Protocol for

Official Title of Study

A Phase 2 Randomized Study of BMS-986207 in Combination with Nivolumab and Ipilimumab as First-line Treatment for Participants with Stage IV Non-Small Cell Lung Cancer

NCT05005273

June 13, 2022

Protocol Number: CA020016
Date: 30-Mar-2021
Revised Date: 13-Jun-2022

CLINICAL PROTOCOL CA020016

A Phase 2 Randomized Study of BMS-986207 in Combination with Nivolumab and Ipilimumab as First-line Treatment for Participants with Stage IV Non-Small Cell Lung Cancer

Brief Title:

Study of BMS-986207 in Combination with Nivolumab and Ipilimumab in Participants with Stage IV NSCLC

Protocol Amendment Number: 02
Incorporates Administrative Letter 01

[redacted]

24-hr Emergency Telephone Number

[redacted]

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REGULATORY AGENCY IDENTIFIER NUMBER(S)

IND: 154609
EudraCT/EU Trial Number: 2021-000039-29
UTN: U1111-1263-4850

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Protocol Amendment 02	13-Jun-2022	The purpose of this amendment is to modify the dose of BMS-986207 based on emerging data from Study CA020002. Study blinding was changed from double-blind to single-blind to permit unblinded safety monitoring by the Sponsor. Treatment information access will not be used by the Sponsor to perform by-arm efficacy analyses. The overall sample size in the BMS-986207-containing arm was increased (from 100 to 120 participants) to allow for sufficient sizing for safety and subgroup efficacy analyses. To maintain a comparable number of total participants, the randomization ratio was updated; thus, decreasing the sample size of the comparator cohort and total sample size. Given the change in randomization ratio and smaller comparator sample size, the planned analysis was updated to a Bayesian augmented control (BAC) design using a Propensity Score Method to select additional control data from historical trial CheckMate 227.
Administrative Letter 01	08-Jul-2021	Study personnel updated.
Protocol Amendment 01	19-May-2021	The purpose of this amendment is to clarify the exclusion criteria for interstitial lung disease, resumption of dosing in limited circumstances after myocarditis, dose-limiting toxicity (DLT) criteria, and an additional serum sample collection at Cycle 1 Day 22 for BMS-986207.
Original Protocol	30-Mar-2021	Not applicable

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 02:

The purpose of this amendment is to modify the dose of BMS-986207 based on emerging data from Study CA020002, a Phase 1/2a dose-escalation and multiple cohort expansion study of BMS-986207 as monotherapy and in combination with nivolumab with and without ipilimumab. In Study CA020002, BMS-986207 600 mg every 3 weeks (Q3W) in combination with nivolumab 360 mg Q3W plus ipilimumab 1 mg/kg every 6 weeks (Q6W) was considered tolerable based on the Bayesian optimal interval (BOIN) design. To align with this emerging data and totality of data available, the dose of BMS-986207 is modified from 1200 mg Q3W to 600 mg Q3W in combination with nivolumab 360 mg Q3W plus ipilimumab 1 mg/kg Q6W, and the safety lead-in was removed. Study blinding was changed from double-blind to single-blind to permit unblinded safety monitoring by the Sponsor. Treatment information access will not be used by the Sponsor to perform by-arm efficacy analyses. The overall sample size in the BMS-986207-containing arm was increased (from 100 to 120 participants) to allow for sufficient sizing for safety and subgroup efficacy analyses. To maintain a comparable number of total participants, the randomization ratio was updated (from 1:1 to 2:1); thus, the sample size of the comparator cohort was decreased (from 100 to 60 participants) and total sample size decreased (from approximately 200 to approximately 180 randomized participants). Given the change in randomization ratio and smaller comparator sample size, the planned analysis was updated to a Bayesian augmented control (BAC) design using a Propensity Score Method to select additional control data from historical trial CheckMate 227, a randomized Phase 3 study that included treatment with nivolumab plus ipilimumab in treatment-naive non-small cell lung cancer.

This amendment also incorporates the changes from the approved Administrative Letter 01, which are not detailed in the summary of key changes below.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	Study title updated to remove "double-blind"	The study design has been updated from double-blind randomized assignment to single-blind randomized assignment. Investigators, site staff, and participants will be blinded to BMS-986207 treatment assignment. Data Monitoring Committee (DMC) and Sponsor will be unblinded to treatment assignment to monitor safety
Protocol Summary	Updated protocol summary to match relevant protocol revisions	Reflect changes in protocol body as summarized below
Table 2-1: Screening Procedural Outline (CA020016)	Updated Tumor Sample Notes section to remove Part 1 language	Updated for clarification

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-1: Screening Procedural Outline (CA020016) Table 2-2: On Treatment Procedural Outline (CA020016) Table 2-3: Long-term Follow-up Procedural Outline (CA020016) Section 3.3.1: Risk Assessment Table 4-1: Objectives and Endpoints Table 9.8-1: Biomarker Sampling Schedule Section 9.8.3: Biomarker Assessments in Peripheral Blood Section 9.8.3.1: Exploratory Serum Biomarkers Section 10.4.5: Other Analyses	Removed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) serology language	Based on the significant advancements in understanding SARS-CoV-2, available treatment options including monoclonal antibodies and effective vaccination, the collection of SARS-CoV-2 serologies is no longer warranted
Table 2-3: Long-term Follow-up Procedural Outline (CA020016)	Updated Clinical Laboratory Assessments procedure to: • Include Follow-up 2 • Delete "To be performed at Follow-up Visit 1, repeat at Follow-up Visit 2 if study drug-related toxicity persists."	Updated for additional safety monitoring at all 3 safety follow-up visits
	Included Follow-up 3 for Survival Status and Subsequent Cancer Therapy procedure	Updated for consistency and clarity
	Updated Body Imaging Notes section to include "death, or withdrawal of consent, whichever occurs first."	Clarification of imaging
Table 2-3: Long-term Follow-up Procedural Outline (CA020016)	Updated footnote "b" to change survival follow-up visits to begin from the last dose of study intervention to the date of randomization	Allows for same duration of follow-up for all participants (up to 4 years)

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-3: Long-term Follow-up Procedural Outline (CA020016) Section 5.1: Overall Design Figure 5.1-1: Study Design Schema Section 5.1.3.3: Survival Follow-up	• Changed length of survival follow-up from randomization to up to 4 years • Updated Clinical Outcome Assessments notes to clarify timing to complete assessments	Allows for same duration of follow-up for all participants (up to 4 years)
Section 3.1: Study Rationale	Added CA020002 language and additional study rationale	Updated with BMS-986207, nivolumab, and ipilimumab combination findings from the CA020002 protocol and provide additional rationale
Section 3.2.2.4: Preliminary Clinical Safety Profile of BMS-986207 Monotherapy Section 3.2.2.5: Preliminary Clinical Safety Profile of BMS-986207 Combined with Nivolumab	Updated to include BMS-986207 safety data from Study CA020002 as of 05-Jan-2022	Updated to align with most recent BMS-986207 Investigator's Brochure (IB)
Section 3.2.2.6: Preliminary Clinical Safety Profile of BMS-986207 Combined with Nivolumab and Ipilimumab	Added section	Updated with clinical safety data from participants treated with BMS-986207 in combination with nivolumab plus ipilimumab in Study CA020002
Section 3.3.1: Risk Assessment	Added sentence to first paragraph "Based on the BOIN design in Study CA020002, BMS-986207 600 mg Q3W in combination with nivolumab 360 mg Q3W plus ipilimumab 1 mg/kg Q6W was considered tolerable."	

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 3.3.3: Overall Benefit/Risk Conclusion	Removed BOIN language	Updated to align with removal of safety lead-in based on data from Study CA020002
	Added sentence "In Study CA020002, no DLTs were reported in the 6 DLT-evaluable participants treated with BMS-986207 600 mg Q3W in combination with nivolumab plus ipilimumab; thus, this dose was considered tolerable."	Updated with clinical safety data from participants treated with BMS-986207 in combination with nivolumab plus ipilimumab in Study CA020002
	Added coronavirus disease 2019 (COVID-19) vaccination text	Address Health Authority request for the benefit-risk of COVID-19 vaccination during participation in the clinical trial
Section 4: Objectives and Endpoints Table 4-1: Objectives and Endpoints	• Removed Part 1 primary objective "To assess the safety, tolerability, and DLTs of BMS-986207 in combination with nivolumab plus ipilimumab in participants with 1L Stage IV NSCLC in the safety lead-in (Part 1)" • Removed Part 1 primary endpoint "Incidence of AEs meeting protocol-defined DLT criteria, AEs, TRAEs, SAEs, AEs leading to discontinuation, and deaths	Updated to align with removal of safety lead-in based on data from Study CA020002
Section 5.4.6: Rationale for Safety Lead-in	Deleted section; as a result, the following sections were re-numbered	
Section 6.1: Inclusion Criteria Section 9.8.1: Tumor Tissue Specimens	Updated inclusion criterion 2)b) to: • Delete text specifying that the central laboratory must provide IRT with confirmation of receipt of evaluable tumor tissue as described in the Laboratory Manual prior to treatment assignment in Part 1. • Updated text to specify that central laboratory must confirm receipt of evaluable tumor tissue as described in the Laboratory Manual prior to randomization. • Deleted "During the safety lead-in, PD-L1 results can be received after treatment assignment."	

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 4: Objectives and Endpoints Table 4-1: Objectives and Endpoints Table 10.4.4-1: Exploratory Endpoints	Updated immunogenicity endpoint to include: • Summary measures of anti-drug antibody (ADA) titers and kinetics • Assessments of ADA effect on efficacy, safety, and pharmacokinetic (PK)	Additional outputs to characterize the development of ADA to BMS-986207, nivolumab, and ipilimumab; additional assessments of the clinical consequences of ADA on safety and efficacy endpoints were included.
Section 5.1: Overall Design	Updated Figure 5.1-1: Study Design Schema	Updated to align with new study design including removal of safety lead-in, change in randomization ratio, sample size, and blinding information
Section 5.1.2: Treatment Period	• Deleted safety lead-in sub-section • Consolidated sub-section regarding randomization under Section 5.1.2 • Updated study blind language	
Section 5.1.3.3: Survival Follow-up	• Deleted sentence "In parallel with the safety and imaging follow-up periods, participants will enter the survival follow-up period." • Removed language about imaging follow-up and survival follow-up periods occurring simultaneously	Updated for clarification
Section 5.1.4: DMC and Other Committees	Updated bullet point regarding data that the Safety Management Team (SMT) will review and if an ad hoc data review by the DMC will be needed	Updated for clarification
Section 5.2: Number of Participants	Updated section based on new randomization ratio of 2:1	Updated to align with new study design including removal of safety lead-in and change in randomization ratio, thus overall sample size is decreased to approximately 180 randomized participants
Section 5.4.7: Rationale for Blinding Section 7.3: Blinding	• Updated section from double-blind to single-blind • Section 7.3: Blinding updated for clarity and consistency	Updated to align with change in blinding. Sponsor will use treatment assignments to monitor safety and will not perform by-arm efficacy analysis
Section 5.5.1: BMS-986207	Updated rationale for BMS-986207 600 mg dose	Updated to align with selected dose of BMS-986207 in combination with nivolumab plus ipilimumab based on the totality of the data emerging from Study CA020002 (eg, safety, tolerability, efficacy, PK, etc)

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 6.4: Screen Failures	Deleted safety lead-in paragraph	Updated to align with removal of safety lead-in information based on data from Study CA020002
Section 7.1: Study Interventions Administered	Updated Table 7.1-1: Study Interventions: • To include ipilimumab 50 mg/vial presentation • Remove 20 mg/mL concentration for reconstituted BMS-986207 • To change BMS-986207 dose from 1200 mg to 600 mg	• Updated to align with ipilimumab drug product presentation • Updated to align with BMS-986207 lyophilized drug product presentation • Updated to align with tolerable dose of BMS-986207 in combination with nivolumab plus ipilimumab determined in Study CA020002
	• Updated BMS-986207 infusion time from 60 to 30 minutes • Decreased participant body weight for longer infusion time from 38 to 22 kg • Removed upper body weight for next-day administration of BMS-986207	Updated to align with BMS-986207 600 mg Q3W
Section 7.2: Method of Study Intervention Assignment	• Deleted safety lead-in sub-section (Section 7.2.1: Safety Lead-in [Part 1]) • Consolidated randomization sub-section under Section 7.2	Updated to align with removal of safety lead-in based on tolerable dose from Study CA020002 and consolidated for clarity
Section 7.4.3: Dose-limiting Toxicities	Deleted sub-section; as a result, the following sub-sections were re-numbered	Updated to align with removal of safety lead-in based on tolerable dose from Study CA020002 and consolidated for clarity
Section 9.2.5: Pregnancy	Deleted sentence "In order for the Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an ICF for disclosure of this information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form."	Male contraception is not required for the study

