide 1	Phase I
6	CYP20A1	cytochrome P450, family 20, subfamily A, polypeptide 1	Phase I
6	CYP20A1	cytochrome P450, family 20, subfamily A, polypeptide 1	Phase I
6	CYP21A2	cytochrome P450, family 21, subfamily A, polypeptide 2	Phase I
6	CYP24A1	cytochrome P450, family 24, subfamily A, polypeptide 1	Phase I
6	CYP26A1	cytochrome P450, family 26, subfamily A, polypeptide 1	Phase I
6	CYP27A1	cytochrome P450, family 27, subfamily A, polypeptide 1	Phase I
6	CYP2A13	cytochrome P450, family 2, subfamily A, polypeptide 13	Phase I
6	CYP2A7	cytochrome P450, family 2, subfamily A, polypeptide 7	Phase I
6	CYP2C18	cytochrome P450, family 2, subfamily C, polypeptide 18	Phase I
6	CYP2F1	cytochrome P450, family 2, subfamily F, polypeptide 1	Phase I
6	CYP2J2	cytochrome P450, family 2, subfamily J, polypeptide 2	Phase I
6	CYP39A1	cytochrome P450, family 39, subfamily A, polypeptide 1	Phase I

Rank	Gene Symbol	Full Gene Name	Class
6	CYP3A43	cytochrome P450, family 3, subfamily A, polypeptide 43	Phase I
6	CYP3A7	cytochrome P450, family 3, subfamily A, polypeptide 7	Phase I
6	CYP4B1	cytochrome P450, family 4, subfamily B, polypeptide 1	Phase I
6	CYP4F11	cytochrome P450, family 4, subfamily F, polypeptide 11	Phase I
6	CYP51A1	cytochrome P450, family 51, subfamily A, polypeptide 1	Phase I
6	EPHX2	epoxide hydrolase 2, cytoplasmic	Phase I
6	FMO1	flavin containing monooxygenase 1	Phase I
6	FMO2	flavin containing monooxygenase 2	Phase I
6	FMO4	flavin containing monooxygenase 4	Phase I
6	FMO5	flavin containing monooxygenase 5	Phase I
6	GPX2	glutathione peroxidase 2 (gastrointestinal)	Phase I
6	GPX3	glutathione peroxidase 3 (plasma)	Phase I
6	GPX7	glutathione peroxidase 7	Phase I
6	GSR	glutathione reductase	Phase I
6	GSTK1	glutathione S-transferase kappa 1	Phase II
6	GSTM5	glutathione S-transferase M5	Phase II
6	GSTZ1	glutathione transferase zeta 1 (maleylacetoacetate isomerase)	Phase II
6	NNMT	nicotinamide N-methyltransferase	Phase II
6	NR1I2	nuclear receptor subfamily 1, group I, member 2	Modifier
6	NR1I3	nuclear receptor subfamily 1, group I, member 3	Modifier
6	PNMT	phenylethanolamine N-methyltransferase	Phase II
6	PON1	paraoxonase 1	Phase I
6	PON2	paraoxonase 2	Phase I
6	PON3	paraoxonase 3	Phase I
6	POR	P450 (cytochrome) oxidoreductase	Modifier
6	PPARD	peroxisome proliferative activated receptor, delta	Modifier
6	PPARG	peroxisome proliferative activated receptor, gamma	Modifier
6	RXRA	retinoid X receptor, alpha	Modifier
6	SLC10A2	solute carrier family 10 (sodium/bile acid cotransporter family), member 2	Transporter
6	SLC13A1	solute carrier family 13 (sodium/sulfate symporters), member 1	Transporter
6	SLC13A2	solute carrier family 13 (sodium-dependent dicarboxylate transporter), member 2	Transporter
6	SLC13A3	solute carrier family 13 (sodium-dependent dicarboxylate transporter), member 3	Transporter
6	SLC16A1	solute carrier family 16 (monocarboxylic acid Transporter), member 1	Transporter
6	SLC19A1	solute carrier family 19 (folate transporter), member 1	Transporter

Rank	Gene Symbol	Full Gene Name	Class
6	SLC22A10	solute carrier family 22 (organic anion/cation transporter), member 10	Transporter
6	SLC22A12	solute carrier family 22 (organic anion/cation transporter), member 12	Transporter
6	SLC22A13	solute carrier family 22 (organic cation transporter), member 13	Transporter
6	SLC22A14	solute carrier family 22 (organic cation transporter), member 14	Transporter
6	SLC22A15	solute carrier family 22 (organic cation transporter), member 15	Transporter
6	SLC22A16	solute carrier family 22 (organic cation transporter), member 16	Transporter
6	SLC22A17	solute carrier family 22 (organic cation transporter), member 17	Transporter
6	SLC22A18	solute carrier family 22 (organic cation transporter), member 18	Transporter
6	SLC22A18AS	solute carrier family 22 (organic cation transporter), member 18 antisense	Transporter
6	SLC22A3	solute carrier family 22 (extraneuronal monoamine transporter), member 3	Transporter
6	SLC22A4	solute carrier family 22 (organic cation transporter), member 4	Transporter
6	SLC22A5	solute carrier family 22 (organic cation transporter), member 5	Transporter
6	SLC22A7	solute carrier family 22 (organic anion transporter), member 7	Transporter
6	SLC22A9	solute carrier family 22 (organic anion/cation transporter), member 9	Transporter
6	SLC27A1	solute carrier family 27 (fatty acid transporter), member 1	Transporter
6	SLC28A1	solute carrier family 28 (sodium-coupled nucleoside transporter), member 1	Transporter
6	SLC28A2	solute carrier family 28 (sodium-coupled nucleoside transporter), member 2	Transporter
6	SLC28A3	solute carrier family 28 (sodium-coupled nucleoside transporter), member 3	Transporter
6	SLC29A1	solute carrier family 29 (nucleoside Transporter), member 1	Transporter
6	SLC29A2	solute carrier family 29 (nucleoside Transporter), member 2	Transporter
6	SLC2A4	solute carrier family 2 (facilitated glucose transporter), member 4	Transporter
6	SLC2A5	solute carrier family 2 (facilitated glucose/fructose transporter), member 5	Transporter
6	SLC5A6	solute carrier family 5 (sodium-dependent vitamin transporter)	Transporter
6	SLC6A6	solute carrier family 6 (neurotransmitter transporter, taurine), member 6	Transporter
6	SLC7A8	solute carrier family 7 (cationic amino acid transporter, y+ system), member 8	Transporter
6	SLCO1C1	solute carrier organic anion transporter family, member 1C1	Transporter
6	SLCO2A1	solute carrier organic anion transporter family, member 2A1	Transporter
6	SLCO3A1	solute carrier organic anion transporter family, member 3A1	Transporter
6	SLCO4A1	solute carrier organic anion transporter family, member 4A1	Transporter
6	SLCO4C1	solute carrier organic anion transporter family, member 4C1	Transporter
6	SLCO5A1	solute carrier organic anion transporter family, member 5A1	Transporter

Rank	Gene Symbol	Full Gene Name	Class
6	SLCO6A1	solute carrier organic anion transporter family, member 6A1	Transporter
6	SULT1C1	sulfotransferase family, cytosolic, 1C, member 1	Phase II
6	SULT1C2	sulfotransferase family, cytosolic, 1C, member 2	Phase II
6	SULT1E1	sulfotransferase family 1E, estrogen-preferring, member 1	Phase II
6	SULT2A1	sulfotransferase family, cytosolic, 2A, DHEA preferring, member 1	Phase II
6	SULT2B1	sulfotransferase family, cytosolic, 2B, member 1	Phase II
6	TAP1	transporter 1, ATP-binding cassette, sub-family B (MDR/TAP)	Transporter
6	UGT1A10	UDP glucuronosyltransferase 1 family, polypeptide A10	Phase II
6	UGT1A4	UDP glucuronosyltransferase 1 family, polypeptide A4	Phase II
6	UGT1A5	UDP glucuronosyltransferase 1 family, polypeptide A5	Phase II
6	UGT2B10	UDP glucuronosyltransferase 2 family, polypeptide B10	Phase II
5	ABCC13	ATP-binding cassette, sub-family C (CFTR/MRP), member 13	Transporter
5	ARSA	arylsulfatase A	Modifier
5	CAT	catalase	Modifier
5	CHST8	carbohydrate (N-acetylgalactosamine 4-0) sulfotransferase 8	Phase II
5	CYP19A1	cytochrome P450, family 19, subfamily A, polypeptide 1	Phase I
5	CYP26C1	cytochrome P450, family 26, subfamily C, polypeptide 1	Phase I
5	CYP27B1	cytochrome P450, family 27, subfamily B, polypeptide 1	Phase I
5	CYP2R1	cytochrome P450, family 2, subfamily R, polypeptide 1	Phase I
5	CYP2S1	cytochrome P450, family 2, subfamily S, polypeptide 1	Phase I
5	CYP46A1	cytochrome P450, family 46, subfamily A, polypeptide 1	Phase I
5	CYP4A11	cytochrome P450, family 4, subfamily A, polypeptide 11	Phase I
5	CYP4F12	cytochrome P450, family 4, subfamily F, polypeptide 12	Phase I
5	CYP4F2	cytochrome P450, family 4, subfamily F, polypeptide 2	Phase I
5	CYP4F3	cytochrome P450, family 4, subfamily F, polypeptide 3	Phase I
5	CYP4F8	cytochrome P450, family 4, subfamily F, polypeptide 8	Phase I
5	CYP4Z1	cytochrome P450, family 4, subfamily Z, polypeptide 1	Phase I
5	CYP7B1	cytochrome P450, family 7, subfamily B, polypeptide 1	Phase I
5	CYP8B1	cytochrome P450, family 8, subfamily B, polypeptide 1	Phase I
5	DHRS13	dehydrogenase/reductase (SDR family) member 13	Phase I
5	DHRS2	dehydrogenase/reductase (SDR family) member 2	Phase I
5	GPX1	glutathione peroxidase 1	Phase I
5	GPX4	glutathione peroxidase 4 (phospholipid hydroperoxidase)	Phase I
5	GPX5	glutathione peroxidase 5 (epididymal androgen-related protein)	Phase I
5	GPX6	glutathione peroxidase 6 (olfactory)	Phase I
5	GSS	glutathione synthetase	Phase I