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 10.2: Sample Size Determination	• Deleted safety lead-in sub-section (Section 10.2.1: Sample Size Determination Safety Lead-in [Part 1]) • Updated section based on new study design	Updated to align with removal of safety lead-in based on tolerable dose from Study CA020002 and change in randomization ratio
	• Added Tables 10.2-1 and 10.2-2	Updated to align with change to BAC design for statistical analyses
Section 10.3: Analysis Sets	Removed response evaluable population	Updated to align with removal of safety lead-in based on tolerable dose from Study CA020002
	Added PK and immunogenicity populations	To accurately define and provide completeness of analysis for PK and immunogenicity populations
Section 10.4.1: General Considerations Section 10.4.1.1: Propensity Score Method to Select Control Data from Historical Trial Section 10.4.1.2: Bayesian Augmented Control Design Section 10.4.1.3: Sensitivity Analyses	• Removed paragraph about efficacy analysis performed with the family-wise error rate • Added subsections: – Propensity Score Method to Select Control Data from Historical Trial – Bayesian Augmented Control Design – Sensitivity Analyses	Updated to align with change to BAC design for statistical analyses
Section 10.4.2: Primary Endpoints	Removed safety lead-in primary endpoint	Updated to align with removal of safety lead-in based on tolerable dose from Study CA020002
Table 10.4.4-1: Exploratory Endpoints	Added timeframe for Biomarker Analysis and Clinical Outcomes Assessments Analysis	Updated for clarification
Section 10.5.1: Safety Continuous Monitoring	Updated Table 10.5.1-1: Safety Continuous Monitoring Boundary for Arm A	Updated to align with change to single-blinding and Sponsor monitoring of safety data
Section 10.5.1.1: Efficacy Interim Analysis	Updated interim analysis for progression-free survival (PFS) and objective response rate (ORR) based on current sample size	Updated statistical plan based on changes in sample size
Section 10.5.1.2: DMC Analysis	Updated DMC involvement	Updated for clarity and to align with study design

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Appendix 2: Study Governance Considerations	Added new section: BMS Commitment to Diversity in Clinical Trials	Align with BMS commitment to diversity in clinical trials
	Added new section: Data Protection, Data Privacy, and Data Security	Align with BMS practice and comply with European Union Clinical Trials Regulation (EU-CTR) requirement
	Added first paragraph in the Dissemination of Clinical Study Data section	To align with EU-CTR and other regulations
Appendix 10: Details of the Propensity Score Matching and Bayesian Augmented Control (BAC) Analysis	Replaced statistical methodology appendix with Details of the Propensity Score Matching and BAC Analysis appendix	Updated to align with change in randomization and use of synthetic control arm for statistical analyses
Throughout	Deleted language: • Treatment assignment (Part 1) • Safety lead-in • Part 2 • Double-blind revised to single-blind	Updated for clarity and to align with modified study design being outlined in this protocol amendment
All	Minor typographical errors were corrected, and edits were made for consistency and clarity	Minor, therefore have not been summarized

TABLE OF CONTENTS

1 PROTOCOL SUMMARY

Protocol Title:

A Phase 2 Randomized Study of BMS-986207 in Combination with Nivolumab and Ipilimumab as First-line Treatment for Participants with Stage IV Non-Small Cell Lung Cancer

Brief Title:

Study of BMS-986207 in Combination with Nivolumab and Ipilimumab in Participants with Stage IV NSCLC

Rationale:

CA020016 is a Phase 2, randomized study of BMS-986207 in combination with nivolumab plus ipilimumab versus nivolumab plus ipilimumab in participants with first-line (1L) Stage IV non-small cell lung cancer (NSCLC). BMS-986207 is a fully human immunoglobulin G1 monoclonal antibody that binds with high affinity to T cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain (TIGIT), a negative regulatory molecule that suppresses activation and functional responses in T cells and natural killer (NK) cells.

Combining immune checkpoint inhibitors, including anti-TIGIT, anti-cytotoxic T-lymphocyte associated protein 4 (CTLA-4), and/or anti-programmed death (ligand)1 (PD-[L]1), is a rational therapeutic strategy that has demonstrated clinical benefit in preclinical and clinical models. TIGIT is a negative regulatory molecule that suppresses activation and functional responses in T cells and NK cells. Poliovirus receptor (PVR), a ligand of TIGIT, expression has been associated with poor response to anti-PD-1 therapy, suggesting that blockade of TIGIT is needed to achieve further reversal of checkpoint suppression. In preclinical models, combining anti-TIGIT with either anti-CTLA-4 or anti-PD-1 agents resulted in greater anti-tumor responses as compared to either agent used as monotherapy. Recent studies have reported clinical benefit in participants with 1L Stage IV NSCLC treated with a combination of anti-TIGIT and anti-PD-L1 (NCT03563716; tiragolumab plus atezolizumab) or anti-PD-1 (NCT02964013; vibostolimab plus pembrolizumab). In Study CA020002 (NCT02913313), a Phase 1/2a dose-escalation and multiple cohort expansion study, BMS-986207 (600 mg every 3 weeks [Q3W]) in combination with nivolumab and ipilimumab was safe and tolerable. Thus, anti-TIGIT in combination with anti-CTLA-4 and/or anti-PD-1 may be a promising therapeutic strategy.

Study CA020016 will evaluate the safety and efficacy of BMS-986207 in combination with nivolumab plus ipilimumab in 1L Stage IV NSCLC. It will utilize nivolumab plus ipilimumab, which has demonstrated efficacy in CheckMate 227 (NCT02477826) and has a known safety profile in NSCLC. The combination of BMS-986207, nivolumab, and ipilimumab is expected to have a synergistic effect in the 1L Stage IV NSCLC population based on the preclinical and clinical activity of the doublet (nivolumab plus ipilimumab, anti-TIGIT plus anti-PD-(L)1, and anti-TIGIT plus anti-CTLA-4) and triplet (BMS-986207 in combination with nivolumab plus ipilimumab) combinations and their complementary mechanisms of action.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To compare the PFS of BMS-986207 in combination with nivolumab plus ipilimumab (Arm A) versus nivolumab plus ipilimumab (Arm B) in participants with 1L Stage IV NSCLC expressing PD-L1 ≥ 1%	• PFS in participants with tumors expressing PD-L1 ≥ 1% based on RECIST v1.1 by BICR
Secondary	
• To compare the PFS of BMS-986207 in combination with nivolumab plus ipilimumab (Arm A) versus nivolumab plus ipilimumab (Arm B) in all randomized participants with 1L Stage IV NSCLC	• PFS in all randomized participants based on RECIST v1.1 by BICR
• To assess the safety and tolerability of BMS-986207 in combination with nivolumab plus ipilimumab (Arm A) and nivolumab plus ipilimumab (Arm B) in participants with 1L Stage IV NSCLC	• Incidence of AEs, SAEs, AEs leading to discontinuation, and deaths
• To estimate the ORR of BMS-986207 in combination with nivolumab plus ipilimumab (Arm A) and nivolumab plus ipilimumab (Arm B) in all randomized participants with 1L Stage IV NSCLC and in subgroups defined by PD-L1 expression	• ORR in all randomized participants and in subgroups defined by PD-L1 expression (PD-L1 ≥ 1%, < 1%, 1% - 49%, and ≥ 50%) based on RECIST v1.1 by BICR assessment
• To compare OS of BMS-986207 in combination with nivolumab plus ipilimumab (Arm A) versus nivolumab plus ipilimumab (Arm B) in randomized participants with tumors expressing PD-L1 ≥ 1%	• OS in participants with tumors expressing PD-L1 ≥ 1%
• To compare OS of BMS-986207 in combination with nivolumab plus ipilimumab (Arm A) versus nivolumab plus ipilimumab (Arm B) in all randomized participants with 1L Stage IV NSCLC	• OS in all randomized participants
• To compare the PFS of BMS-986207 in combination with nivolumab plus ipilimumab (Arm A) versus nivolumab plus ipilimumab (Arm B) in all randomized participants and in participants with tumors expressing PD-L1 ≥ 1% with 1L Stage IV NSCLC	• PFS in all randomized participants and in participants with tumors expressing PD-L1 ≥ 1% based on RECIST v1.1 by investigator's assessment
• To estimate the PFS of BMS-986207 in combination with nivolumab plus ipilimumab (Arm A) and nivolumab plus ipilimumab (Arm B) in participants with 1L Stage IV NSCLC in subgroups defined by PD-L1 expression	• PFS in subgroups defined by PD-L1 expression (PD-L1 < 1%, 1% - 49%, and ≥ 50%) based on RECIST v1.1 by BICR and investigator's assessment
• To estimate the ORR of BMS-986207 in combination with nivolumab plus ipilimumab (Arm A) and nivolumab plus ipilimumab (Arm B) in all randomized participants with 1L Stage IV NSCLC and in subgroups defined by PD-L1 expression	• ORR in all randomized participants and in subgroups defined by PD-L1 expression (PD-L1≥1%, < 1%, 1% - 49%, and ≥ 50%) based on RECIST v1.1 by investigator's assessment

Objectives	Endpoints
• To estimate the DOR of BMS-986207 in combination with nivolumab plus ipilimumab (Arm A) and nivolumab plus ipilimumab (Arm B) in all randomized participants with 1L Stage IV NSCLC and in subgroups defined by PD-L1 expression	• DOR in all randomized participants and in subgroups defined by PD-L1 expression (PD-L1 < 1%, ≥ 1%, 1% - 49%, and ≥ 50%) based on RECIST v1.1 by BICR and investigator's assessment
• To estimate OS of BMS-986207 in combination with nivolumab plus ipilimumab (Arm A) and nivolumab plus ipilimumab (Arm B) in subgroups defined by PD-L1 expression	• OS in subgroups defined by PD-L1 expression (< 1%, 1% - 49% and ≥ 50%)

Abbreviations: 1L, first-line; AE, adverse event; BICR, blinded independent central review; DOR, duration of response; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, severe adverse event.

Overall Design:

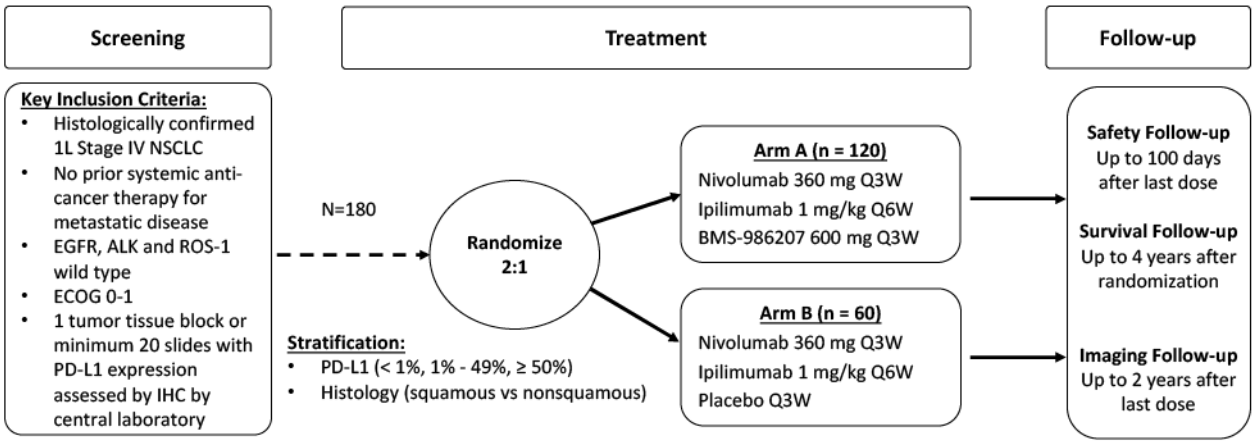
This multi-center, randomized Phase 2 trial will evaluate the efficacy and safety of BMS-986207 in combination with nivolumab plus ipilimumab versus nivolumab plus ipilimumab in adult participants with 1L Stage IV NSCLC. All participants will complete up to 3 study periods: screening (up to 28 days), treatment (up to 2 calendar years regardless of treatment delays [up to 18 cycles, 42 days/cycle]), safety follow-up (100 days from last dose of study intervention), response follow-up (up to 2 years from last dose of study intervention), and survival follow-up (up to 4 years from randomization). The duration of study participation will be approximately 4 years.

Images will be submitted to a central imaging vendor and may undergo Blinded Independent Central Review (BICR) at any time during the study. Prior to scanning the first participant, sites should be qualified and understand the image acquisition guidelines and submission process as outlined in the CA020016 Imaging Manual provided by the central imaging vendor.

Method of Study Intervention Assignment

Participants who have met all eligibility criteria will be randomized through an Interactive Response Technology (IRT). Stratification will be by tumor histology (squamous versus nonsquamous) and PD-L1 expression (< 1%, 1% - 49%, and ≥ 50%).

Figure 1-1: Study Design Schema



Abbreviations: 1L, first-line; ALK, anaplastic lymphoma kinase; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; IHC, immunohistochemistry; N, number; NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1; ROS-1, c-ros oncogene 1; Q3W, every 3 weeks; Q6W, every 6 weeks.

Number of Participants:

Approximately 180 randomized participants are expected to be randomized in a 2:1 ratio to the 2 treatment arms stratified by PD-L1 expression and histology in pre-specified subgroups.

To ensure the randomized population is representative of the NSCLC population and to allow for appropriate subgroup analyses, total enrollment and/or enrollment in specific PD-L1 subgroups may be adjusted to ensure enrollment of at least 105 randomized participants with tumor cell PD-L1 expression ≥ 1% with at least 75 randomized participants with tumor cell PD-L1 expression 1% - 49%, and at least 75 randomized participants with tumor cell PD-L1 expression < 1%, based on central laboratory results.

Study Population:

Participants must be at least 18 years old or local age of majority at the time of signing the informed consent.

Key Inclusion Criteria:

- Histologically confirmed metastatic 1L Stage IV NSCLC of squamous or nonsquamous histology
- No prior systemic anti-cancer treatment given as primary therapy for advanced or metastatic NSCLC
- Measurable disease as per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
- Eastern Cooperative Oncology Group (ECOG) performance status 0-1
- A formalin-fixed, paraffin-embedded (FFPE) tumor tissue block (preferred, equivalent to 20 sections) or a minimum of 20 unstained slides of tumor tissue 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 prior to randomization. Samples may be from core biopsy, punch biopsy, excisional biopsy, or surgical specimen. Fine needle aspirates or other cytology samples are NOT acceptable. Central laboratory must confirm receipt of evaluable tumor tissue as described in the Laboratory Manual prior to randomization.

– Assessment of tumor-cell PD-L1 expression by immunohistochemistry must be performed by central laboratory using pre-treatment tissue sample, and results must be reported to IRT prior to randomization.

Key Exclusion Criteria:

- Participants with epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), or c-ros oncogene 1 (ROS-1) mutations which are sensitive to available targeted inhibitor therapy. All participants with nonsquamous histology must have been tested for EGFR, ROS-1, and ALK mutation status. Participants with nonsquamous histology and unknown EGFR, ALK, or ROS-1 status are excluded.
- Participants with known B-rapidly accelerated fibrosarcoma proto-oncogene (BRAF) V600E mutations that are sensitive to available targeted inhibitor therapy. Participants with unknown or indeterminate BRAF mutation status are eligible.
- Participants with untreated central nervous system metastases.
- Participants with leptomeningeal metastases (carcinomatous meningitis).
- Concurrent malignancy requiring treatment.
- Participants with an active, known, or suspected autoimmune disease.
- Prior treatment with anti-TIGIT, anti-PD-(L)1, anti- CTLA-4 antibody or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways.

Intervention Groups and Duration:

Screening

The screening period will be up to 28 days and begins by establishing the participant's initial eligibility and signing of the informed consent form. Informed consent will be obtained prior to any study-specific procedures. Participants will be evaluated based on the inclusion and exclusion criteria and will be enrolled using an IRT.

A pre-treatment biopsy is required for enrollment into the study if an archived FFPE sample less than 3 months old without any intervening therapy is unavailable for the participant.

Treatment Period

The randomized treatment period will assess efficacy and safety of BMS-986207 in combination with nivolumab plus ipilimumab (Arm A) versus nivolumab plus ipilimumab (Arm B).

After central laboratory confirmation of PD-L1 expression, approximately 180 participants will be stratified by PD-L1 expression (< 1%, 1% - 49%, or ≥ 50%) and tumor histology (squamous versus nonsquamous) and randomized in a 2:1 ratio to:

- **Arm A:** Nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W + BMS-986207 600 mg Q3W
- **Arm B:** Nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W + placebo Q3W

Participants, investigators, and site staff will be blinded (single-blind) to treatment assignment. The Data Monitoring Committee (DMC) and Sponsor will be unblinded to treatment assignment for the purpose of safety evaluation. Treatment information access will not be used by the Sponsor to perform by-arm efficacy analyses.

All participants will be treated for up to 2 calendar years from start of study intervention regardless of treatment delays (up to 18 cycles, 42 days/cycle), until progression, unacceptable toxicity, death, or withdrawal of consent, whichever occurs first. Continuous safety evaluation and tumor assessment will guide the decision to treat a participant with additional cycles of study intervention if the participant has confirmed clinical benefit (up to a maximum of 2 years).

Dose Modification

Intra-participant dose escalation/reduction of BMS-986207 (or its placebo), nivolumab, or ipilimumab (except per weight-based dosing) is not permitted. Dose delays are permitted. Separate assessments of study interventions will be used in considering criteria for dose delay, resumption and discontinuation.

Follow-up Period

Safety Follow-up: At the end of treatment (EOT), all participants will enter a safety follow-up period upon completion of study intervention (up to a maximum of 2 years from first dose of study intervention, if applicable) or once the decision is made to discontinue the participant from treatment. All participants will be evaluated for any new adverse events (AEs) (serious and non-serious) for at least 100 days after the last dose of study intervention.

Imaging Follow-up: Participants that have discontinued treatment without having BICR-assessed disease progression will continue to have radiologic tumor assessments after treatment discontinuation for up to 2 years after last dose of study intervention.

Survival Follow-up: Participants will be followed by phone contact or office visit every 12 weeks (± 2 weeks) until death, loss to follow-up, withdrawal of consent, or conclusion of the study, whichever comes first, for a period of up to 4 years from randomization. A follow-up more than 4 years after randomization could be considered in selected cases if an efficacy signal is apparent.

Study Intervention:

Study Intervention for CA020016		
Medication	**Potency**	**IP/Non-IP/AxMP**
Nivolumab	100 mg/vial (10 mg/mL)	IP
Ipilimumab	50 mg/vial (5 mg/mL); 200 mg/vial (5 mg/mL)	IP
BMS-986207	160 mg/vial	IP
Placebo	NA	IP

Abbreviations: AxMP, auxiliary medicinal product; IP, Investigational Product; NA, not applicable.

Statistical Methods

Statistical Hypotheses

It is expected that the progression-free survival (PFS) in participants with 1L Stage IV NSCLC and PD-L1 expression ≥ 1% randomized to the BMS-986207 with nivolumab plus ipilimumab (Arm A) will be improved as compared to the PFS in participants receiving nivolumab plus ipilimumab (Arm B).

Sample Size Determination

The sample size of the study is calculated to have a sufficient probability of making the correct decision and have a low probability of making an incorrect decision under the pre-defined go criteria of primary efficacy endpoint of PFS in the PD-L1 ≥ 1% subgroup. Using a Bayesian augmented control (BAC) design, a portion of the control cohort for Study CA020016 will be borrowed from participants treated with nivolumab plus ipilimumab in Study CheckMate 227 whose baseline prognostic factors are similar to the current randomized population. Based on the results in the CheckMate 227 study, it is assumed that the median PFS in Arm B is 5 months with a constant hazard ratio (HR) of 0.605 of Arm A vs Arm B for the PD-L1 ≥ 1% subgroup. The pre-defined go criteria at the end of the trial is probability (Pr) (HR < 1) > 0.9 and Pr (HR < 0.7) > 0.5. With the above assumption, 64 PFS events will need to be observed across the 2 arms, and there is 72.2% probability of making a go decision for a scenario at the interim analysis occurring at about 70% of the events, and 78.1% probability of making a go decision at the final analysis. This assumes 12 months for accrual and a minimum of 10 months follow up, for a total of 105 randomized participants with PD-L1 ≥ 1% expression, with approximately 180 participants randomized under current assumptions of prevalence in the primary subgroup. The participants will be randomized to the BMS-986207 with nivolumab plus ipilimumab (Arm A) and the nivolumab plus ipilimumab (Arm B) in a 2:1 ratio.

The sample size of the study is planned to ensure a sufficient probability of making the correct decision and a low probability of making an incorrect decision under the pre-defined go criteria for the primary objective and is based on assumptions of expected prevalence of PD-L1 expression in the different PD-L1 subgroups. To ensure the randomized population is representative of the NSCLC population and to allow for appropriate subgroup analyses, total enrollment may be adjusted to ensure at least 105 randomized participants with tumor cell PD-L1 expression ≥ 1%, at least 75 randomized participants with tumor cell PD-L1 expression 1% - 49%, and at least 75 randomized participants with tumor cell PD-L1 expression < 1%, based on central laboratory results.

Analysis Sets

For the purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign informed consent and are registered in IRT
Treated	All participants who received any amount of study intervention
Randomized	All participants who were randomized using IRT
Randomized PD-L1 ≥ 1%	All participants who were randomized using IRT with ≥ 1% PD-L1 tumor expression
Safety-evaluable	All randomized participants who have received study intervention (all 3 components) and have completed the safety-evaluation period of 12 weeks, or who discontinued any study intervention due to toxicity prior to completing the safety-evaluation period.
PK	All participants who received at least 1 dose of study intervention and had any available concentration-time data
Immunogenicity	All treated participants who have baseline and at least 1 post-baseline pre-infusion immunogenicity assessment

Abbreviations: IRT, interactive response technology; PD-L1, programmed death-ligand 1; PK, pharmacokinetic.

Statistical Analyses

The SAP will be developed and finalized before database lock and will describe the selection of participants to be included in the analyses and procedures for accounting for missing, unused, and spurious data. A description of the participant population will be included in a statistical output report including subgroups of age, gender, and race.

Data Monitoring Committee: Yes

An independent DMC will be used in the study.

Other Committee: Yes

A BICR committee will be used in this study.

Brief Summary:

Combining immunotherapies has proven to be clinically beneficial in some tumor types, including NSCLC. Study CheckMate 227 recently demonstrated that combining nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) was safe, tolerable, and improved survival in 1L Stage IV NSCLC in comparison to chemotherapy. BMS-986207 is a monoclonal antibody to TIGIT, another immune checkpoint inhibitor. In Study CA020002, BMS-986207 (600 mg every 3 weeks [Q3W]) in combination with nivolumab and ipilimumab was tolerable.

This study, CA020016, is a Phase 2, multi-center, randomized study of BMS-986207 in combination with nivolumab plus ipilimumab in comparison to nivolumab plus ipilimumab in participants with 1L Stage IV NSCLC. The purpose of this study is to evaluate the safety and efficacy of BMS-986207 in combination with nivolumab plus ipilimumab in 1L Stage IV NSCLC. It is expected that BMS-986207 in combination with nivolumab plus ipilimumab will improve clinical responses (PFS) in participants with 1L Stage IV NSCLC as compared to those receiving nivolumab plus ipilimumab.

Study Duration: The maximum duration for a participant on-study is 4 years from randomization.

Study Intervention Duration: Each dosing cycle lasts 6 weeks (42 days) for up to 2 calendar years (up to 18 cycles), regardless of dose delays.

Health Measurement/Observation: The study will assess the safety and efficacy (PFS, objective response rate [ORR]) in participants treated with BMS-986207 in combination with nivolumab plus ipilimumab in comparison to nivolumab plus ipilimumab.

Study Visit Frequency: Study intervention will be given Q3W. Two biopsies are required: one prior to starting treatment and a second biopsy 29 days after starting treatment (Cycle 1 Day 29). Physical examination is performed weekly for the first 4 weeks, and then approximately every 3 weeks along with the study intervention administration day. Imaging for tumor assessments is done every 6 weeks for 48 weeks, then every 12 weeks. Safety is monitored continuously throughout the study.

2 SCHEDULE OF ACTIVITIES

Study assessments and procedures are presented in Table 2-1 (Screening Procedural Outline), Table 2-2 (On Treatment Procedural Outline), and Table 2-3 (Long-term Follow-up Procedural Outline).

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

Table 2-1: Screening Procedural Outline (CA020016)

Procedure	Screening Visit (Day -28 to -1)	Screening Visit (Day -14 to -1)	Notes[a]
Eligibility Assessments			
Informed Consent	X		Must be obtained prior to performing any screening procedures. A participant is considered enrolled only when a protocol-specific informed consent is signed. Study allows for re-enrollment of a participant who has discontinued the study as a pretreatment failure. If re-enrolled, the participant must be re-consented and assigned a new participant number from IRT.
Contact IRT	X		Register in IRT to obtain participant number.
Inclusion/Exclusion Criteria	X		Must be confirmed prior to randomization.
Medical History	X		All medical history relevant to disease under study.
Safety Assessments			
PE, Measurements, Vital Signs, and PS		X	Includes height, weight, BMI, PS (see Appendix 7), seated BP, heart rate, temperature and oxygen status by pulse oximetry. BP and heart rate should be measured after the participant has been resting quietly for at least 5 minutes. Must be collected within 14 days prior to randomization.
Assessment of Signs and Symptoms		X	Within 14 days prior to randomization.
Concomitant Medication Collection		X	Within 14 days prior to randomization. Vaccine use within 30 days prior to first study intervention.
ECG		X	At rest. Within 14 days prior to randomization. ECGs should be recorded after the participant has been supine for at least 5 minutes, and prior to blood draws.
AE and SAE Assessment	X		All SAEs must be collected from the date of participant's written consent. All AEs (SAEs or non-serious AEs) associated with SARS-CoV-2 infection collected from time of consent.