Rank	Gene Symbol	Full Gene Name	Class
5	GSTCD	glutathione S-transferase, C-terminal domain containing	Phase II
5	HNF4A	hepatocyte nuclear factor 4, alpha	Modifier
5	HNMT	histamine N-methyltransferase	Phase II
5	HSD11B1	hydroxysteroid (17-beta) dehydrogenase 11	Phase I
5	HSD17B11	hydroxysteroid (17-beta) dehydrogenase 11	Phase I
5	HSD17B14	hydroxysteroid (17-beta) dehydrogenase 14	Phase I
5	LOC731356	similar to dehydrogenase/reductase (SDR family) member 4 like 2	Phase I
5	MGST1	microsomal glutathione S-transferase 1	Phase II
5	MGST2	microsomal glutathione S-transferase 2	Phase II
5	MGST3	microsomal glutathione S-transferase 3	Phase II
5	MPO	myeloperoxidase	Modifier
5	NOS1	nitric oxide synthase 1 (neuronal)	Phase I
5	NOS2A	nitric oxide synthase 2A (inducible, hepatocytes)	Phase I
5	NOS3	nitric oxide synthase 3 (endothelial cell)	Phase I
5	PPARA	peroxisome proliferator-activated receptor alpha	Modifier
5	SERPINA7	serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 7	Modifier
5	SLC7A7	solute carrier family 7 (cationic amino acid transporter, y+ system), member 7	Transporter
5	SOD1	superoxide dismutase 1, soluble (amyotrophic lateral sclerosis 1 (adult))	Modifier
5	SOD2	superoxide dismutase 2, mitochondrial	Modifier
5	SOD3	superoxide dismutase 3, extracellular precursor	Modifier
5	SULF1	sulfatase 1	Phase I
5	SULT4A1	sulfotransferase family 4A, member 1	Phase II
5	TAP2	transporter 2, ATP-binding cassette, sub-family B (MDR/TAP)	Transporter
5	UGT8	UDP glycosyltransferase 8 (UDP-galactose ceramide galactosyltransferase)	Phase II
5	XDH	xanthine dehydrogenase	Phase I
4	ADHFE1	alcohol dehydrogenase, iron containing, 1	Phase I
4	CHST1	carbohydrate (keratan sulfate Gal-6) sulfotransferase 1	Phase II
4	CHST10	carbohydrate sulfotransferase 10	Phase II
4	CHST11	carbohydrate (chondroitin 4) sulfotransferase 11	Phase II
4	CHST12	carbohydrate (chondroitin 4) sulfotransferase 12	Phase II
4	CHST13	carbohydrate (chondroitin 4) sulfotransferase 13	Phase II
4	CHST2	carbohydrate (N-acetylglucosamine-6-O) sulfotransferase 2	Phase II
4	CHST3	carbohydrate (chondroitin 6) sulfotransferase 3	Phase II
4	CHST4	carbohydrate (N-acetylglucosamine 6-O) sulfotransferase 4	Phase II

Rank	Gene Symbol	Full Gene Name	Class
4	CHST5	carbohydrate (N-acetylglucosamine 6-O) sulfotransferase 5	Phase II
4	CHST6	carbohydrate (N-acetylglucosamine 6-O) sulfotransferase 6	Phase II
4	CHST7	carbohydrate (N-acetylglucosamine 6-O) sulfotransferase 7	Phase II
4	CHST9	carbohydrate (N-acetylgalactosamine 4-0) sulfotransferase 9	Phase II
4	CYP2D7P1	cytochrome P450, family 2, subfamily D, polypeptide 7 pseudogene 1	Phase I
4	DDO	D-aspartate oxidase	Phase I
4	DHRS1	dehydrogenase/reductase (SDR family) member 1	Phase I
4	DHRS12	dehydrogenase/reductase (SDR family) member 12	Phase I
4	DHRS3	dehydrogenase/reductase (SDR family) member 3	Phase I
4	DHRS4	dehydrogenase/reductase (SDR family) member 4	Phase I
4	DHRS4L1	dehydrogenase/reductase (SDR family) member 4 like 1	Phase I
4	DHRS4L2	dehydrogenase/reductase (SDR family) member 4 like 2	Phase I
4	DHRS7	dehydrogenase/reductase (SDR family) member 7	Phase I
4	DHRS7B	dehydrogenase/reductase (SDR family) member 7B	Phase I
4	DHRS7C	dehydrogenase/reductase (SDR family) member 7C	Phase I
4	DHRS9	dehydrogenase/reductase (SDR family) member 9	Phase I
4	DHRSX	dehydrogenase/reductase (SDR family) X-linked	Phase I
4	DPEP1	dipeptidase 1 (renal)	Phase I
4	FMO6P	flavin containing monooxygenase 6	Phase I
4	HAGH	hydroxyacylglutathione hydrolase	Phase I
4	IAPP	islet amyloid polypeptide	Modifier
4	KCNJ11	potassium inwardly-rectifying channel, subfamily J, member 11	Modifier
4	LOC728667	similar to dehydrogenase/reductase (SDR family) member 2 isoform 1	Phase I
4	LOC731931	similar to dehydrogenase/reductase (SDR family) member 2 isoform 1	Phase I
4	MAT1A	methionine adenosyltransferase I, alpha	Modifier
4	METAP1	methionyl aminopeptidase 1	Phase I
4	PDE3A	phosphodiesterase 3A, cGMP-inhibited	Phase I
4	PDE3B	phosphodiesterase 3B, cGMP-inhibited	Phase I
4	PLGLB1	plasminogen-like B1	Phase I
3	ATP7A	ATPase, Cu++ transporting, alpha polypeptide (Menkes syndrome)	Modifier
3	ATP7B	ATPase, Cu++ transporting, beta polypeptide	Modifier
3	CFTR	cystic fibrosis transmembrane conductance regulator	Modifier

APPENDIX 8 EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

ECOG PERFORMANCE STATUS[a]	
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

[a] Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, and Carbone PP. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5: 649-655.

APPENDIX 9 NEW YORK HEART ASSOCIATION (NYHA) FUNCTIONAL CLASSIFICATION

Heart failure is usually classified according to the severity of their symptoms. The table below describes the most commonly used classification system, the New York Heart Association (NYHA) Functional Classification. It places patients in one of four 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, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, 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 10 CONSORT PUBLISHING REQUIREMENTS

The Consolidated Standards of Reporting Trials (CONSORT) encompasses various initiatives developed by the CONSORT Group to alleviate the problems arising from inadequate reporting of randomized controlled trials.

The CONSORT Statement

The main product of CONSORT is the CONSORT Statement, which is an evidence-based, minimum set of recommendations for reporting randomized trials. It offers a standard way for authors to prepare reports of trial findings, facilitating their complete and transparent reporting, and aiding their critical appraisal and interpretation. CONSORT 2010 is the current version of the statement and supersedes the 2001 and 1996 versions.

The CONSORT Statement comprises a 25-item checklist and a flow diagram. The checklist items focus on reporting how the trial was designed, analyzed, and interpreted. The flow diagram displays the progress of all participants through the trial. The checklist and flow diagram are freely available for viewing and downloading at the CONSORT website (http://www.consort-statement.org/consort-2010). The CONSORT Statement is endorsed by general medical journals, specialty medical journals, and leading editorial organizations. CONSORT is part of a broader effort, to improve the reporting of different types of health research, and indeed, to improve the quality of research used in decision-making in healthcare.

CONSORT 2010 Guideline

The CONSORT (CONsolidated Standards of Reporting Trials) 2010 guideline is intended to improve the reporting of parallel-group randomized controlled trial (RCT), enabling readers to understand a trial's design, conduct, analysis and interpretation, and to assess the validity of its results. This can only be achieved through complete adherence and transparency by authors. CONSORT 2010 was developed through collaboration and consensus between clinical trial methodologists, guideline developers, knowledge translation specialists, and journal editors (see CONSORT group). CONSORT 2010 is the current version of the guideline and supersedes the 2001 and 1996 versions.

CONSORT “Explanation and Elaboration” Document

The CONSORT “Explanation and Elaboration” document explains and illustrates the principles underlying the CONSORT Statement, and should preferably be used in conjunction with the CONSORT Statement. In addition, extensions of the CONSORT Statement have been developed to give additional guidance for RCTs with specific designs, data and interventions. The CONSORT website (http://www.consort-statement.org/consort-2010) contains the current definitive version of the CONSORT 2010 Statement and up-to-date information on extensions.

APPENDIX 11 CHILD-PUGH CLASSIFICATION

Scoring

The score employs five clinical measures of liver disease. Each measure is scored 1-3, with 3 indicating most severe derangement.

	Points Assigned		
Parameter	**1**	**2**	**3**
Ascites	Absent	Slight	Moderate
Bilirubin (mg/dL)	≤ 2	2 to 3	> 3
Albumin (g/dL)	> 3.5	2.8 to 3.5	< 2.8
Prothrombin Time (seconds over control)	1-3	4 to 6	> 6
INR	< 1.7	1.8 to 2.3	> 2.3
Encephalopathy	None	Grade 1 to 2	Grade 3 to 4

Interpretation

Chronic liver disease is classified into Child-Pugh class A to C, employing the summation of score from above. These scores correlate with one and two year survival:

Points	Class	One year survival	Two year survival
5-6	A (well compensated disease)	100%	65%
7-9	B (significant functional compromise)	80%	60%
10-15	C (decompensated disease)	45%	35%

APPENDIX 12 STATISTICAL METHODOLOGY

DETAILS FOR BAYESIAN LOGISTIC REGRESSION MODEL (BLRM AND BLRM-COPULA), PARTS 1A, 1B, AND BAYESIAN OPTIMAL INTERVAL (BOIN), PART 1C DESIGN

1 BLRM MODEL SETUP FOR BMS-986207 MONOTHERAPY

1.1 Monotherapy Methodology Description

An adaptive 2-parameter Bayesian Logistic Regression Model (BLRM) guided by the escalation with overdose control (EWOC) principle[1,2,3] will be used to guide the dose escalation of BMS-986207 monotherapy in the monotherapy phase, providing dose recommendation during dose escalation.