Table 2-1: Screening Procedural Outline (CA020016)

Procedure	Screening Visit (Day -28 to -1)	Screening Visit (Day -14 to -1)	Notes[a]
Laboratory Tests			
Clinical Laboratory Assessments	X	X	Day -14 to -1: On-site/local laboratory tests must be performed within 14 days prior to randomization. Day -28 to -1: Viral testing to be completed within 28 days prior to randomization. For HIV: testing at sites where locally mandated. Refer to Section 9.4.4 for list of laboratory tests to conduct.
Pregnancy Test (WOCBP only)		X	Serum or urine pregnancy test (minimum sensitivity equivalent units 25 IU/L or equivalent units of HCG) to be done at screening visit and repeated within 24 hours prior to first dose of study intervention.
FSH		X	FSH screening - only required to confirm menopause in women < 55 years of age.
Biomarker Assessments			
Tumor Sample	X		A FFPE tumor tissue block (preferred, equivalent to 20 sections) or a minimum of 20 unstained slides* of tumor tissue 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 prior to randomization. Samples may be from core biopsy, punch biopsy, excisional biopsy or surgical specimen. Fine needle aspirates or other cytology samples are NOT acceptable. Prior to randomization, central laboratory must provide IRT with assessment of tumor-cell PD-L1 expression by IHC using pre-treatment tissue sample as described in the Laboratory Manual. *If despite best efforts, a minimum of 20 slides is not obtainable, submission of fewer slides may be acceptable in some circumstances following discussion with Sponsor or designee. Please refer to Section 9.8 for additional information.

Table 2-1: Screening Procedural Outline (CA020016)

Procedure	Screening Visit (Day -28 to -1)	Screening Visit (Day -14 to -1)	Notes[a]
EGFR, ALK, ROS-1, KRAS, and BRAF V600E Mutation Status	X		EGFR, ALK, and ROS-1 results required for all nonsquamous participants prior to randomization. Historical results obtained as standard of care prior to screening period are acceptable. EGFR mutation, ALK, and ROS-1 tests should be performed by site. The use of FDA-approved or local Health Authority tests for EGFR and ALK are strongly encouraged. • EGFR mutation test (tumor tissue or blood) will be performed using PCR-based assay or next generation sequencing. Tests other than PCR or next generation sequencing will be requested to be repeated using PCR or next generation sequencing-based methods. • ALK translocations and ROS-1 rearrangement tests are mandatory for participants with nonsquamous histology. Participants with known ALK translocations/ROS-1 rearrangements which are sensitive to available targeted inhibitor therapy are excluded. • If known status of BRAF V600E mutations (which are sensitive to available targeted inhibitor), participant is excluded. If BRAF mutation status is unknown or indeterminate, participant may enroll. • If known, KRAS mutation status should be documented for all participants.
Biomarker Sample Collections	Refer to biomarker collection table in Section 9.8 for timing of collections.		
Tumor Assessments			
Body Imaging	X		Contrast enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease, within 28 days prior to randomization. See Section 9.1.1.1 for further details.
Brain Imaging	X		MRI of the brain (without and with contrast) is required for ALL participants during screening to rule out brain metastases, within 28 days prior to randomization. CT of the brain (without and with contrast) can be performed if MRI is contraindicated. See Section 9.1.1.1 for further details.

Abbreviations: AE, adverse event; ALK, anaplastic lymphoma kinase; BMI, body mass index; BP, blood pressure; BRAF, b-rapidly accelerated fibrosarcoma proto-oncogene; CRF, case report form; CT, computed tomography; ECG, electrocardiogram; EGFR, epidermal growth factor receptor; FDA, Food and Drug Administration; FFPE, formalin-fixed paraffin-embedded; FSH, follicle-stimulating hormone; HCG, human chorionic gonadotropin; HIV, human immunodeficiency virus; IHC, immunohistochemistry; IRT, interactive response technology; KRAS, Kirsten rat sarcoma viral oncogene homolog; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; PD-L1, programmed death-ligand 1; PE, physical examination; PS, performance status; ROS-1, c-ros oncogene 1; SAE, severe adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WOCBP, women of childbearing potential.

[a] Some of the assessments referred to in this section may not be captured as data in the CRF. 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 2-2: On Treatment Procedural Outline (CA020016)

Procedure	Cycle 1[a] Visit Window = -3 Days for C1D1, ± 3 Days for All Others					Each Subsequent Cycle		EOT	Notes[b] 1 Cycle = 6 Weeks
	D1	D8	D15	D22	D29	D1 (± 3 Days)	D22 (± 3 Days)		
Safety Assessments									
Complete PE, Vital Signs, Physical Measurements, and PS	X					X		X	Includes weight, BMI, heart rate, seated BP, temperature, oxygen saturation by pulse oximetry and PS (see Appendix 7). BP and heart rate should be measured after the participant has been resting quietly for at least 5 minutes.
Targeted PE, Vital Signs, Physical Measurements, and PS		X	X	X	X		X		Includes weight, BMI, heart rate, seated BP, temperature, oxygen saturation and PS (see Appendix 7). BP and heart rate should be measured after the participant has been resting quietly for at least 5 minutes.
ECGs	X					X		X	ECGs should be recorded after the participant has been supine for at least 5 minutes, and prior to blood draws.
Concomitant Medication Use	Continuously during the study							X	Record at each visit
AE and SAE Assessment	Continuously during the study							X	Record at each visit. All AEs (SAEs or non-serious AEs), including those associated with SARS-CoV-2 infection, must be collected continuously during the treatment period. For reporting purposes, all AEs/SAEs must be graded using CTCAE v5. All SAEs must be collected from the date of participant's written consent until 100 days post discontinuation of dosing.

Table 2-2: On Treatment Procedural Outline (CA020016)

Procedure	Cycle 1[a] Visit Window = -3 Days for C1D1, ± 3 Days for All Others					Each Subsequent Cycle		EOT	Notes[b] 1 Cycle = 6 Weeks
	D1	D8	D15	D22	D29	D1 (± 3 Days)	D22 (± 3 Days)		
Laboratory Tests									
Clinical Laboratory Assessments	X			X		X	X	X	Perform on site/local laboratory testing within 72 hours prior to each dose. For the first treatment visit, labs need not be repeated if they were performed within 72 hours and the results are available and have been reviewed for eligibility. Refer to Section 9.4.4 for the list of laboratory tests to be conducted.
Pregnancy Test (WOCBP only)	X			X		X	X	X	Serum or urine within 24 hours prior to first dose, and then every 3 weeks regardless of dosing schedule.
PK and Immunogenicity Assessments									
PK and Immunogenicity Collections	Refer to PK/Immunogenicity collection table in Section 9.5 for timing of collections								
Biomarker Assessments									
Tumor Biopsy					X				Mandatory on-treatment biopsies (if medically feasible) required for all participants. Biopsy window for C1D29 is ± 5 days. EOT/Progression biopsy is optional.
Biomarker Sample Collections	Refer to biomarker collection table in Section 9.8 for timing of collections.								

Table 2-2: On Treatment Procedural Outline (CA020016)

Procedure	Cycle 1[a] Visit Window = -3 Days for C1D1, ± 3 Days for All Others					Each Subsequent Cycle		EOT	Notes[b] 1 Cycle = 6 Weeks
	D1	D8	D15	D22	D29	D1 (± 3 Days)	D22 (± 3 Days)		
Tumor 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 (± 7 days) starting from randomization for the first 48 weeks, then every 12 weeks (± 7 days) until BICR confirmed disease progression or treatment discontinuation (including treatment beyond progression), whichever occurs later. See Section 9.1.1.1 for further details.								
Brain Imaging	Participants with a history of brain metastasis or symptoms should have surveillance MRIs (without and with contrast) per standard of care (approximately Q12W) or sooner if clinically indicated. CT of the brain without and with contrast can be performed if MRI is contraindicated. See Section 9.1.1.1 for further details.								
Clinical Outcomes Assessments									
NSCLC-SAQ	X					X		X	Completed electronically prior to dosing on Day 1 of each cycle from Cycle 1 and then every cycle thereafter for the remainder of the treatment period. See Section 9.1.2 for further details.
FACT-G7	X					X		X	
EQ-5D-5L	X					X		X	
PGIS	X					X		X	
PGIC						X		X	Completed electronically prior to dosing on Day 1 of each cycle from Cycle 2 and then every cycle thereafter for the remainder of the treatment period. The PGIC is not administered on C1D1. See Sections 9.1.2 and 9.1.2.4 for further details.

Table 2-2: On Treatment Procedural Outline (CA020016)

Procedure	Cycle 1[a] Visit Window = -3 Days for C1D1, ± 3 Days for All Others					Each Subsequent Cycle		EOT	Notes[b] 1 Cycle = 6 Weeks
	D1	D8	D15	D22	D29	D1 (± 3 Days)	D22 (± 3 Days)		
Study Intervention									
IRT Randomization	X								Participant must receive the first dose of study medication within 3 calendar days from vial allocation.
BMS-986207 or Placebo	X			X		X	X		BMS-986207 600 mg Q3W. See Sections 5.1.2 and 7.1 for further details. Details of study drug preparation are found in the Pharmacy Manual.
Nivolumab	X			X		X	X		Nivolumab 360 mg Q3W. Participants may be dosed no less than 19 days from the previous dose.
Ipilimumab	X					X			Ipilimumab 1 mg/kg Q6W. Use body weight for dosing calculations. It is not necessary to re-calculate subsequent doses if the participant weight is within 10% of the baseline weight or the weight used to calculate the previous dose. Round all doses to the nearest milligram per institutional standard.

Abbreviations: AE, adverse event; BICR, blinded independent central review; BMI, body mass index; BP, blood pressure;C1D1, cycle 1 day 1; CRF, case report form; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; D, day; ECG, electrocardiogram; EOT, end of treatment; EQ-5D-5L, 5 Level EQ-5D Questionnaire; FACT-G7, Functional Assessment of Cancer Therapy - General - 7 item version; IgG, immunoglobulin G; IRT, interactive response technology; MRI, magnetic resonance imaging; NSCLC-SAQ, Non Small Cell Lung Cancer Symptom Assessment Questionnaire; PE, physical examination; PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Severity; PK, pharmacokinetic; PS, performance status; Q3W, every 3 weeks; Q6W, every 6 weeks; Q12W, every 12 weeks; SAE, severe adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WOCBP, women of childbearing potential.

[a] If a dose is delayed, the procedures schedule for that same time point must also be delayed to coincide with when that time point's dosing actually occurs, with the exception of tumor assessments which must occur as scheduled.

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

Table 2-3: Long-term Follow-up Procedural Outline (CA020016)

Procedure	Safety Follow-up (relative to the last dose of study intervention)[a]			Imaging Follow-up (assessed Q12W for 2 years from last dose of study intervention)[b]	Survival Follow-up (assessed Q12W for 4 years from randomization)[b]	Notes[c]
	Follow-up 1 30 Days (± 7 Days)	Follow-up 2 60 Days (± 7 Days)	Follow-up 3 100 Days (± 7 Days)			
Safety Assessments						
Targeted PE, Vital Signs, and PS	X	X	X			Record at each visit.
Concomitant Medication Use	X	X	X			Record at each visit.
AE and SAE Assessment	X	X	X			All SAEs and non-serious AEs should be collected continuously for a minimum of 100 days following discontinuation of study intervention. Beyond 100 days from the last dose of study therapy, participants will be followed for drug-related AEs/SAEs until resolution, returns to baseline, or is deemed irreversible, or until the participant is lost to follow-up or withdraws study consent. Participants will be followed for all SAEs, non-serious AEs of special interest (as defined in Section 9.2), and all AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection until resolution, the condition stabilizes, the event is otherwise explained, the event is deemed irreversible, the participant is lost to follow-up (as defined in Section 8.3), or for suspected cases, until SARS-CoV-2 infection is ruled-out.

Table 2-3: Long-term Follow-up Procedural Outline (CA020016)

Procedure	Safety Follow-up (relative to the last dose of study intervention)[a]			Imaging Follow-up (assessed Q12W for 2 years from last dose of study intervention)[b]	Survival Follow-up (assessed Q12W for 4 years from randomization)[b]	Notes[c]
	Follow-up 1 30 Days (± 7 Days)	Follow-up 2 60 Days (± 7 Days)	Follow-up 3 100 Days (± 7 Days)			
Laboratory Tests						
Clinical Laboratory Assessments	X	X	X			Refer to Section 9.4.4 Clinical Safety Laboratory Assessments for the list of laboratory tests.
Pregnancy Test (WOCBP only)	X	X	X			Serum or urine.
Efficacy Assessments						
Survival Status and Subsequent Cancer Therapy	X	X	X		X	Collect every 3 months (12 weeks) in survival visits until death, lost to follow-up, or withdrawal of study consent. May be performed by phone contact or office visit. Additional subsequent cancer therapy details such as regimen, setting of the regimen, line of therapy, start date and end date of each regimen, best response to the regimen, and date of progression after second-line therapy will be collected. During Safety Follow-up (Follow-up Visits 1, 2, and 3) and every 3 months (clinic visit or by telephone) during Survival Follow-up. Include documentation of subsequent cancer therapy (ie, systemic therapy, tumor-directed surgery, or radiation therapy).

Table 2-3: Long-term Follow-up Procedural Outline (CA020016)

Procedure	Safety Follow-up (relative to the last dose of study intervention)[a]			Imaging Follow-up (assessed Q12W for 2 years from last dose of study intervention)[b]	Survival Follow-up (assessed Q12W for 4 years from randomization)[b]	Notes[c]
	Follow-up 1 30 Days (± 7 Days)	Follow-up 2 60 Days (± 7 Days)	Follow-up 3 100 Days (± 7 Days)			
Tumor Assessments						
Body Imaging				X		For participants who have not experienced BICR-confirmed PD radiographic assessments, or who discontinue study intervention for reasons other than PD, contrast-enhanced CT of the chest and CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease should continue Q6W (± 7 days) starting from date of randomization until Week 48, and then Q12W (± 7 days) beginning on Week 49 until BICR confirmed disease progression, death, or withdrawal of consent, whichever occurs first. See Section 9.1.1.1 for further details.
Brain Imaging				X		Participants with a history of brain metastasis or symptoms should have a surveillance MRI (without and with contrast) 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 9.1.1.1 for further details.

Table 2-3: Long-term Follow-up Procedural Outline (CA020016)

Procedure	Safety Follow-up (relative to the last dose of study intervention)[a]			Imaging Follow-up (assessed Q12W for 2 years from last dose of study intervention)[b]	Survival Follow-up (assessed Q12W for 4 years from randomization)[b]	Notes[c]
	Follow-up 1 30 Days (± 7 Days)	Follow-up 2 60 Days (± 7 Days)	Follow-up 3 100 Days (± 7 Days)			
PK and Immunogenicity Assessments	Refer to PK/Immunogenicity collection table in Section 9.5 for timing of collections.					
Biomarker Collection and Assessments	Refer to biomarker collection table in Section 9.8 for timing of collections.					
Clinical Outcome Assessments						
NSCLC-SAQ	X	X	X		X	To be completed electronically at Safety Follow-Up (Visits 1, 2, and 3 after last dose or date of treatment discontinuation) and only during Survival Follow-up beginning every 12 weeks from Follow-up Visit 3 (100 day Safety Follow-up). To be completed prior to any other study procedure. See Section 9.1.2 for further details.
FACT-G7	X	X	X		X	
EQ-5D-5L	X	X	X		X	

Abbreviations: AE, adverse event; BICR, blinded independent central review; CT, computed tomography; D, day; EQ-5D-5L, 5 Level EQ-5D Questionnaire; FACT-G7, Functional Assessment of Cancer Therapy - General - 7 item version; IgG, immunoglobulin G; MRI, magnetic resonance imaging; NSCLC-SAQ, Non Small Cell Lung Cancer Symptom Assessment Questionnaire; PD, progressive disease; PE, physical examination; PK, pharmacokinetic; PS, performance status; Q6W, every 6 weeks; Q12W, every 12 weeks; SAE, severe adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WOCBP, women of childbearing potential.

[a] Participants must be followed for at least 100 days after last dose of study intervention. Follow-Up Visit 1 must occur 30 days from the last dose (± 7 days) or can be performed on the date of discontinuation if that date is greater than 30 days after last dose. Follow-up Visits 2 and 3 occur approximately 60 and 100 days (± 7 days) from last dose of study medication.

[b] Survival follow-up visits to occur every 3 months (12 weeks) (± 14 days) from the date of randomization. Survival follow-up assessments may be conducted in clinic or by telephone. BMS may request that survival data be collected on all treated participants outside of the 3 month specified window. At the time of this request, each participant will be contacted to determine their survival status unless the participant has withdrawn consent for all contact.

[c] Some of the assessments referred to in this section may not be captured as data in the CRF. 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.

3 INTRODUCTION

Study CA020016 is a Phase 2, randomized study of BMS-986207 in combination with nivolumab plus ipilimumab versus nivolumab plus ipilimumab in participants with first-line (1L) Stage IV non-small cell lung cancer (NSCLC). BMS-986207 is a fully human immunoglobulin (Ig) G1 monoclonal antibody (mAb) that binds with high affinity to T cell immunoreceptor with Ig and immunoreceptor tyrosine-based inhibitory motif domain (TIGIT), a negative regulatory molecule that suppresses activation and functional responses in T cells and natural killer (NK) cells.

3.1 Study Rationale

Immunotherapeutic approaches have recently demonstrated clinical efficacy in several cancer types, including NSCLC.[1] Tumors may modulate and evade the host immune response through a number of mechanisms, including downregulation of tumor-specific antigen expression and presentation, secretion of anti-inflammatory cytokines, and upregulation of inhibitory ligands.

Nivolumab (BMS-936558) is a fully human, IgG4 (kappa) isotype mAb that binds the programmed death-1 (PD-1) receptor on activated immune cells and disrupts engagement of the receptor with its ligands programmed death-ligand 1 (PD-L1) (B7-H1/cluster of differentiation [CD]274) and programmed death-ligand 2 (PD-L2) (B7-DC/CD273), thereby abrogating inhibitory signals and augmenting the host antitumor response. In clinical trials, nivolumab has demonstrated activity in several tumor types, including melanoma, renal cell cancer (RCC), and NSCLC (see Section 3.2.3.1 for more details on the mechanism of action of nivolumab).

Ipilimumab (BMS-734016, MDX010, MDX-CTLA4) is a fully human monoclonal IgG1 kappa specific for human cytotoxic T-lymphocyte antigen 4 (CTLA-4), which is expressed on a subset of activated T cells. Inhibition of CTLA-4 with ipilimumab contributes to a general increase in T-cell responsiveness and the anti-tumor response. In clinical trials, ipilimumab has demonstrated efficacy as monotherapy in melanoma (see Section 3.2.4.1 for more details on the mechanism of action of ipilimumab).

While targeting individual immune checkpoint receptors has been clinically successful in multiple tumor types, combining immunotherapies can also be beneficial. CheckMate 227 (CA209227; NCT02477826), a randomized Phase 3 study in participants with treatment-naive NSCLC, demonstrated that treatment with a combination of nivolumab plus ipilimumab is safe, tolerable, and improved clinical responses (PD-L1 $\geq$ 1% overall survival [OS] hazard ratio [HR] = 0.79 and PD-L1 < 1% OS HR = 0.62) in comparison to chemotherapy.[2] Given this study, the combination of nivolumab and ipilimumab is approved in the United States (US) for the treatment of adults with metastatic NSCLC expressing PD-L1 $\geq$ 1% and was recently approved in Japan for the treatment of patients with unresectable advanced or recurrent NSCLC independent of PD-L1 status.[3] Thus, combination strategies can be clinically beneficial and targeting additional checkpoints is a promising approach.

Combining immune checkpoint inhibitors, including anti-TIGIT, anti-CTLA-4, and/or PD-(L)1, is a rational therapeutic strategy that has demonstrated clinical benefit in preclinical and clinical models. TIGIT is a negative regulatory molecule that suppresses activation and functional

responses in T cells and NK cells. Poliovirus receptor (PVR), a ligand of TIGIT, expression has been associated with poor response to anti-PD-1 therapy, suggesting that blockade of TIGIT may help to achieve further reversal of checkpoint suppression.[4] In preclinical models, combining anti-TIGIT with either anti-CTLA-4 or anti-PD-1 agents resulted in greater anti-tumor responses as compared to either agent used as monotherapy. Thus, anti-TIGIT in combination with anti-CTLA-4 and/or anti-PD-1 may be a promising therapeutic strategy.

Recent studies have reported clinical benefit in patients with 1L Stage IV NSCLC treated with a combination of anti-TIGIT plus anti-PD-(L)1.[5,6] In a randomized Phase 2 study conducted in 1L Stage IV NSCLC participants comparing the anti-TIGIT agent tiragolumab plus atezolizumab versus placebo plus atezolizumab, clinically meaningful improvement was observed in the tiragolumab plus atezolizumab group with high PD-L1 (≥ 50% PD-L1) expression: objective response rate (ORR [66% versus 24%]) and progression-free survival (PFS) (HR: 0.30, 95% confidence interval [CI]: 0.15 - 0.61). 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 vibostolimab, an anti-TIGIT antibody, plus pembrolizumab in participants with anti-PD-(L)1-naive NSCLC demonstrated promising anti-tumor activity (ORR 46% and median PFS 8.4 months in tumor proportion score [TPS] ≥ 1%). These data suggest combining TIGIT blockade with anti-PD-(L)1 can be safe, tolerable and have clinical benefit in 1L NSCLC.

Study CA020002 (NCT02913313) is a Phase 1/2a dose-escalation and multiple cohort expansion study of BMS-986207 as monotherapy and in combination with nivolumab with and without ipilimumab. As monotherapy, BMS-986207 was safe and tolerable up to maximum dose tested (BMS-986207 1600 mg every 2 weeks [Q2W]), but no clinical benefit was observed. In comparison, BMS-986207 (up to 1600 mg Q4W) in combination with nivolumab or BMS-986207 (600 mg Q3W) in combination with nivolumab plus ipilimumab was also safe and tolerable, and there was also preliminary evidence of clinical benefit in some patients treated with combination therapy. Thus, BMS-986207 in combination with nivolumab plus ipilimumab may be a novel therapeutic combination to improve clinical response.[7]

Study CA020016 will evaluate the safety and efficacy of BMS-986207 in combination with nivolumab plus ipilimumab in 1L Stage IV NSCLC. It will utilize nivolumab plus ipilimumab, which has demonstrated efficacy in CheckMate 227 and has a known safety profile in NSCLC. The combination of BMS-986207, nivolumab, and ipilimumab is expected to have a synergistic effect in the 1L Stage IV NSCLC population based on the preclinical and clinical activity of the doublet (nivolumab plus ipilimumab, anti-TIGIT plus anti-PD-(L)1, and anti-TIGIT plus anti-CTLA-4) and triplet (BMS-986207 in combination with nivolumab plus ipilimumab) combinations and their complementary mechanisms of action.

3.2 Background

A detailed description of the chemistry, pharmacology, efficacy, and safety of nivolumab, ipilimumab, and BMS-986207 are provided in their respective Investigator's Brochures (IBs).[7,8,9]

3.2.1 Indication Background

Lung cancer remains the leading cause of cancer-related mortality worldwide, accounting for approximately 18% of all cancer deaths.[10] Until recently, the treatment of patients with advanced NSCLC whose tumors did not have a targetable genetic alteration was cytotoxic chemotherapy alone. The introduction of immune checkpoint inhibitors targeting the PD-1 signaling pathway in the treatment of patients with NSCLC has had a significant effect on patient survival. In PD-L1 positive tumors, pembrolizumab or atezolizumab in the front-line setting has demonstrated an improvement in OS in NSCLC patients as compared to chemotherapy alone.[11,12,13,14,15,16,17] More recently, nivolumab plus ipilimumab also showed a clinical benefit over chemotherapy in participants with 1L Stage IV NSCLC in both PD-L1 positive and PD-L1 negative tumors.[2] However, despite these advances, there remains an unmet need for patients with NSCLC.

3.2.2 BMS-986207 Mechanism of Action

BMS-986207 is a fully human IgG1 mAb that binds with high affinity to TIGIT, a negative regulatory molecule that suppresses activation and functional responses in T cells and NK cells. BMS-986207 was designed with an inert isotype (termed IgG1.1) to eliminate fragment crystallizable region (Fc) effector function.[18,19] TIGIT upregulation has been observed in cancer patients, in particular on T cells and is co-expressed with markers of T cell exhaustion.[20,21] Binding of PVR and nectin-2 (TIGIT ligands) to TIGIT results in suppression of T cell and NK cell function.[22] Blockade of TIGIT therefore may increase the anti-tumor immune response both by removing the suppressive signal emanating from TIGIT as well as by freeing its ligands to bind to the stimulatory receptor CD226 (DNAX accessory molecule 1 [DNAM-1]), which shares these ligands. BMS-986207 blocks the interaction of TIGIT with its ligands and thereby may induce or enhance anti-tumor immune responses.

3.2.2.1 Nonclinical Pharmacology

BMS-986207 inhibits the binding of PVR and nectin-2 to TIGIT in a dose-dependent manner with a half maximal effective concentration (EC50) of 0.2 nM. BMS-986207 binds recombinant TIGIT with an equilibrium dissociation constant of 0.05 nM and to cell surface TIGIT on activated CD8+ T cells with an EC50 of 0.46 nM. The antibody binds to recombinant cynomolgus monkey TIGIT with an EC50 of 0.07 nM and to activated cynomolgus monkey CD8+ T with an EC50 of 0.44 nM. BMS-986207 inhibits the binding of PVR and nectin-2 to TIGIT in a dose-dependent manner with an EC50 of 0.2 nM. 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 (IFN-γ) secretion and an elevated percentage of IFN-γ producing T cells.

Due to its engineered inert Fc region, as expected, BMS-986207 does not induce antibody-dependent cellular cytotoxicity- or antibody-dependent cellular phagocytosis -mediated killing of

TIGIT-expressing target cells. In addition, BMS-986207 does not bind complement 1q. 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 mice suggested dual blockade of TIGIT and PD-1 may be beneficial in the treatment of cancer through enhanced antitumor immunity. 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 blockade by surrogate antibodies resulted in a greater number of tumor-free mice than either agent alone.

The in vitro and in vivo data indicated 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.