The BLRM will be fitted on the dose-limiting toxicity (DLT) data during the first 4 weeks of treatment accumulated throughout the dose escalation to model the dose-toxicity relationship of BMS-986207 in the monotherapy dose escalation phase.

The dose-toxicity relationships for BMS-986207 monotherapy is assumed to follow a logistic model:

$$\text{logit}(p_i) = \log(a_1) + \beta_1 \log(d_{1i}/d_1^*),$$

where p_i is the probability of toxicity at dose level d_{1i}. Note that the a_1 and β_1 parameters are assumed positive, and d_1^* is the reference dose for BMS-986207 (please refer to the meaning of a_1 and β_1 in Section 1.2.1 for detailed implementation).

1.2 Prior Specification for BMS-986207 Monotherapy

The Bayesian approach requires the specification of prior distributions for model parameters, which include parameters (a_1, β_1) for BMS-986207. The prior distributions for BMS-986207 single agent activity were derived using a weakly informative prior, as well as discussion with the Bristol-Myers Squibb (BMS) clinical team.

Derivation of prior distribution of these parameters is provided in the following subsections.

1.2.1 Prior Derivation for BMS-986207 Parameters ($\log(a_1), \log(P_1)$)

A weakly informative prior will be used for parameters (a_1, β_1) for BMS-986207 to reflect the potential of the different toxicities of BMS-986207 and allow for considerable prior uncertainty.

Further details are provided below.

Weakly Informative Prior

- The median DLT rate at the reference dose (BMS-986207 at 1600 mg qd) was assumed to be 30%, that is, mean ($\log(a_1)$) = logit (0.3) = log(0.3/(1-0.3)) = -0.847.
- A doubling in dose was assumed to double the odds of DLT, that is, mean($\log(\beta_1)$) = 0.
- The standard deviation of $\log(a_1)$ was set to 1.53 using the following steps:

- If the toxicity probability range was set to be [1%, 99%], then the toxicity interval would be logit (0.99)-logit (0.01) = 9.19.
- To cover 99.7% of the variance, the toxicity interval will cover 6*sd ($\log(a_1)$), which gives us sd ($\log(a_1)$) = 9.19/6 = 1.53.

Correspondingly, the standard deviation of $\log(\{3_1)$ was set to 1, which allows for considerably larger prior uncertainty for the dose toxicity.

1) The correlation between $\log(a_1)$ and $\log(\{3_1)$ was set to 0.
2) $\log(a_1)$ and $\log(\{3_1)$ follow a bivariate normal distribution.

Table 1: Prior Distribution for Model Parameters for BMS-986207

Parameter	Means	Standard Deviations	Correlation
$\log(a_1)$, $\log(\beta_1)$	(-0.847, 0)	(1.53, 1)	0

2 BLRM MODEL SETUP FOR BMS-986207 AND NIVOLUMAB COMBINATION

2.1 Methodology Description for Combination Therapy

Toxicity profiles of both BMS-986207 monotherapy and nivolumab monotherapy will be incorporated to develop the combination model framework. A copula-type model will be used to cover all general combination cases, including additive and synergistic effects. The combination of the 2 treatments will be explored using a Bayesian hierarchical model by utilizing the toxicity profiles of the single agents as prior marginal profiles for the combination. The following copula-type model[4] will be used to describe the probability p_{ij} of toxicity when dose level i of agent A and dose level j of agent B are administered in combination:

$$p_{ij} = 1 - \exp(-[\{-\log(1-p_i^m)\}^{1/y_1} + \{-\log(1-q_j^n)\}^{1/y_1}]^{y_1}),$$

where p_i is the prespecified best guess toxicity probability for agent A, q_j is the prespecified best guess toxicity probability for agent B, m and n characterize the individual drug effect, and y_1 characterizes the drug-drug interactive effect.

The joint toxicity framework models the toxicity rates of both agents as well as their interaction effects in a 7-parameter hierarchical model, where each monotherapy dose-toxicity relationship will be characterized by a 2-parameter BLRM model (see Section 1.1). There are 3 additional parameters for the copula-type model, 1 for each agent (m and n) as well as 1 for the interaction term (y_1). A dose-toxicity surface will be characterized for different dose combinations of these 2 agents.

As there are currently no historical data or prior knowledge to indicate how much information is to be borrowed for each of the single agents, parameters m and n are both set to be 1, meaning

borrowing 100% of the information from the 2 agents. The above formula is then simplified into a 5-parameter model as follows:

$$p_{ij} = 1 - \exp(-[\{-\log(1-p_i)\}^{1/y_1} + \{-\log(1-q_j)\}^{1/y_1}]^{y_1}.$$

Since only a fixed nivolumab dose (240 mg) will be used in the BMS-986207 and nivolumab combination, this surface will be simplified into a 2-dimensional dose-toxicity curve. Posteriors for the corresponding 5 parameters (2 logistic regression parameters [a_1, β_1] for BMS-986207 and 2 logistic regression parameters [a_2, β_2] for nivolumab, as well as 1 interaction parameter for the copula-type model [y_1, which will be discussed in detail in the following section]) will be fitted into the in-house developed model. It implements the above-described theoretical setup.

2.2 Prior Specification for Combination Therapy

2.2.1 Marginal Prior for BMS-986207

Posterior information on $\log(\alpha_1)$ and $\log(\beta_1)$ from the monotherapy part of the study will be used as marginal BMS-986207 prior for combination with nivolumab. This prior information is not prespecified and will be continuously updated when additional DLT information from the monotherapy is available. In the simulation (see Section 3, the prior of BMS-986207 as described in Section 1.2.1 (Table 1) is used for illustration purposes because no real-time DLT data are available at this time.

2.2.2 Marginal Prior Derivation for Nivolumab Parameters ($\log(\alpha_2)$, $\log(\beta_2)$)

Similar to BMS-986207 monotherapy in the monotherapy phase, the logistic model for nivolumab is as follows:

$$\text{logit}(q_j) = \log(a_2) + \beta_2 \log(d_{2j}/d_2^*),$$

where q_j is the probability of toxicity at dose level d_{2j}. Note that the a_2 and β_2 parameters are assumed positive, and d_2^* is the reference dose for nivolumab.

The toxicity profile of nivolumab has been studied in several studies. A bivariate normal prior for the nivolumab model parameters ($\log(\alpha_2)$, $\log(\beta_2)$) was obtained by extracting a posterior of nivolumab using DLT and safety data from the Study CA209003, which is used later as the meta-analytical-predictive (MAP) prior for nivolumab.

The MAP prior for the model parameters ($\log(\alpha_2)$, $\log(\beta_2)$) was obtained in the following steps.

First, a prior distribution for nivolumab was developed:

- The medianb DLT rate at the reference dose (3 mg/kg every 2 weeks) was assumed to be 10%, that is, mean ($\log(\alpha_2)$) = logit(1/10) = log(1/9) = -2.197.
- A doubling in dose was assumed to double odds of DLT, that is, mean($\log(\beta_2)$) = 0.
- The standard deviation of $\log(\alpha_2)$ was set to 2, and the standard deviation of $\log(\beta_2)$ to 1, which allows for considerable prior uncertainty for the dose-toxicity profile.

- The correlation between log(α_2) and log(β_2) is assumed to be 0 (assuming independence of log(α_2) and log(β_2)).
- In addition, heterogeneity between the historical study and current study was incorporated using a meta-analytic predictive approach by defining between-trial standard deviations τ_1 and τ_2 for log(α_2) and log(β_2), respectively. The between-trial variability is assumed to be moderate. Therefore, τ_1 and τ_2 were set to follow a log-normal distribution, with mean log(0.25) and log(0.125), respectively, with a common standard deviation log(2)/1.96.

With this prior, the clinical trial data below (Table 2) were used to generate the posterior for nivolumab, which is then used as the MAP prior for this study (Table 3).

Table 2: Data from Single-agent Nivolumab Study CA209003

Dose of Nivolumab (mg/kg)	Every 2 Weeks
	No. of DLTs/No. of Evaluable Patients in the Escalation Phase
0.1	0/3
0.3	0/3
1	0/3
3	0/3
10	1/6

Abbreviation: DLT = dose limiting toxicity.

Table 3: Marginal Prior Distribution for Model Parameters for Nivolumab (ie, Posterior from MAP Method)

Parameter	Means	Standard Deviations	Correlation
log(α_2), log(β_2)	(-3.269, -0.152)	(1.186, 0.771)	-0.369

Note: Nivolumab prior information was based on a milligram-per-kilogram dosing instead of flat dosing. If real pharmacokinetic (PK) data from this study show difference from the milligram-per-kilogram assumption, the nivolumab prior will be revisited and modified accordingly.

2.2.3 Prior for Interaction Parameters for Joint Toxicity of BMS-986207 and Nivolumab Combination

A gamma prior distribution for the interaction parameter γ_1 is derived to reflect the current uncertainty about the toxicity profile of the combination of BMS-986207 and nivolumab. Although no PK drug-drug interaction is expected, the possibility of a significant positive interaction between BMS-986207 and nivolumab cannot be totally excluded. The interaction parameter γ_1 was chosen accordingly but with a degree of uncertainty to allow for the possibility that the interaction may be positive or negative. Therefore, the following assumptions are made for the interaction parameter:

- γ_1 follows a gamma distribution and with a mean centered at 1.1, which means the combination of 2 agents is likely to have only a small synergistic effect.
- The 97.5 percentile of γ_1 is log(3), that is, a 3-fold increase in odds of DLT due to the interaction over independence at the starting dose of the combination.

This model assigns the highest probability to there being small synergistic interaction and also allows for the potential of larger synergism of the toxic profiles. It also does not completely ignore the possibility of antagonism because there is a 40% prior probability that γ_1 is less than 1.

3 BLRM DECISION RULE FOR DOSE ESCALATION AND SIMULATION

Dose escalation recommendations for BMS-986207 monotherapy and in combination with nivolumab will be based on the inference from the Bayesian posterior and the probability that the true DLT rate for each dose lies in 1 of the following categories:

- [0%, 16%) under-dosing
- [16%, 33%) targeted toxicity
- [33%, 100%] excessive toxicity

These boundaries are similar to the toxicity boundaries 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. Following the principle of EWOC, dose recommendations for the next cohort will be based on the Bayesian model after DLT information becomes available during the DLT period, accounting for all of the available data from the administered doses, and the candidate doses are the ones fulfilling the overdose criterion that there is less than 30% chance of excessive toxicity. Only the candidate doses will be considered for the next cohort. While the Bayesian model will use DLT information from the DLT period only, clinical assessment will take into consideration of the totality of available data including PK/[redacted] from all treated participants.