3.2.2.2 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 intravenous (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 (EC50 values of 0.56 nM and 0.28 nM to 0.58 nM, respectively), and is pharmacologically active in monkeys; it 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 markers 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 for 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 anti-drug antibody (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 is 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). Pharmacodynamic responses were observed at all doses and included NK cell activation and CD8+ T cell activation and proliferation were generally dose-independent. Based on the lack of direct BMS-986207-related adverse findings, the no-observed-adverse-effect level was considered to be 100 mg/kg/week (mean area under the concentration-time curve from 0 hour to 168 hours (AUC [0-168h]) ≤ 452,000 µg•h/mL). In addition, for determination of the maximum recommended human starting dose, 100 mg/kg was also considered the highest non-severely toxic dose.

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

3.2.2.3 Clinical Pharmacokinetics and Immunogenicity of BMS-986207 Monotherapy or in Combination with Nivolumab

CA020002 is a Phase 1/2a, first-in-human, dose-escalation, and multiple cohort expansion study of BMS-986207 alone, in combination with nivolumab, and in combination with nivolumab and ipilimumab in participants with advanced solid tumors. BMS-986207 PK was evaluated in participants with advanced solid tumors receiving BMS-986207 Q2W (20, 80, 240, 800, or 1600 mg) and every 4 weeks (Q4W) (480 or 1600 mg). 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 clearance appears consistent across doses. For participants who received combination of BMS-986207 with nivolumab (Part 1B), the PK of BMS-986207 is generally consistent with that reported for monotherapy (Parts 1A and 2A).

Immunogenicity potential of BMS-986207 was also evaluated in all the cohorts of Study CA020002. Of the 63 immunogenicity-evaluable participants, 2 participants (1 participant each in the 800 mg Q2W monotherapy and the 240 mg Q2W cohort in combination with nivolumab) were reported as ADA positive with observed titers < 4 at 1 time point. Overall, there was a low incidence of ADA with BMS-986207 administration.

3.2.2.4 Preliminary Clinical Safety Profile of BMS-986207 Monotherapy

Overall, based on preliminary data from Study CA020002, a Phase 1/2a study of BMS-986207 alone and in combination with nivolumab with and without ipilimumab in participants with advanced solid tumors, the safety profile of BMS-986207 monotherapy was manageable at the doses tested.[7]

As of 05-Jan-2022, the safety profile of BMS-986207 monotherapy (n = 42) was evaluated at doses ranging from an intra-participant dose-escalation approach of 2 mg, 6 mg, and 20 mg (n = 1), and 20 mg to 1600 mg Q2W (20 mg: n = 2; 80 mg: n = 3; 240 mg: n = 4; 800 mg: n = 28; 1600 mg: n = 4).[7] There were no dose limiting toxicities (DLTs) observed in monotherapy. There was no relationship between the incidence, severity, or causality of adverse events (AEs) and BMS-986207 dose level. Among the 42 participants treated with monotherapy, most treatment-related adverse events (TRAEs) were Grade 1 to Grade 2. Grade 3 TRAEs were reported in 4 participants, including 2 participants receiving BMS-986207 240 mg Q2W (aspartate

aminotransferase [AST] increased and hyponatraemia [n = 1 each]) and 2 participants receiving BMS-986207 800 mg Q2W (hypertension, lipase increased, hyperglycaemia, and hyponatraemia [n = 1 each]). No Grade 4 or 5 TRAEs were reported with BMS-986207 monotherapy. There were no treatment-related serious adverse events (SAEs) reported with monotherapy. A total of 28 deaths were reported in participants treated with BMS-986207 monotherapy. All deaths were considered to be due to complications from disease progression except for 1 death attributed to aspiration pneumonia, and all were considered by the investigator to be not related to BMS-986207.

3.2.2.5 Preliminary Clinical Safety Profile of BMS-986207 Combined with Nivolumab

As of 05-Jan-2022, the safety profile of BMS-986207 in combination with nivolumab (n = 30) was evaluated in Study CA020002 at the following doses: BMS-986207 80 mg (n = 4) or 240 mg (n = 4) in combination with nivolumab 240 mg Q2W, and BMS-986207 480 mg (n = 18) or 1600 mg (n = 4) in combination with nivolumab 480 mg Q4W. There were no reported DLTs with combination therapy. There was no relationship between the incidence, severity, or causality of AEs and dose levels of the combination regimen. Most AEs were Grade 1 and Grade 2. Among the 30 participants treated with BMS-986207 plus nivolumab, Grade 3 to Grade 4 TRAEs were reported in 3 participants (10%): 1 participant receiving BMS-986207 240 mg Q2W + nivolumab 240 mg Q2W and 2 participants receiving BMS-986207 480 mg Q4W + nivolumab 480 mg Q4W.

There were no Grade 3 or higher TRAEs reported in participants treated with BMS-986207 1600 mg Q4W + nivolumab 480 mg Q4W, which was the highest dose tested. Two (out of 30 [6.7%]) participants, both of whom received BMS-986207 480 mg Q4W + nivolumab 480 mg Q4W, were reported to have a total of 3 treatment-related SAEs: Grade 3 adrenal insufficiency (n = 2) and Grade 3 complete atrioventricular block (n = 1). With combination therapy, TRAEs were similar to those expected with nivolumab alone. A total of 15 deaths were reported in participants treated with BMS-986207 in combination with nivolumab, all of which were considered to be due to disease progression and not related to treatment by the investigator.[7]

3.2.2.6 Preliminary Clinical Safety Profile of BMS-986207 Combined with Nivolumab and Ipilimumab

As of 15-Mar-2022, the safety profile of BMS-986207 in combination with nivolumab and ipilimumab in Study CA020002 was evaluated at the following doses: BMS-986207 600 mg (n = 7) or 1200 mg (n = 6) in combination with nivolumab 360 mg every 3 weeks (Q3W) and ipilimumab 1 mg/kg every 6 weeks (Q6W).

DLTs were reported in 2 out of 4 DLT-evaluable participants treated with BMS-986207 1200 mg Q3W in combination with nivolumab plus ipilimumab: Grade 3 encephalitis and Grade 3 bullous dermatitis (n = 1 each). TRAEs were reported in 4 participants (66%) treated with BMS-986207 1200 mg Q3W in combination with nivolumab plus ipilimumab: skin rash (n =2 [33.3%]), pneumonitis, bullous dermatitis, encephalitis, lipase increase, and amylase increase (n = 1 [16.7%] each). Grade 3 TRAEs were reported in 3 participants (50%): bullous dermatitis, encephalitis, and amylase increase. No Grade 4 or Grade 5 TRAEs were reported. Based on the Bayesian optimal

interval (BOIN) study design in the CA020002 protocol, the dose of BMS-986207 was de-escalated to 600 mg Q3W administered in combination with nivolumab 360 mg Q3W and ipilimumab 1 mg/kg Q6W.

No DLTs were reported in the 6 DLT-evaluable participants treated with BMS-986207 600 mg Q3W in combination with nivolumab plus ipilimumab. TRAEs were reported in 5 participants (71%) treated with BMS-986207 600 mg Q3W in combination with nivolumab plus ipilimumab: pneumonitis (n = 2 [28.6%]), AST increase, alanine aminotransferase (ALT) increase, pruritus, skin rash, fever, chill, diarrhea, gastric pain, and pain (n = 1 [14.3%] each). All TRAEs were Grade 1 or Grade 2; no Grade 3 or higher TRAEs were reported. Based on these data, BMS-986207 600 mg Q3W in combination with nivolumab plus ipilimumab was considered tolerable per the BOIN study design in Study CA020002.[7]

3.2.3 Nivolumab

3.2.3.1 Nivolumab Mechanism of Action

Nivolumab (also referred to as BMS-936558, MDX1106, or ONO-4538) is a human monoclonal antibody (HuMAb; IgG4-S228P) that targets the PD-1 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, 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 (OPDIVO™) 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).

3.2.3.2 Nivolumab Clinical Activity

Nivolumab has demonstrated durable responses exceeding 6 months as monotherapy in several tumor types, including NSCLC, melanoma, 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. Nivolumab in combination with ipilimumab therapy, demonstrated a statistically significant increase in OS and PFS in 1L NSCLC participants compared to chemotherapy (see Section 3.2.5 for more information). Details of the clinical activity in these various malignancies are provided in the US Prescribing Information (USPI) and Summary of Product Characteristics (SmPC).[23,24]

3.2.4 Ipilimumab

3.2.4.1 Ipilimumab Mechanism of Action

Ipilimumab (BMS-734016, MDX010, MDX-CTLA4) is a fully human monoclonal IgG1 kappa specific for human CTLA-4, CD152, which is expressed on a subset of activated T cells. CTLA-4 is a negative regulator of T-cell activity. Ipilimumab is a mAb that binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation, including the activation and proliferation of tumor-infiltrating T-effector cells. Inhibition of CTLA-4 signaling can also reduce T-regulatory cell (Treg) function, which may contribute to a general increase in T-cell responsiveness, including the anti-tumor response.

3.2.4.2 Ipilimumab Clinical Activity

Ipilimumab has been administered to more than 22,571 participants (total number of participants enrolled in ipilimumab studies) in several cancer types in completed and ongoing studies, as well as a compassionate use program. Ipilimumab has been approved for use in over 47 countries including the US, the European Union, and Australia.[8]

The focus of the monotherapy clinical program has been in melanoma, with advanced melanoma and adjuvant melanoma being the most comprehensively studied indications. Ipilimumab is being investigated in combination with other modalities, such as chemotherapy, radiation therapy, and other immunotherapies in multiple tumor types. Details of the clinical activity in these various malignancies are provided in the USPI and SmPC.[25,26]

3.2.5 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 response and 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, microsatellite instability-high or mismatch repair deficient colorectal cancer, and NSCLC. Participants with treatment-naive Stage IV or recurrent NSCLC, demonstrated that a combination of nivolumab plus ipilimumab therapy improved 3-year OS (PD-L1 $\geq$ 1% HR = 0.79 and PD-L1 < 1% HR = 0.64) and 3-year PFS (PD-L1 $\geq$ 1% HR = 0.81 and PD-L1 < 1% HR = 0.75) compared to chemotherapy. Details of the clinical activity and safety profile of nivolumab and ipilimumab in these various malignancies are provided in the USPI and SmPC.

3.3 Benefit/Risk Assessment

Extensive details on the safety profile of nivolumab, ipilimumab, and BMS-986207, including nivolumab in combination with ipilimumab and nivolumab in combination with BMS-986207, are available in the IBs, and will not be repeated herein.[7,8,9]

3.3.1 Risk Assessment

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 (IO) drugs, a general principle is to monitor for immune-mediated adverse events (IMAEs) in various organ systems. To date, BMS-986207 has demonstrated a safe and tolerable profile based on preclinical studies and clinical data from Study CA020002. The nonclinical toxicology assessment of BMS-986207 has demonstrated an acceptable safety profile, supporting clinical use in oncology patients. In vitro treatment of human mononuclear cells with BMS-986207 did not induce markers of lymphocyte activation or cytokine release. Moreover, there was no evidence for CRS in cynomolgus monkeys treated with BMS-986207. In addition, in Study CA020002, BMS-986207 (up to 1600 mg Q4W) in combination with nivolumab or BMS-986207 (600 mg Q3W) in combination with nivolumab and ipilimumab, demonstrated a safe and tolerable profile. Based on the BOIN design in Study CA020002, BMS-986207 600 mg Q3W in combination with nivolumab 360 mg Q3W plus ipilimumab 1 mg/kg Q6W was considered tolerable.

In combination therapy, BMS-986207 may potentiate IMAEs caused by nivolumab and ipilimumab. The safety profile of BMS-986207 in combination with nivolumab plus ipilimumab is expected to have no new categories of AEs compared to combination therapies with either nivolumab plus ipilimumab or BMS-986207 plus nivolumab. The safety profile of 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 in the combination are variable and depend on the specific doses and schedule used. In the dose levels and schedules selected for use in this study, these events were mostly low grade and manageable with the use of corticosteroids. The frequency and types of IMAEs associated with nivolumab and ipilimumab are similar across multiple tumor types and are further described in the Reference Safety Information in their respective IBs.

Participants who develop IMAEs may require prolonged treatment with high dose corticosteroids and other immunosuppressive agents. This could increase the risk of opportunistic infections. IMAE management algorithms in the protocol recommend antibiotic prophylaxis against opportunistic infections in such situations (see Appendix 6). 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.

Whether nivolumab, ipilimumab, and/or BMS-986207 administration increases the risk for contracting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or increases the severity or duration of symptoms is currently unknown. This unknown risk must be considered when enrolling a participant. No additional safety monitoring or routine screening tests will be required due to the SARS-CoV-2 pandemic. Participants with recent or acute infections will be excluded or delay start of treatment. If a participant has a confirmed SARS-CoV-2 infection while on study intervention, dose delay or interruption of study intervention is required to meet the criteria for resuming study intervention (see Section 7.4.2).

The mandated biopsies pose limited risk to the participant, and include discomfort, pain and bleeding. Section 9.8.1 provides guidance on lesions that are appropriate for a research biopsy, and participants who are not able to undergo a biopsy with an acceptable risk can participate in some situations. Because of the need to develop predictive biomarkers for participants treated with BMS-986207 in future studies or the clinical setting, the limited risk of a research biopsy in selected (low risk) participants is considered appropriate. See Table 3.3.1-1 for a summary of risk assessments and mitigation strategies.

Table 3.3.1-1: Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s)		
IMAEs (eg, pneumonitis, colitis, hepatitis, nephritis, endocrinopathy, myocarditis, neurologic and skin AEs)	Nivolumab IB; Ipilimumab IB; BMS-986207 IB	Recommended IMAE management algorithms are included in Appendix 6
Potential Infusion-related Reaction	Nivolumab IB; Ipilimumab IB; BMS-986207 IB	Recommended treatment of infusion-related reactions are included in Section 7.4.4
Study Procedures		
Tumor Biopsy	Limited participant risk including pain, bleeding, and infection	Per institutional protocol/investigator discretion
Phlebotomy	Limited participant risk including pain, ecchymosis, bleeding, and syncope	Per institutional protocol/investigator discretion
Other (if applicable)		
Allergy to Contrast Agent	Potential anaphylaxis	Prophylaxis and/or treatment per institutional protocol/investigator discretion

Abbreviations: AE, adverse event; IB, Investigator's brochure; IMAE, immune-mediated adverse event.

3.3.2 Benefit Assessment

There remains a need to improve long-term outcomes in participants with 1L Stage IV NSCLC. Recent studies using anti-TIGIT antibodies in combination with PD-(L)1 inhibition have shown some clinical benefit in 1L Stage IV NSCLC.[5,6,27] Data from Study CA020002 demonstrates that BMS-986207 when used in combination with nivolumab plus ipilimumab is safe and tolerable, and provides evidence suggesting some preliminary clinical efficacy in participants with advanced solid tumors. CA020016 is one of the first studies to test BMS-986207 in combination with nivolumab plus ipilimumab in 1L NSCLC, thus its potential benefit is not yet known. However, the combination of nivolumab and ipilimumab is approved in the US for the treatment of adults with metastatic NSCLC expressing PD-L1 $\geq$ 1% and was recently approved in Japan for the

treatment of patients with unresectable advanced or recurrent NSCLC independent of PD-L1 status.[3]

3.3.3 Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risk to participants in this study, the potential risks identified in association with combination therapy of BMS-986207 with nivolumab plus ipilimumab are justified by the anticipated benefits that may be afforded to participants with 1L Stage IV NSCLC.

An independent Data Monitoring Committee (DMC) will evaluate safety based on all available data with particular attention to: (i) AEs or other safety trends whose character, severity, and/or frequency suggest that participants would be exposed to an unreasonable and significant risk of illness or injury; (ii) new nonclinical data suggesting unreasonable and significant risk of illness or injury. In addition to the DMC, the Bristol-Myers Squibb Company (BMS) Safety Management Team (SMT) routinely monitors for actual or potential issues related to participant safety, including clinical trial data, information from literature and non-clinical toxicology reports, which could result in a change in the medical risk-benefit balance associated with study treatment. In this study, the SMT will also use quantitative approaches for continuous safety monitoring of specific AE signals (eg, Grade 3 to Grade 4 treatment-related AEs) in addition to their standard review of the safety data (see Section 10.5.1). If a safety signal is detected by the SMT, then an ad hoc DMC meeting may occur to assess the risk/benefit and make recommendations about the safety.

If such evaluation suggests that the risk/benefit profile of the study has become unfavorable to participants, the Sponsor will pause enrollment and/or treatment until further evaluation of data and interaction with the appropriate Health Authority(ies) can take place to discuss potential actions. That may include (but are not limited to) a substantial protocol amendment or termination of the study.

The clinical studies of BMS-986207 have been designed to minimize the overall risk to participants. In Study CA020002, no DLTs were reported in the 6 DLT-evaluable participants treated with BMS-986207 600 mg Q3W in combination with nivolumab plus ipilimumab; thus, this dose was considered tolerable. In comparison to other anti-TIGIT antibodies in development that have a wild type Fc region, BMS-986207 has an inert Fc region that may provide less toxicity in participants when used as monotherapy or in combination with PD-(L)1 or CTLA-4 inhibitors. To minimize potential risks, a lower dose of ipilimumab 1 mg/kg at a 6-week dosing interval will be used, which is also the same dose and dosing interval used in CheckMate 227. All study interventions will occur at infusion centers with medical monitoring and the capability to manage infusion reactions, including anaphylaxis. 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.

Please see Section 7.4.4 for treatment algorithm for infusion reactions and Section 7.4.1 for toxicity management of study intervention.

Nivolumab and ipilimumab combinations have a well-defined toxicity profile based on a safety database of patients treated with the combination across multiple tumor types. Multiple dose administration regimens were evaluated and nivolumab plus low-dose ipilimumab at 1 mg/kg was shown to be safe and tolerable. In CheckMate 227, a TRAE was reported in the majority (76.7%) of participants with 1L NSCLC treated with nivolumab plus ipilimumab while Grade 3 to Grade 4 TRAEs were reported in 32.8% of participants. Moreover, a TRAE leading to discontinuation was reported in 18.1% of participants. A pattern of immune-related adverse events 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.

Non-live coronavirus disease 2019 (COVID-19) vaccination is considered a simple concomitant medication within the study. However, the efficacy and safety of non-live vaccines (including non-live COVID-19 vaccines) in participants receiving nivolumab plus ipilimumab +/- BMS-986207 is unknown.

Additional details on the safety profile of nivolumab and ipilimumab, including results from other clinical studies, are also available in the nivolumab and ipilimumab IBs.[8,9]

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Primary	
• To compare the PFS of BMS-986207 in combination with nivolumab plus ipilimumab (Arm A) versus nivolumab plus ipilimumab (Arm B) in participants with 1L Stage IV NSCLC expressing PD-L1 ≥ 1%	• PFS in participants with tumors expressing PD-L1 ≥ 1% based on RECIST v1.1 by BICR
Secondary	
• To compare the PFS of BMS-986207 in combination with nivolumab plus ipilimumab (Arm A) versus nivolumab plus ipilimumab (Arm B) in all randomized participants with 1L Stage IV NSCLC	• PFS in all randomized participants based on RECIST v1.1 by BICR
• To assess the safety and tolerability of BMS-986207 in combination with nivolumab plus ipilimumab (Arm A) and nivolumab plus ipilimumab (Arm B) in participants with 1L Stage IV NSCLC	• Incidence of AEs, SAEs, AEs leading to discontinuation, and deaths
• To estimate the ORR of BMS-986207 in combination with nivolumab plus ipilimumab (Arm A) and nivolumab plus ipilimumab (Arm B) in all randomized participants with 1L Stage IV NSCLC and in subgroups defined by PD-L1 expression	• ORR in all randomized participants and in subgroups defined by PD-L1 expression (PD-L1 ≥ 1% , < 1%, 1% - 49%, and ≥ 50%) based on RECIST v1.1 by BICR assessment

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
• To compare OS of BMS-986207 in combination with nivolumab plus ipilimumab (Arm A) versus nivolumab plus ipilimumab (Arm B) in randomized participants with tumors expressing PD-L1 ≥ 1%	• OS in participants with tumors expressing PD-L1 ≥ 1%
• To compare OS of BMS-986207 in combination with nivolumab plus ipilimumab (Arm A) versus nivolumab plus ipilimumab (Arm B) in all randomized participants with 1L Stage IV NSCLC	• OS in all randomized participants
• To compare the PFS of BMS-986207 in combination with nivolumab plus ipilimumab (Arm A) versus nivolumab plus ipilimumab (Arm B) in all randomized participants and in participants with tumors expressing PD-L1 ≥ 1% with 1L Stage IV NSCLC	• PFS in all randomized participants and in participants with tumors expressing PD-L1 ≥ 1% based on RECIST v1.1 by investigator's assessment
• To estimate the PFS of BMS-986207 in combination with nivolumab plus ipilimumab (Arm A) and nivolumab plus ipilimumab (Arm B) in participants with 1L Stage IV NSCLC in subgroups defined by PD-L1 expression	• PFS in subgroups defined by PD-L1 expression (PD-L1 < 1%, 1% - 49%, and ≥ 50%) based on RECIST v1.1 by BICR and investigator's assessment
• To estimate the ORR of BMS-986207 in combination with nivolumab plus ipilimumab (Arm A) and nivolumab plus ipilimumab (Arm B) in all randomized participants with 1L Stage IV NSCLC and in subgroups defined by PD-L1 expression	• ORR in all randomized participants and in subgroups defined by PD-L1 expression (PD-L1≥1%, < 1%, 1% - 49%, and ≥ 50%) based on RECIST v1.1 by investigator's assessment
• To estimate the DOR of BMS-986207 in combination with nivolumab plus ipilimumab (Arm A) and nivolumab plus ipilimumab (Arm B) in all randomized participants with 1L Stage IV NSCLC and in subgroups defined by PD-L1 expression	• DOR in all randomized participants and in subgroups defined by PD-L1 expression (PD-L1 < 1%, ≥ 1%, 1% - 49%, and ≥ 50%) based on RECIST v1.1 by BICR and investigator's assessment
• To estimate OS of BMS-986207 in combination with nivolumab plus ipilimumab (Arm A) and nivolumab plus ipilimumab (Arm B) in subgroups defined by PD-L1 expression	• OS in subgroups defined by PD-L1 expression (< 1%, 1% - 49% and ≥ 50%)
Exploratory	
• To characterize the PK and immunogenicity of BMS-986207, nivolumab, and ipilimumab when administered in combination	• Summary measures of Ctrough and EOI concentrations, incidence of ADA to BMS-986207, nivolumab, and ipilimumab, summary measures of ADA titers and kinetics (onset and duration), and assessments of ADA effect on efficacy, safety, and PK
• To explore the pharmacodynamic activity of BMS-986207 administered in combination with nivolumab and ipilimumab via assessment of translational biomarkers	• Summary measures of change (or % change) from baseline in intratumoral and peripheral biomarkers of immune activation and their association with anti-tumor activity

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
• To explore potential associations between anti-tumor activity and select biomarker measures in the tumor and peripheral blood prior to treatment	• Summary measures of anti-tumor activity by pretreatment level of biomarkers of interest
• To characterize the threshold for meaningful change in disease-related symptoms as measured by the NSCLC-SAQ in participants with Stage IV NSCLC	• Analysis of meaningful change threshold for the NSCLC-SAQ total score based on the PGIS and PGIC as anchor measures
• To characterize changes in disease related symptoms and health-related quality of life in participants with Stage IV NSCLC	• Mean change from baseline in NSCLC-SAQ total score and FACT-G7
• To characterize patient-reported health status in participants with Stage IV NSCLC	• Mean change from baseline in EQ-5D-5L utility index and EQ VAS scores

Abbreviations: 1L, first-line; ADA, anti-drug antibody; AE, adverse event; BICR, blinded independent central review; Ctrough, observed serum trough concentration; DOR, duration of response; EOI, end of infusion; EQ-5D-5L, 5 Level EQ-5D Questionnaire; EQ VAS, EuroQol visual analog scale; FACT-G7, Functional Assessment of Cancer Therapy - General - 7 item version; NSCLC, non-small cell lung cancer; NSCLC-SAQ, Non Small Cell Lung Cancer Symptom Assessment Questionnaire; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Severity; PK, pharmacokinetic; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, severe adverse event.

5 STUDY DESIGN

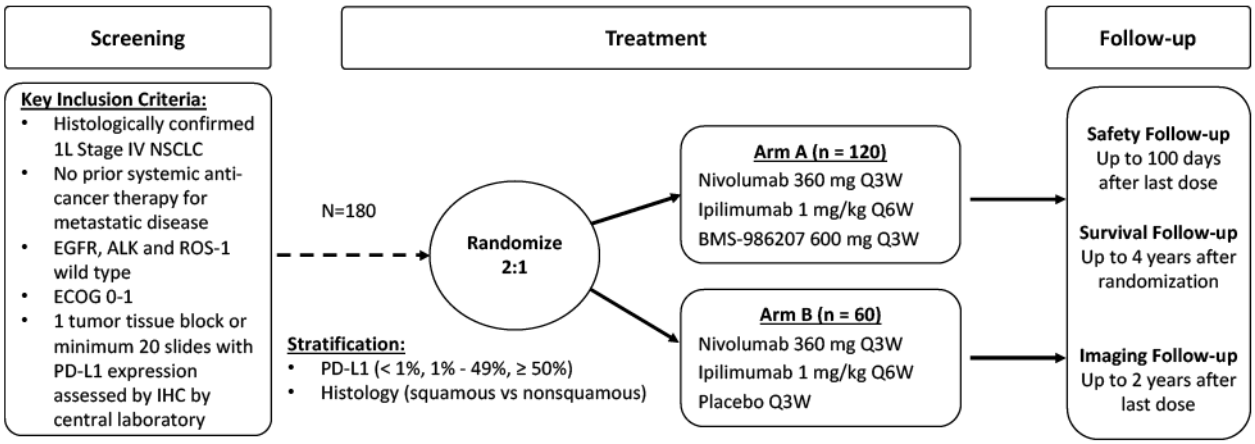
5.1 Overall Design

This multi-center, randomized Phase 2 trial will evaluate the efficacy and safety of BMS-986207 in combination with nivolumab plus ipilimumab versus nivolumab plus ipilimumab in adult participants with 1L Stage IV NSCLC. All participants will complete up to 3 study periods: screening (up to 28 days), treatment (up to 2 calendar years regardless of treatment delays [up to 18 cycles, 42 days/cycle]), safety follow-up (100 days from last dose of study intervention), response follow-up (up to 2 years from last dose of study intervention), and survival follow-up (up to 4 years from randomization). The duration of study participation will be approximately 4 years.