Stopping Rules:

The following is the general stopping rules of BLRM (-Copula) during Dose Escalation:

- If all of 30 DLT evaluable participants are treated.
- If all of the current pre-specified doses are considered intolerable according to the pre-specified cutoff (ie, EWOC criteria), then the model will recommend stopping the current dose level and a new dose level lower than the current lowest dose level will need to be identified.
- The maximum number of participants in a dose level will be 12. This limit is set to avoid instances in which the model could recommend adding subjects indefinitely to a specific dose level due to uncertainty in the tolerability profile.
- If, for a specific dose level, 6 subjects have been treated and the chance of determining that the dose level to be the "target" dose is > 50%, then the model will suggest to stop and declare the current dose level to be MTD.
- **Model-recommended MTD:**
- The MTD is the dose that satisfies the following 3 conditions:

- (1) The empirical posterior probability that the 'DLT rate of 16% -< 33%' is greater than 50%,
- (2) This probability needs to be the largest among the dose levels that satisfy the EWOC condition (ie, the probability that 'DLT rate ≥ 33%' must be less than 30%);
- (3) Minimum number of participants (ie, 6), were treated at this dose level.

Final MTD/RP2D:

The final recommended MTD/RP2D will be based on the recommendation from the BLRM/BLRM-copula and overall clinical assessment of all available safety, PK/[redacted] and efficacy data. Lower doses of BMS-986207 may be tested if none of the planned doses are found to be tolerable as monotherapy or in combination with nivolumab. Such decisions will be made after discussion and agreement between the investigators and the BMS Medical Monitor.

3.2 Simulation Parameters

One thousand trial simulations were used for each scenario. All simulations were run using EAST 6.3.1® software for BLRM model for BMS-986207 monotherapy and in-house developed code via R and Openbugs for BLRM-copula method for BMS-986207 in combination with nivolumab. The number of subjects to be treated in each cohort in a specific dose level and the stopping rules used to declare MTD are defined as:

- Fixed cohort size: 3
- Probability of overdosing: < 30%
- Probability of achieving the target toxicity: > 50%
- Maximum number of participants treated: 30
- Minimum number of participants treated at a given dose level in order to declare MTD: 6
- Maximum number of participants at a dose:12

The provisional dose levels for BMS-986207 monotherapy are 80-1600 mg. For the combination therapy, nivolumab is fixed at 240 mg flat dose for q2w.

3.3 Operating Characteristics

Section 3.2.1 demonstrates operating characteristics of BLRM for monotherapy and Section 3.2.2 demonstrates operating characteristics of BLRM-copula for combination therapy accounting for joint toxicity of the combination therapy.

3.3.1 Operating Characteristics of BLRM for Monotherapy

Three scenarios were investigated by selecting (1) dose-DLT relationship derived by prior, (2) narrow safety window in order to explore how EWOC limits the risk of exposing participants from a toxic dose level, and (3) all doses above the target toxicity.

Table 4: Simulation Results of BLRM for Monotherapy

Scenario	BMS-986207 Dose	80	240	800	1600	MTD not selected (%)	Fitted MTD	Toxicity Observed (%)	Avg # Pts
By prior	% DLT	*5*	*10*	***20***[a]	***30***[a]	1.0	1384	17.9	19.9
	% MTD	0.9	18.1	51.7	28.3				
	# Pts	3.6	4.8	7.2	4.3				
	# DLTs	0.2	0.3	1.4	1.3				
Narrow safety window	% DLT	*5*	*10*	***20***[a]	*80*	1.8	1063	21.5	19.3
	% MTD	0.7	26.2	71	0.3				
	# Pts	3.6	5.4	8.5	1.8				
	# DLTs	0.2	0.4	1.7	1.5				
All high	% DLT	*50*	*60*	*75*	*80*	93.3	30	62.0	5.6
	% MTD	5.7	1.0	0	0				
	# Pts	4.7	0.5	0.4	0.02				
	# DLTs	2.4	0.3	0.3	0.02				

% DLT, true DLT rate; % MTD, proportion of the dose selected as the MTD; # Pts, average number of participants by assuming 3 participants for skipped dose level where the true toxicity rate is below the target rate; # DLTs, average number of DLTs by assuming no DLT for skipped dose level where the true toxicity rate is below the target rate; Fitted MTD: fitted MTD at 30% as the target toxicity rate; % toxicity observed, average proportion of DLTs given the doses were tried

[a] Doses with true target toxicity within the target toxicity interval [16%, 33%)

The average sample size was no more than 20 participants. The results for the scenarios of narrow safety window and all high show how the EWOC principle limits the risk of exposing participants from a toxic dose level. Overall, the scenarios illustrated above demonstrate that the model performs well in the hypothetical scenarios investigated by correctly identifying the MTD at least 71% of the time while limiting participants from receiving excessive/unacceptable toxic dose levels.

3.3.2 Operating Characteristics of BLRM-copula for Combination Therapy

Three hypothetical scenarios were investigated: (1) additive joint toxicity; (2) toxicity rates 25% higher than the additive scenario; (3) toxicity rates 50% higher than the additive scenario;

Table 5: Simulation Results of BLRM-copula for Various Doses of BMS-986207 in Combination with Nivolumab 240 mg q2w

Scenario	BMS-986207 Dose	80	240	800	1600	MTD not selected (%)	Fitted MTD	Toxicity Observed (%)	Avg # Pts
Additive	% DLT	10	14	**25**[a]	40	3.2	1335	20.0	19.9
	% MTD	3.9	30.3	51.4	11.2				
	# Pts	4.3	5.0	8.4	2.2				
	#DLT	0.4	0.7	2.0	0.9				
25% higher	% DLT	13	**18**[a]	**32**[a]	50	6.2	1019	30.0	18.4
	% MTD	8.0	39.8	43.4	2.6				
	# Pts	4.8	5.8	6.7	1.1				
	#DLT	0.6	1.0	2.0	0.6				
50% higher	% DLT	15	**21**[a]	38	60	11.4	788	30.0	17.2
	% MTD	10.8	49.8	27.5	0.5				
	# Pts	5.1	6.2	5.3	0.6				
	#DLT	0.8	1.3	2.0	0.3				

% DLT, true DLT rate; % MTD, proportion of the dose selected as the MTD; #DLT, average number of DLTs; MTD not selected: dose was below lowest dose or above highest dose; Fitted MTD: fitted MTD at 30% as the target toxicity rate and the dose range falls into the target toxicity range of [16%, 33%); Toxicity observed: Average proportion of DLTs out of all simulated trials; # Pts, average number of participants

[a] Doses with true target toxicity within the target toxicity interval [16%, 33)

The average sample size was no more than 20 participants. The results show how the EWOC principle limits the risk of exposing participants from unacceptable toxic dose levels, eg, 50% or above. Overall, the scenarios illustrated above demonstrate that the model performs well by correctly identifying the MTD ranging from 50% to 83% in the hypothetical scenarios investigated while limiting participants from receiving unacceptable toxic dose levels

4 BLRM INTERIM MONITORING CASE STUDY TO ILLUSTRATE PROVISION OF DOSE RECOMMENDATIONS DURING DOSE-ESCALATION

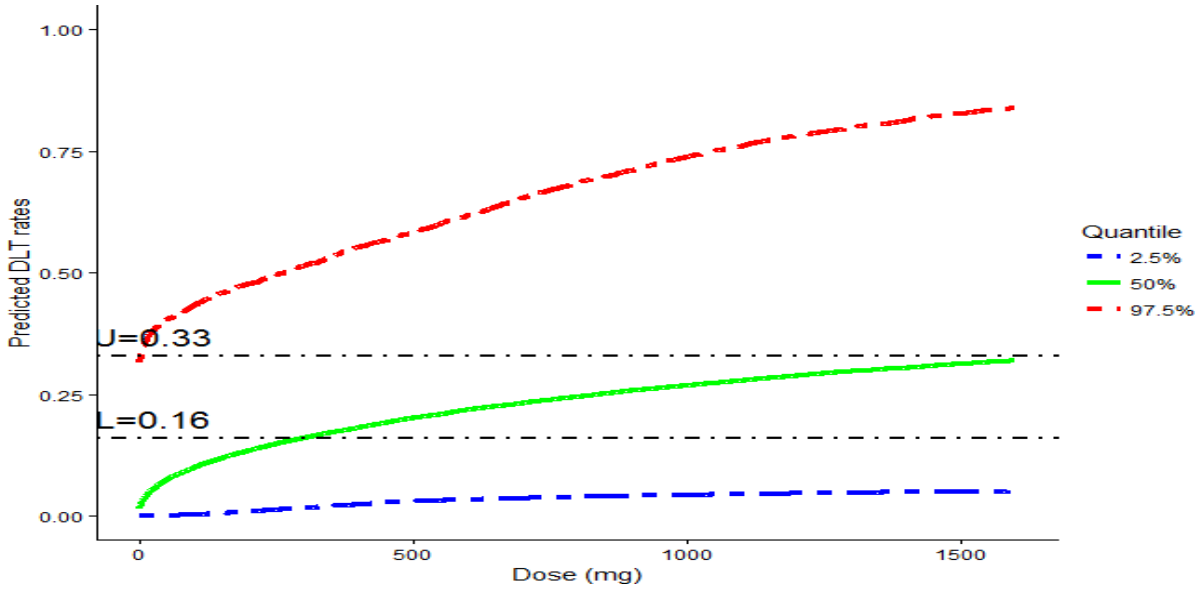
In order to provide a comprehensive view of the dynamics of the models, different hypothetical scenarios exploring all possibilities are examined. For the simplicity of illustration purposes, a static cohort size of 3 subjects is applied for dose levels 80 mg, 240 mg, 800 mg and 1600 mg in the BMS-986207 monotherapy and for the dose level 80 mg in the combination setting. This cohort size could vary during the actual clinical trial, and the BLRM (-Copula) models are designed to fit various different cohort sizes, adaptively. In general, there are 4 possible scenarios for a specific dose level, which are 0 DLT observed in 3 total subjects in that cohort (denoted as 0/3), 1 DLT

observed in 3 subjects (1/3), 2 DLTs observed in 3 subjects (2/3), and 3 DLTs observed in 3 subjects (3/3).

During interim monitoring, posterior probabilities will be updated when there is new DLT information available. The following three visualization plots will be produced to reflect the real time dose-DLT relationship, to quantify benefit (in the form of target dosing) and risk (in the form of overdosing and underdosing) during model's recommendation process, and to facilitate clinical team's interpretation of the model recommendations for the final decision making:

- Dose-DLT profile for the doses ranging between 0 mg and 1600 mg (Figure 1).
- Stacking histograms displaying predictive probabilities on DLT rates classified into 3 different categories (Underdosing, Target dosing and Overdosing) (Figure 2).
- Box plots summarizing the Markov Chain Monte Carlo (MCMC) samples of predicted DLT rates for the 5 pre-specified dose levels (Figure 3).

Figure 1: Updated dose-DLT profile after incorporating prior information and all previous DLT information up to 80 mg (including all monotherapy DLT data for BMS-986207 up to 240 mg)



Interpretation and usage of Figure 1:
Figure 1 is a snapshot of an updated dose-DLT profile with DLT information available at dose level 80 mg for combination studies. The dose-DLT profile is captured with a continuous dose spectrum ranging from 0 mg to 1600 mg, which is a slice of the dose-DLT surface of the combination of two drugs with Nivolumab fixed at 240 mg. For each dose within the range, there is a corresponding distribution of the predicted DLT rates calculated from the posterior samples of the model parameters. This figure will be updated each time new DLT information becomes

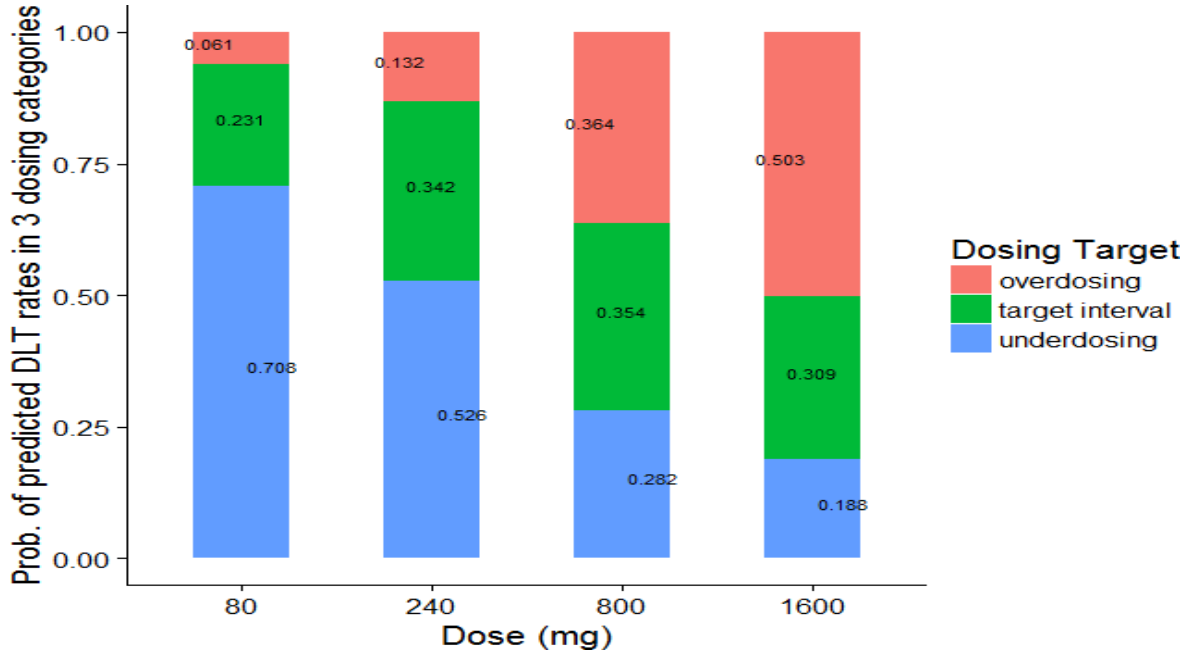
available from the combination studies. Similar graphs will also be produced for the BMS-986207 monotherapy.

In Figure 1, there are 3 different quantiles (2.5%, 50%, and 97.5%) plotted to characterize the current trend of the toxicity profile (as shown by the 50% quantile), as well as the variation of the dose-DLT profile (as shown by the 2.5% percentile and the 97.5% percentile), according to the accumulation of DLT data from all previous and current dose levels. The toxicity boundaries (0.16 and 0.33) are illustrated in two dotted horizontal lines to benchmark the way in which the dose-DLT profile is trending.

Intermediate dose levels can be identified using different boundary cutoffs. For example, using the 50% percentile curve (green highlight), which represents the nearly average DLT distribution for each dose level, the 300 mg could be a potential intermediate dose level corresponding to the lower pre-specified DLT rate boundary of 0.16, and the 1600 mg could be a fitted MTD dose level associated with the upper boundary of 0.33.

Moreover, if all of the current pre-specified doses are considered intolerable (overdosing probabilities > 0.3 for combination therapy, a case not shown on the current Figure 1), the model will recommend to stop the current dose level, and the clinical team can leverage the current updated dose-DLT curve to pinpoint a new dose, which is lower than pre-specified lowest dose (80 mg) by using the DLT rate boundaries.

Figure 2: **Updated stacking histogram after incorporating prior information and all previous DLT information up to 80 mg (including all monotherapy DLT data up to 240 mg for BMS-986207) to classify predicted DLT rates into 3 categories (Underdosing, Target Dosing and Overdosing)**



Interpretation and usage of Figure 2:

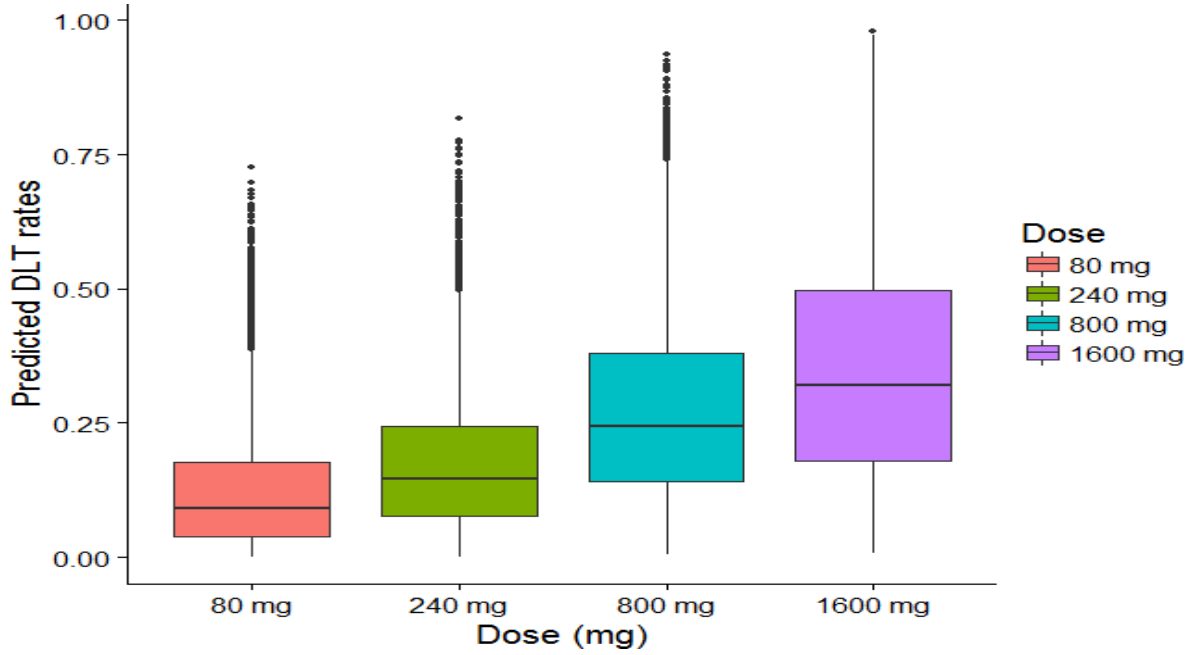
Figure 2 is a snapshot of stacking histogram with DLT information available at dose level 80 mg for the combination studies. This figure will be updated each time new DLT information becomes available in the combination setting. Similar graphs will also be produced for the BMS-986207 monotherapy.

When recommending the next dose level, the model will first exclude doses that are intolerable (with overdosing probabilities > 30%, the rate that has been specified for BMS-986207 in combination with nivolumab). Among those qualified candidate doses that are considered "tolerable", the model will select the dose that maximizes the probability of being within the target toxicity range (DLT rate of 16% up to 33%).

As illustrated in Figure 2, when there is 0 DLT observed out of 3 subjects for the dose level 80 mg and 1 DLT out of 3 subjects for the dose level 240 mg, the distribution of predicted DLT rates will be characterized into possibilities falling into 3 different categories. First, dose levels of 800 mg and 1600 mg for BMS-986207 are excluded according to the higher-than-cutoff (0.3 for combination therapy) overdosing probabilities (0.364 for 800mg and 0.503 for 1600mg). Among the remainder of tolerable dose levels (80 mg and 240 mg), the BLRM-Copula model recommends the dose that maximizes the probability of being within the target dosing interval. Therefore, the model's recommendation would be to escalate to 240 mg, which is associated with the highest target dosing probability of 0.342 compared with that of 80 mg (0.231).

Similarly (although not shown on Figure 2), according to the rules specified above, the model could possibly recommend to de-escalate to a lower dose level than current treated dose level, extend the current dose level, or even recommend to stop and identify a new dose level lower than 80mg, the lowest pre-specified dose level. Please refer to description of Figure 1 for details on how to specify the new dose levels.

Figure 3: Updated box plot after incorporating prior information and all previous DLT information up to 80 mg in combination setting (including all monotherapy DLT data up to 240 mg for BMS-986207) for pre-specified dose levels



Interpretation and usage of Figure 3:

Figure 3 is a snapshot with DLT information available at dose level 80 mg for the combination setting. The dose-DLT distributions calculated from the posterior samples of the model parameters are characterized in the format of boxplots for the pre-specified dose levels. This figure will be updated each time there is new DLT information available. Similar graphs will also be produced for the BMS-986207 monotherapy.

This plot supplements the information provided in Figure 1. It allows for a more in-depth and focused visualization of general trend of dose-DLT relationship, as well as the magnitude and variability in the DLT rates for each pre-specified dose level.

4.1 Example of the BLRM using BMS-986207 Monotherapy Dose Escalation

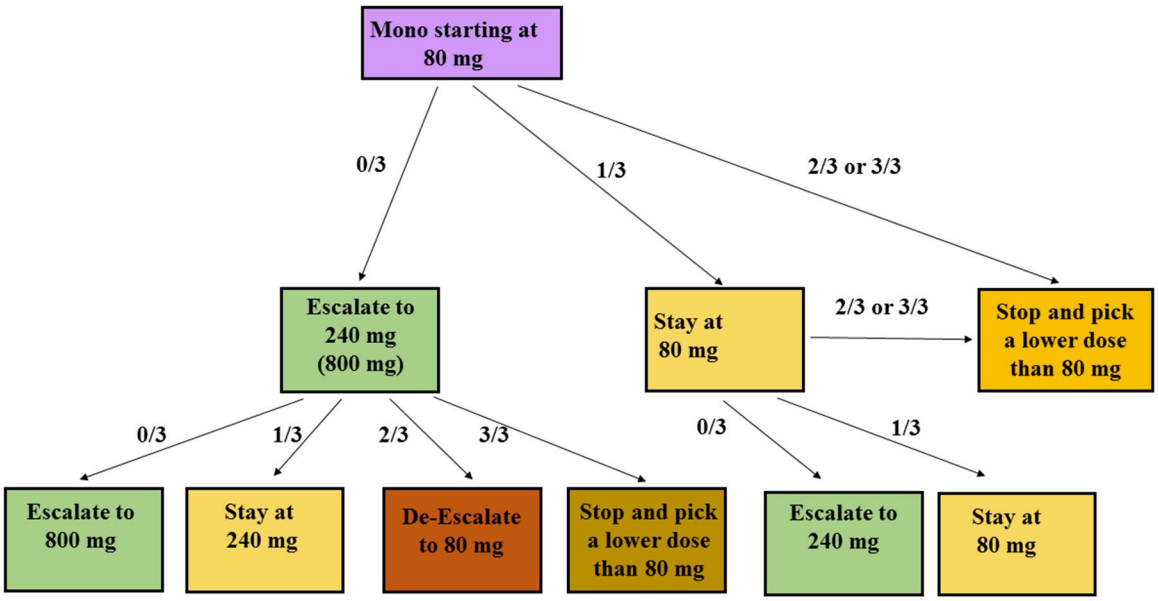
According to safety consideration and clinical judgement, the dose level 80 mg is recommended as the starting dose for BMS-986207 monotherapy. With the current BMS-986207 prior specified in the Section 1.2.1 and all available DLT information up to 240 mg, a corresponding decision tree illustrating various models' recommendations under all possible scenarios (for dose levels of 800 mg and 1600 mg) is provided in Figure 4.

Tracing a branch of the decision tree in Figure 4 illustrates the decision making process. Taking the left-most branch of the tree as an example, starting at 80 mg, there was 0 DLT observed at 80 mg in the real clinical trial, the model recommended to escalate to 240 mg (The BLRM actually recommends escalating to dose level 800 mg but since this is a 10 fold increrase of dose and this

type of dose skipping is not allowed the dose level 240 mg is selected), one level above the current treated dose level according escalation rules per protocol (as detailed in Protocol Section 5.1). Additionally, there was 0 DLT observed at 240 mg in real data, the model recommended to escalate further one dose level to 800 mg.

As illustrated in Figure 4, there are 6 potential decision paths for dose levels 800 mg and moving onwards up to 800 mg. During the actual clinical study, the tree would be narrowed or deepened based on actual DLT. The clinical team will be able to leverage this decision tree to preview decisions at each interim monitoring step and to plan proactively.

Figure 4: The BLRM model hypothetical decision tree for BMS-986207 monotherapy during dose escalation (up to 800 mg; E: escalation; S: stay; DE: de-escalation)



5 BOIN ESCALATION DESIGN SIMULATION WITH 2 DOSE LEVELS, PART 1C

The Bayesian optimal interval (BOIN) design framework will be used to guide the safety evaluation of BMS-986207 in combination with nivolumab and ipilimumab in Part 1C. The design is typically also used to determine maximum tolerated dose (MTD) selection in cases where more doses are evaluated.[5,6]

As a single dose level of BMS-986207 will be evaluated in this triplet combination (with potential for a de-escalation if needed), the goal in this study part is to assess if the dose is tolerable. Therefore MTD reference below (as in typical multi-dose level design) represents a 'tolerable

dose' in Part 1C. As an escalation decision is not of interest in Part 1C, a design recommendation to declare a dose as tolerable is based on meeting the same criteria needed to escalate.

The target toxicity rate for the MTD is $\phi = 0.3$ and the maximum sample size is 12. Participants will be enrolled in cohorts of 3. The BOIN design framework uses the following rule optimized to minimize the probability of incorrect dose assignment, to guide dose escalation/de-escalation:

- If the observed DLT rate at the current dose is ≤ 0.236, declare the dose tolerable;
- If it is ≥ 0.359, de-escalate the dose to the next lower dose level;
- Otherwise, stay at the current dose.

The design MTD selection approach described next, is included for general information on the design; however, it is not used in this study. After the trial is completed, selection of the MTD is based on isotonic regression as specified in Liu and Yuan (2015).[5] Specifically, the MTD is the dose for which the isotonic estimate of the DLT rate is closest to the target DLT rate. If there are ties, select the higher dose level when the isotonic estimate is lower than the target DLT rate and select the lower dose level when the isotonic estimate is greater than or equal to the target DLT rate.

5.1 Operating characteristics of BOIN design with 2 dose levels

Table 6 shows the operating characteristics of the trial design based on 1000 simulations of the trial using the BOIN Design Desktop Program.[7] The operating characteristics show that the design selects the true MTD (tolerable dose), if any, with high probability and allocates more patients to the dose levels with the DLT rate closest to the target of 0.3.

Table 6: Operating Characteristics of the BOIN Design

	Dose Level		Number of Participants	% Early Stopping
	1	2		
Scenario 1				
True DLT Rate	0.30	0.48		
Selection %	60.8	31.9		7.3
% Pts Treated	40.8	59.2	11.8	
Scenario 2				
True DLT Rate	0.16	0.30		
Selection %	22.1	77.8		0.1
% Pts Treated	16.3	83.7	12.0	

Scenario 3				
True DLT Rate	0.20	0.35		
Selection %	33.7	65.2		1.1
% Pts Treated	22.9	77.1	12.0	

Abbreviations: BOIN, Bayesian optimal interval; DLT, dose limiting toxicity. Pts, participants.
Note: "% Early Stopping" refers to early stopping due to excessive DLTs.

6 REFERENCES

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[5] Liu S. and Yuan Y. Bayesian Optimal Interval Designs for Phase I Clinical Trials, Journal of the Royal Statistical Society: Series C, 2015;64: 507-523.

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APPENDIX 13 PRELIMINARY SAFETY COHORT

1 PRELIMINARY SAFETY COHORT FOR PHASE 1, PART 1A

1.1 Justification for the Preliminary Safety Cohort (PSC):

The FIH starting dose of BMS-986207 monotherapy, as an immune-mediated anti-cancer agent, was determined using both toxicology- and pharmacology- ([redacted] efficacy)-based approaches to ensure participant safety while limiting the number of participants receiving nonpharmacologically active doses. The toxicology-based approach utilized the HNSTD determined from a 1-month repeat-dose toxicity study in cynomolgus monkeys. The pharmacology-based approach leveraged the pharmacology data (ie, [redacted] efficacy) obtained from mouse surrogates to project the human effective dose, from which the FIH starting dose was selected. The starting doses determined from both approaches were integrated, and the lower dose of 1 mg/kg (or 80 mg flat dose, assuming an average body weight of 80 kg in cancer participants) was recommended as the starting monotherapy dose for BMS-986207.

Subsequent to discussions with FDA, to further ensure a sufficient safety margin for the monotherapy starting dose, given the absence of previous clinical experience with BMS-986207, a Preliminary Safety Cohort (PSC) was added to the study. In the PSC, a single participant will receive BMS-986207 monotherapy starting at the 2-mg dose, with intra-participant dose escalation to 6 mg, and then to 20 mg. Following a 5-day safety observation period for this participant following the initial administration of the 20-mg dose, 2 additional participants will begin the study at the 20-mg BMS-986207 dose level.

At the conclusion of the 4-week DLT period for these 3 participants in the PSC, which respectively begins with the first administration of the 20-mg dose for each of the 3 participants in the PSC, if no DLT is observed, the main study protocol will begin with participants receiving BMS-986207 monotherapy at the 80 mg dose level. If a DLT is observed in the PSC, the BLRM will be initiated. A decision whether to treat additional patients at the same dose level, or escalate the dose, will be based on a recommendation from the BLRM and overall clinical assessment with all the safety, pharmacokinetic [redacted] data..

1.2 Study Design for PSC:

In the PSC, the first cohort of 3 participants will be administered intravenous (IV) doses of BMS-986207 as follows:

The starting dose of 2 mg of BMS-986207 will be assigned to the first participant, followed by intra-participant dose escalation after 2 weeks to 6 mg, and then 2 weeks later to 20 mg, if no DLTs are observed in any of the dose intervals. After the participant clears a 5-day safety observation period at the 20-mg dose level, 2 additional participants will be enrolled at the 20-mg dose level. The 4-week DLT period for all participants in the PSC begins with the first 20-mg dose administration. For these PSC participants, subsequently, flat dose levels of 20 mg will be given q2w, in 8-week cycles, for up to 3 cycles of study therapy.

All the procedures for this PSC, in regard to the study design, study population, treatment, discontinuation criteria and study assessments/procedures, are the same as described in respective

Sections 5, 6, 7, 8 and 9 of the main protocol. The objectives, endpoints, and statistical considerations (Section 4 and Section 10) of the main protocol also apply to the PSC. The only exceptions to the provisions of the main protocol for the PSC are the Treatment Periods and the Pharmacokinetics, Immunogenicity [redacted] sampling schedules for the first participant undergoing intra-participant dose escalation. These exceptions to the main protocol are detailed below.

1.2.1 Treatment Periods

The first participant will receive BMS-986207 as monotherapy at the starting dose of 2 mg. The infusion will take place over 5 minutes and will require a 60-minute observation period following the completion of the infusion. A 60-minute post infusion safety observation period is considered appropriate given BMS-986207 is a fully human monoclonal antibody that is an antagonist (not an agonist) and has a low likelihood of resulting in infusion reactions. The participant will follow the assessments and procedures described below and, after 2 weeks, if no DLT occurs in that 2-week interval, the participant will proceed to the next dose infusion of BMS-986207 at 6 mg. This infusion will take place over 10 minutes and will require a 60-minute observation period following the completion of the infusion. After another 2-week observation period, if no DLT occurs in that 2-week interval, the participant will then escalate to the next dose level of 20 mg. At this dose level, a treatment cycle will be comprised of 4 doses of BMS-986207 administered q2w. At the 20-mg dose level, BMS-986207 infusions will take place over 60 minutes and will require a 60-minute observation period following the completion of the infusion for the first 4 doses of Cycle 1 for the participant, as described in Section 5.1.2 of the main protocol. After the first participant clears a sentinel period of 5 days with no safety issues observed, 2 new participants will be enrolled in the study to start treatment of BMS-986207 at the 20-mg dose level. These 2 participants will follow all the same study procedures and evaluations as described in the main protocol. The PSC Treatment Scheme is summarized in Table 1.2.1-1 below.

Vital signs and pulse oximetry monitoring, as outlined in Section 2, will be performed for all dose level administrations of BMS 986207.

Table 1.2.1-1: Preliminary Safety Cohort Treatment Scheme

Patient	Treatment Time	Dose (mg)	Infusion Time, min
[redacted]	Day 1	2	5
	Day 15	6	10
	Day 29	20	60
	> Day 34[b]	20	60
	> Day 34[b]	20	60

[redacted]

[b] Patient [redacted] could be enrolled at 20 mg dose level after Patient [redacted] has cleared a 5 day sentinel period after he received the first dose of 20 mg. These two participants will follow all the same study procedures and evaluations as described in the main protocol.

1.2.2 Study assessments and procedures:

The first participant enrolled in the PSC will follow the same study assessments and procedures for respective day number of the cycle as described in Section 9 and as outlined in Section 2 of the main protocol, including physical exams and safety laboratory assessment, with the exception of pharmacokinetic and immunogenicity sample collections, as detailed below in Table 1.2.2-1, and triplet ECGs which will be performed on both CAD1 and CBD1.

Table 1.2.2-1: Pharmacokinetic and Immunogenicity Sampling Schedule for PSC - Intra-Participant Dose Escalation

Study Cycle (C) and Day (D) of Sample Collection	Days on Treatment	Event	Time (relative to dose administration) Hour: Min	BMS-986207 Blood Sample (all participants)	BMS-986207 ADA Samples (all participants)
CAD1 (2 mg)	1	Predose[a]	00.00	X	X
		EOI[b]	60 to 90 min	X	
			4:00	X	
CAD8[c] (2 mg)	8		168:00	X	
CBD1 (6 mg)	15	Predose[a]	00: 00	X	X
		EOI	01:00	X	
			4:00	X	
CBD8c (6 mg)	22		168:00	X	
C1D1 (20 mg)	29	Predose[a]	00: 00	X	X
		EOI[b]	01:00	X	
			4:00		
C1D8	36		168: 00	X	
C2D1	85	Predose[a]	00: 00	X	
		EOI[b]	60 to 90 min	X	
C3D1	141	Predose[a]	00: 00	X	X
C4D1		Predose[a]	00: 00	X	X
C5D1		Predose[a]	00: 00	X	X
EOT				X	X
30-day follow-up				X	X
60-day follow-up				X	X

Abbreviations: ADA, anti-drug antibody, BMS, Bristol-Myers Squibb; C, cycle; D, day; EOI, end of infusion, EOT, end of treatment; PSC, preliminary safety cohort.

[a] Predose: All predose samples for BMS-986207 should be taken prior to the start of the infusion. If the predose sample has been taken, however, and an unscheduled, missing, or delayed dose occurs, an additional predose sample shall be taken.

[b] EOI samples for BMS-986207 should be collected immediately prior to stopping the infusion (preferably within 2 minutes prior to the end of the infusion). If the end of infusion is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.

[c] Day 8 sample may be taken during Days 7-9 of a cycle.

[redacted]

APPENDIX 14 REVISED PROTOCOL SUMMARY OF CHANGE HISTORY

Overall Rationale for the Protocol Amendment 03, 02-Jan-2021

[redacted]

The study design has been updated to include 2 new cohorts, Part 1C, BMS 986207 + nivolumab + ipilimumab in participants with advanced solid tumors and Part 2C, BMS 986207 + nivolumab + ipilimumab in participants with 1L NSCLC with tumor cell PD-L1 expression ≥ 50%. Primary endpoints have been added that are specific to Parts 1C and 2C. A secondary objective related to [redacted] has been changed [redacted] because known downstream [redacted] are not specific to TIGIT, but instead are measures of general increases in inflammation [redacted] in the tumor.

Other key changes include additional schedule of activities tables, pharmacokinetic sampling tables, [redacted] for Parts 1C and 2C, and response to the SARS-Cov-2 pandemic. Information within the appendices, including adverse events (AEs) and serious AEs (SAEs; Appendix 3), contraceptive methods (Appendix 4), and immune-mediated AE management algorithms (Appendix 6) have been updated to align with BMS standard language and the most recent safety information for investigational products used in this study. Minor editorial changes have been made throughout the protocol and the Synopsis has been amended to reflect the changes listed below.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	• Updated Medical Monitor contact information and added Clinical Scientist Contact information.	• Updated Medical Monitor name and contact information supersedes Administrative Letter 05
Title Page	• Updated study title	• To accurately describe the study given the addition of the BMS-986207 + nivolumab + ipilimumab treatment groups
Section 2, Schedule of Activities	• Table 2-1 Screening: Updated [redacted] rows to add instructions for Parts 1C and 2C, added [redacted] row for participants in Part 2C, and serum collection of [redacted]. • Added new Table 2-4:On Study Assessments Triplet Safety (Parts 1C and 2C) • Added information to Table 2-5 on follow-up tumor assessments for Parts 1C and 2C, sample collection and AE monitoring for	• These changes were made to clarify and align expectations and timing of scheduled activities with the study design.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
	participants with known or suspected SARS-CoV-2 infection	
Section 3.1, Study Rationale	• Added rationale for current amendment	• To align with proposed changes to study design
Section 3.2, Background	• Added and/or updated text and references to literature and Investigator Brochures throughout these sections and subsections. • Added new Section 3.2.1.4 describing the preliminary safety profile for BMS-986207. • Updated Section 3.2.2 Nivolumab • Added new Section 3.2.3 Ipilimumab • Added new Section 3.2.4 Nivolumab Combined with Ipilimumab Clinical Activity	• Aligned the description of background information and experience with study treatments with currently available data.
Section 3.3, Benefit/Risk Assessment	• Added benefit/risk assessment for treating non-small cell lung cancer participants • Added benefit/risk assessment for combination of BMS-986207 + nivolumab + ipilimumab • Added benefit/risk assessment for participants with confirmed SARS-CoV-2 infection	• Additional benefit/risk information was added to support the changes to study design and to address risks associated with SARS-CoV-2 infection
Section 4, Objectives and Endpoints	• Added primary objectives for Parts 1C and 2C and modified secondary [redacted] objectives to include combination therapy with BMS-986207 + nivolumab + ipilimumab	• Objectives modified to support changes in study design.
	• Reclassified the secondary objective related to [redacted] assessments [redacted]	• [redacted] objectives were modified because known downstream [redacted] are not specific to TIGIT, but instead are measures of general increases in [redacted] in the tumor.
	[redacted]	
Section 5.1, Overall Design	• Updated description of overall design	• Added for clarity and to describe substudy conducted under site specific amendments 6, 7, and 8.
Section 5.1.2, Treatment Period	• This section was modified as follows: • Added description of treatment and details of study drug infusion for Part 2C.	• To describe changes in study design

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
	• Added Section 5.1.2.2 describing treatment in Part 1C and 2C • Updated Figure 5.1.2.2-1 (Overall Study Design) and added Figure 5.1.2.2-2 (Treatment Cohorts) • Added Section 5.1.2.6 describing safety monitoring during Part 1C • Added description of Part 2C to Section 5.1.2.7 Cohort Expansion • Section describing treatment beyond progression was moved to Section 5.1.4	
Section 5.1.3, Safety Follow-up Period	• Added section describing 2-year duration of treatment for Parts 1C and 2C • Indicated that Section 5.1.3.4 Retreatment is only applicable to Parts 1A, 1B, 2A, and 2B.	• To align with standard 2-year duration of treatment for nivolumab-containing regimens. Retreatment was included in Parts 1A, 1B, 2A, and 2B, but is not needed in Parts 1C and 2C because of this longer duration of treatment.
Section 5.1.4, Treatment Beyond Progression and Section 8.1.1, Treatment Beyond Progression	• The previous Section 5.1.2.6 and previous text in Section 8.1.1 were relocated to Section 5.1.4, and language related to tumor/lesion size was added to text describing the decision to continue treatment beyond progression.	• Treatment beyond progression language was combined into 1 section and relocated for clarity and improved readability. Text was added to clarify expectations for decisions and documentation for continuing treatment beyond progression.
Section 5.1.5, Data Monitoring Committee and Other External Committees	• Updated rationale for no Data Monitoring Committee and language describing BMS multi-layered process to ensure safety monitoring during the study.	• Clarified BMS process to ensure safety monitoring.
Section 5.2, Number of Participants	• Updated to reflect additional participants to be enrolled in Parts 1C and 2C.	• To reflect updates in study design
Section 5.4, Scientific Rationale for Study Design;	• Updated text description of overall study design to incorporate Parts 1C and 2C. • Added new Section 5.4.3 to provide rationale for combination of BMS-986207 + nivolumab + ipilimumab • Added new Section 5.4.4 to provide rationale for triplet therapy in NSCLC • Updated Section 5.4.5 Rationale for Treatment Duration to provide a rationale for 2-year duration of treatment in Parts 1C and 2C • Updated Section 5.4.7 Rationale for Tumor Selection to include NSCLC • Updated Section 5.4.8 Rationale for Dose Escalation Phase Design to include Part 1C	• To support updates to study design.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.5.2, Rationale for Dosing Schedule	• Updated Section 5.5.2.1 to summarize preliminary pharmacokinetics (PK) parameters for BMS-986207 at steady state and receptor occupancy (RO) data from Part 1 of the study. • Updated Section 5.5.2.2. Changed title to "Nivolumab" and updated text to provide most current information on nivolumab dosing • Added Section 5.5.2.3 Ipilimumab providing rationale for ipilimumab dosing • Updated Section 5.5.2.4 to provide rationale for ipilimumab infusion time	• This section has been updated to provide rationale for dosing in Parts 1C and 2C and to reflect the most current information available for each of the study drugs.
Section 6.1, Inclusion Criteria	• Added inclusion criteria 2) w) i) through 2) w) viii) that are applicable to Part 2C participants only (participants with NSCLC who are treatment naive with PD-L1 expression ≥50%) • Added inclusion criterion 2) x) for participants with confirmed or suspected SARS-CoV-2 • Laboratory values in 3) a) updated • Inclusion criterion 7) f) contraception requirements for male participants not applicable per Protocol Amendment 03	• To align with updates to the study design and to reflect the most current safety information for nivolumab. • Contraceptive requirements for male participants removed to conform to most recent safety information for these investigational products
Section 6.2, Exclusion Criteria	• Exclusion criteria 1) b) and 1) c) added that are applicable to Part 2C participants only • Exclusion criteria 3) e) xii, 3) e) xiii, and 3) e) ix added to account for participants with known or suspected SARS-CoV-2 infection	• To align with updates to the study design and to mitigate risks to participants with known or suspected SARS-CoV-2 infection
Section 6.4.1, Retesting During Screening or Lead-In Period	• Instruction added for management of participants with known or suspected SARS-CoV-2 infection	• To mitigate risks to participants with known or suspected SARS-CoV-2 infection
Section 7.1, Treatments Administered	• Table 7.1-1: Removed 40 mg vial of Nivolumab Solution for Injection and added BMS-734016 Solution for Injection (ipilimumab)." • Table 7.1-2: Added rows for 1200 mg BMS-896207, 360 mg nivolumab, and 1 mg/kg ipilimumab • In text, added treatment duration and description of dosing for Parts 1C and 2C	• Added new study drug (ipilimumab) and removed dose form of nivolumab that is no longer in use. • Aligned tables and text with updates to study design
Section 7.2, Method of Treatment Assignment	• Updated text to describe treatment assignment for Part 2C.	• Aligned treatment assignment methods with updates to the study design described above.
Section 7.4.1 Dose Limiting Toxicities	• Added DLT period for Parts 1C and 2C	• To reflect changes to the study design

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 7.4.2, Treatment Algorithms	• Added myocarditis to the list of immune-related AEs	• To align with the most recent safety information for nivolumab
Section 7.4.3.3 Criteria to Resume Treatment	• Added criteria to resume treatment for participants with known or suspected SARS-CoV-2 infection	• To mitigate risks to participants with known or suspected SARS-CoV-2 infection
Section 7.6.1, Prohibited and/or Restricted Treatments	• Added live/attenuated vaccines, investigational vaccines, and investigational therapies for treatment of SARS-CoV-2 to list of prohibited and/or restricted treatments.	• To align with the most recent safety information for nivolumab and to exclude investigational treatment of SARS-CoV-2
Section 8.1, Discontinuation from Study Treatment	Text was modified as follows: • Added note that under specific circumstances, a participant who has been imprisoned may be permitted to continue as a participant. • Modified text related to pregnancy cases to: o Add that BMS/Medical Monitor must be notified within 24 hours of a pregnancy event. o Remove text related to possible favorable benefit-risk ratio discussion. Added reference to Section 9.2.5 Pregnancy.	• Clarified scenarios in which imprisoned participants may be permitted to continue on the study and expectations for reporting pregnancy.
Section 9.1 Efficacy Assessments	• Imaging assessments for Parts 1C and 2C described	• To reflect updates to the study design.
Section 9.2.3 Follow-up of AEs and SAEs	• Added instructions for follow-up of participants with known or suspected SARS-CoV-2 infection	• To mitigate risks to participants with known or suspected SARS-CoV-2 infection
Section 9.3 Overdose	• Modified SAE reporting requirements for overdose	• To align with updates in Appendix 3
Section 9.5, Pharmacokinetics and	• Added description of sample collection • Added Table 9.5-4 describing PK sample collection in Part 1C and 2C	• Updated text to provide clarity on sample collection • Updated tables for PK and immunogenicity sampling schedules to align with updates to the study design.

[redacted]

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 10.1, Sample Size Determination	• Added Section 10.1.2: Safety Evaluation Phase (Part 1C) • Added Section 10.1.3.2 Cohort Expansion in Part 2C	• Added new sections to describe sample size determination in Parts 1C and 2C.
Section 10.3, Statistical Analyses	• Modified Table 10.3.1-1: added statistical methods for efficacy assessment in Part 2C.	• To align with updates to study design.
Section 10.3.3, Pharmacokinetic Analyses for BMS-986207, Nivolumab, and Ipilimumab	• Removed Ceoi as an endpoint measure	• Cmax will be measured and derived to capture maximum observed concentration.
Section 10.3.8, Interim Analyses for Parts 2A, 2B, and 2C	• Expanded to describe interim analyses for Part 2C	• To align with updates to study design
Appendix 2: Study Governance Considerations	Modified Good Clinical Practice section in Appendix 2 to: • Add bullet to clarify that the study will also be conducted in accordance with ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines Good Clinical Practice. • Align with revised definition of serious breach to Regulation No 536/2014 of the European Parliament and of the Council.	• Modified text to align with statement in the informed consent form and most current BMS standard language.
Appendix 3: Adverse Events and Serious Adverse Events Definitions and Procedures for Recording, Evaluating, and Follow-up and Reporting	Added the following sections: • Events Meeting the AE Definition. • Events Not Meeting the AE Definition. • Definition of SAE. Modified the following sections: • SAEs (text related to pregnancy and drug-induced liver injury). • Evaluating AEs and SAEs (updated and rearranged bulleted information). • Reporting of SAEs to Sponsor or Designee (updated and rearranged bulleted information related to pregnancy and paper report forms).	• Modifications made to information related to AEs and SAEs to align with the most current BMS standard language, regulatory definition EMA GVP Module VI (EMA/873138/2011) and ICH E2A, and clarify the instructions for reporting pregnancy.
Appendix 4: Women of Childbearing Potential and	• Added additional details for hormonal, oral, intravaginal, and intrauterine hormone-releasing system contraceptive methods.	• Clarified contraceptive methods for women of childbearing potential and male participants.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Methods of Contraception	• Removed contraceptive requirements for male participants	
Appendix 6: Management Algorithms for Immuno-oncology Agents	• Modified the footnote in the Hepatic Adverse Event Management algorithm. • Added an additional algorithm for management of myocarditis.	• Language was modified to align protocol with current study treatment Investigator Brochures and program safety parameters.
Appendix 12: Statistical Methodology	• Added additional details to the escalation design simulation for Part 1C	• Clarified use of the Bayesian Optimal Interval design to guide determination of the maximum tolerated dose in Part 1C.
All	• Minor formatting and typographical corrections.	• Corrections for clarity and consistency within the document were minor, and therefore have not been summarized.

Overall Rationale for the Revised Protocol 02, 06-Jul-2017

The main purpose of this amendment is to add q4w dosing regimen to both the BMS-986207 monotherapy and the combination nivolumab and BMS-986207 dosing schedule. The less frequent The main purpose of this amendment is to add q4w dosing regimen to both the BMS-986207 monotherapy and the combination nivolumab and BMS-986207 dosing schedule. The less frequent q4w dosing schedule may benefit patients by decreasing the number of time drug is infused and will also reduce the potential medical burden from the care givers and cancer treatment institutions.

Additional changes to the protocol provide clarity in executing the clinical study.

Revisions apply to future participants enrolled in the study.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 1 Synopsis Section 2 Schedule of Activities Section 5 Study Design Section 7 Treatment Section 9 Study Assessment and Procedures	Addition of q4w dosing regimen	The addition of q4w dosing regimen will provide data for more convenience dosing regimens in the future
Section 6 Study Population	Inclusion criteria numbering for the Target Population was changed.	Inclusion criteria numbering changed to ensure clear identification of specific inclusion criteria.
Section 6 Population	Inclusion criteria 3c) changed to include subjects that have clinical stable thyroid	Criteria was updated to ensure appropriate review of subjects and to ensure eligible subjects are not excluded unnecessarily.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
	function and Exclusion criteria 3e, x) was modified to include "unless agreed by the medical monitor"	
Section 2 Schedule of Activities	Extension of the window period for all Laboratory collections to 72 hours	Logistically it is difficult to collect samples within 24 hours.
Section 9 Study Assessment and Procedures	Table 9.4.4-1 Clarification of reflex assessments Addition of D0 assessments for Retreatment eligible subjects where applicable	
Section 9 Study Assessment and Procedures	Table 9.5-2 Removal of some erroneous samples and clarification on time points. Addition of Table 9.5.3 for the q4w dosing	
Section 9 Study Assessment and Procedures	[redacted] to the US and Canada sites.	[redacted] are out of scope for the [redacted] plan for this clinical study To ensure the integrity of [redacted] only samples from US and Canada sites will be collected.
All	Minor formatting and typographical corrections	