Images will be submitted to a central imaging vendor and may undergo Blinded Independent Central Review (BICR) at any time during the study. Prior to scanning the first participant, sites should be qualified and understand the image acquisition guidelines and submission process as outlined in the CA020016 Imaging Manual provided by the central imaging vendor.

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

Figure 5.1-1: Study Design Schema



Abbreviations: 1L, first-line; ALK, anaplastic lymphoma kinase; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; IHC, immunohistochemistry; N, number; NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1; ROS-1, c-ros oncogene 1; Q3W, every 3 weeks; Q6W, every 6 weeks.

5.1.1 Screening

The screening period will be up to 28 days and begins by establishing the participant's initial eligibility and signing of the informed consent form. Informed consent will be obtained prior to any study-specific procedures. Participants will be evaluated based on the inclusion and exclusion criteria (see Section 6) and will be enrolled using an Interactive Response Technology (IRT).

If a participant exceeds the 28-day screening period due to a study-related procedure (eg, scheduling of a tumor biopsy or waiting for a study-related laboratory value), the participant must be re-consented, 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.

Re-enrollment after screen failure will be allowed. A new participant number will be assigned by the IRT at the time of re-enrollment. Imaging of the brain with magnetic resonance imaging (MRI) (with and without contrast) is required of all participants during Screening. Computed tomography (CT) of the brain (without and with contrast) can be performed if MRI is contraindicated. A 12-lead ECG is required during screening.

Tumor tissue must be obtained and submitted to a central laboratory prior to randomization. See Section 6.1 and Section 9.8.1 for specifications. The central laboratory must confirm receipt of evaluable tumor tissue as described in the Laboratory Manual prior to randomization. Assessment of tumor-cell PD-L1 expression by immunohistochemistry (IHC) must be performed by the central laboratory using pre-treatment tissue sample as described in the Laboratory Manual and results must be reported to IRT prior to randomization.

A pretreatment biopsy is required for enrollment into the study if an archived formalin-fixed paraffin-embedded (FFPE) sample less than 3 months old without any intervening therapy is unavailable for the participant.

5.1.2 Treatment Period

Treatment arms are illustrated in Figure 5.1-1.

The randomized treatment period will assess efficacy and safety of BMS-986207 in combination with nivolumab plus ipilimumab (Arm A) versus nivolumab plus ipilimumab (Arm B).

After central laboratory confirmation of PD-L1 expression, approximately 180 participants (see Section 10.2) will be stratified by PD-L1 expression (< 1%, 1% - 49%, or ≥ 50%) and tumor histology (squamous versus nonsquamous) and randomized in a 2:1 ratio to:

- **Arm A:** Nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W + BMS-986207 600 mg Q3W
- **Arm B:** Nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W + placebo Q3W

Participants, investigators, and site staff will be blinded (single-blind) to treatment assignment. The DMC and Sponsor will be unblinded to treatment assignment for the purpose of safety evaluation. Treatment information access will not be used by the Sponsor to perform by-arm efficacy analyses. See Section 5.1.4 for further information regarding the DMC and Section 7.3 for further information regarding blinding. Additional information regarding blinding will also be provided in the statistical analysis plan (SAP).

All participants will be treated for up to 2 calendar years from start of study intervention regardless of treatment delays (up to 18 cycles, 42 days/cycle), until progression, unacceptable toxicity, death, or withdrawal of consent, whichever occurs first. Continuous safety evaluation and tumor assessment will guide the decision to treat a participant with additional cycles of study intervention if the participant has confirmed clinical benefit (up to a maximum of 2 years).

Dose reductions of study interventions are not permitted. Separate assessments of study interventions will be used in considering criteria for dose delay, resumption, and discontinuation (see Sections 7.4.1, 7.4.2, and 8.1.1).

Physical examinations, vital sign measurements, 12-lead ECG, and clinical laboratory evaluations will be performed at selected times throughout the dosing interval (see Section 2). Participants will be closely monitored for AEs throughout the study. Samples will be collected before and after study drug administration for PK analysis and pharmacodynamic parameter measurements (see Section 9.5 for further details).

Imaging for tumor assessments will be performed according to Section 9.4.5. Participants with unconfirmed progressive disease (PD), stable disease (SD), partial response (PR), or complete response (CR) at the end of a given cycle will continue to the next treatment cycle. Participants will be allowed to continue study intervention until the first occurrence of any of the following:

- Completion of up to 2 calendar years (up to 18 cycles) of study therapy, regardless of treatment delays
- PD defined by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (Appendix 5) per investigator assessment, unless participants meet criteria for treatment beyond progression (Section 8.1.2)

- Clinical deterioration suggesting that no further benefit from treatment is likely
- Intolerability to therapy
- Participant meets criteria for discontinuation of study intervention as shown in Section 8.1

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 with discussion and agreement with Sponsor/Medical Monitor (or designee).

5.1.3 Follow-up Period

5.1.3.1 Safety Follow-up

At the end of treatment (EOT), all participants will enter a safety follow-up period upon completion of study intervention (up to a maximum of 2 years from first dose of study intervention, if applicable) or once the decision is made to discontinue the participant from treatment.

All participants will be evaluated for any new AEs (serious and non-serious) for at least 100 days after the last dose of study intervention. Follow-up visits should occur at Days 30, 60, and 100 (± 7 days for all study visits) after the last dose or date of discontinuation.

5.1.3.2 Imaging Follow-up

Participants that have discontinued treatment without having BICR-assessed disease progression will continue to have radiologic tumor assessments after treatment discontinuation for up to 2 years after last dose of study intervention as per Table 2-3 (see Section 9.1.1 for further details).

5.1.3.3 Survival Follow-up

Participants will be followed by phone contact or office visit every 12 weeks (± 2 weeks) until death, loss to follow-up, withdrawal of consent, or conclusion of the study, whichever comes first, for a period of up to 4 years from randomization. A follow-up more than 4 years after randomization could be considered in selected cases if an efficacy signal is apparent. Subsequent therapies will also be recorded in this survival follow-up period.

5.1.4 DMC and Other Committees

An independent DMC will be utilized to provide general oversight and safety considerations during the study. The independent DMC will provide advice to the Sponsor regarding actions the committee deems necessary for the continuing protection of participants enrolled in this study. The independent DMC will be charged with assessing such actions in light of an acceptable benefit-risk profile for nivolumab, ipilimumab, and BMS-986207. The independent DMC will act in an advisory capacity to BMS and will monitor participant safety data of the study.

BMS will have responsibility for the overall conduct of the study, including managing the communication of study data. BMS will be responsible for promptly reviewing the DMC recommendations, for providing guidance regarding the continuation or termination of the study, and for determining whether amendments to the protocol or changes to the study conduct are required. The DMC charter will describe the procedures related to the committee operations in

greater detail and will include an initial safety review after the first 12 randomized safety-evaluable participants have completed 6 weeks of treatment.

In addition to the DMC, BMS has in place a multi-layered process for ensuring participant safety through close collaboration of study site investigators, the BMS study team, and the BMS Worldwide Patient Safety (WWPS)-led SMT. This collaborative process constitutes the Data Safety Monitoring Plan for the study as detailed below.

- Study safety is evaluated continuously by representatives of BMS WWPS, who operate independently from the clinical team and monitor safety across all BMS protocols. AEs are monitored continuously by WWPS. Signal detection is performed at least monthly and ad hoc throughout the study by the SMT and composed, at a minimum, of the WWPS medical safety assessment physician (Chair of the SMT) and WWPS single-case review physician, the study Sponsor/Medical Monitor (or designee), the study biostatistician, pharmacovigilance scientist, and the epidemiologist. The SMT monitors actual or potential issues related to participant safety that could result in a significant change in the medical benefit-risk balance associated with the use of study intervention. Furthermore, investigators will be kept updated of important safety information during teleconferences between investigators and the BMS clinical team, which will be held on a regularly scheduled basis. If appropriate, select safety issues may be escalated to a senior-level, multidisciplinary, BMS-wide Medical Review Group for further evaluation and action. To support safety oversight, BMS has established an ongoing processes for collection, review, analysis, and submission of individual AE reports and their aggregate analyses.
- The SMT will review the totality of the safety data available throughout the study. Safety data will be continuously monitored and will be informed by a Bayesian framework (see Section 10.5.1). After considering overall safety and if an excessive number of pre-specified safety events are observed, an ad hoc data review by the DMC will be considered as needed.

The minutes of these meetings will be documented in the Trial Master File. The SMT will not share responsibilities with the DMC. Decisions on safety, toxicity, and benefit-risk will be solely the responsibility of BMS and will take account of the totality of the data available and in consideration of any DMC recommendations (see Section 3.3 for additional details).

5.1.5 Blinded Independent Radiology Central Review

A BICR is recommended by regulatory agencies in situations where clinical site image interpretation is variable and results of image measurements are important for eligibility determination, safety, and/or efficacy endpoints. Specifically, BICR review of scans may mitigate bias regarding endpoint assessment due to the subjectivity involved in lesion measurement and interpretation of PFS. Sites should submit all images to BICR on a continuing basis. However, should the BICR interpretation be in conflict with the local evaluation, treatment decisions will be based on investigator assessment and not the BICR results provided to the site.

5.2 Number of Participants

Approximately 180 randomized participants are expected to be randomized in a 2:1 ratio to the 2 treatment arms stratified by PD-L1 expression and histology in pre-specified subgroups.

To ensure the randomized population is representative of the NSCLC population and to allow for appropriate subgroup analyses, total enrollment and/or enrollment in specific PD-L1 subgroups may be adjusted to ensure enrollment of at least 105 randomized participants with tumor cell PD-L1 expression ≥ 1% with at least 75 randomized participants with tumor cell PD-L1 expression 1% - 49%, and at least 75 randomized participants with tumor cell PD-L1 expression < 1%, based on central laboratory results.

5.3 End of Study Definition

The start of the trial is defined as the first participant first visit or first participant screened or scheduled procedure shown in the Schedule of Activities (see Section 2).

End of trial is defined as the last participant last visit or scheduled procedure shown in the Schedule of Activities (see Section 2) for the last participant, whichever occurs later.

Study completion is defined as the final date on which data for the primary endpoint was or is expected to be collected, if this is not the same.

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

5.4 Scientific Rationale for Study Design

The purpose of this study is to evaluate BMS-986207 in combination with nivolumab plus ipilimumab, in participants with 1L Stage IV NSCLC.

The study design includes the following:

- Exclusion of participants with known epidermal growth factor (EGFR), anaplastic lymphoma kinase (ALK), c-ros oncogene 1 (ROS-1), and B-rapidly accelerated fibrosarcoma proto-oncogene (BRAF) V600E alterations
- Nivolumab and ipilimumab as backbone therapy
- Combination with BMS-986207, nivolumab, and ipilimumab
- Up to 2 years duration of treatment
- Allowance for continued treatment in select cases of PD
- Single-blind design
- Stratification by histology (squamous versus nonsquamous) and PD-L1 expression (< 1%, 1% - 49%, or ≥ 50%)
- PFS as a primary endpoint
- Clinical outcomes assessments

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

5.4.1 Rationale for Exclusion of Participants with Known EGFR, ALK, ROS-1, and BRAF V600E Alterations

First-line standard of care for participants with clinically actionable alterations (eg, EGFR mutation, ALK translocation, ROS-1 rearrangements and BRAF V600E) is targeted therapy rather

than immunotherapy and/or chemotherapy. Participants known to have these abnormalities will be excluded from this study. Excluding these participants will help to reduce the potentially confounding effects of these alterations on the study endpoints. EGFR-mutant tumors commonly display lower tumor infiltrating lymphocytes (TILs), PD-L1 expression, and tumor mutational burden (TMB) than EGFR-wild-type tumors. Consistent with this, patients with EGFR-mutated carcinomas derive less clinical benefit from PD-1 axis blockade. In addition, clinical trials have demonstrated that patients with actionable molecular alterations such as EGFR mutations or ALK translocations have lower response rates to checkpoint inhibition with PD-(L)1 inhibitors. Treatments for EGFR mutations, ALK translocations, ROS-1 rearrangements, and BRAF V600E mutations have shown impressive results and are now Food and Drug Administration (FDA)-approved in NSCLC. Since BRAF V600E is not yet widely tested, it will not be a requirement to test for BRAF mutations at screening in this study. However, participants with a known BRAF V600E mutation will be excluded.

5.4.2 Rationale for Nivolumab and Ipilimumab as Backbone in NSCLC

Immunotherapeutic approaches such as checkpoint pathway blockade have demonstrated clinical efficacy in several cancers, including melanoma, renal cell, lung, and hormone-refractory prostate cancers. The combination of nivolumab and ipilimumab has distinct but complementary mechanisms of actions: nivolumab restores anti-tumor T-cell function; while ipilimumab induces de novo anti-tumor T-cell responses, including an increase in memory T cells.

CheckMate 227 is a randomized, open-label Phase 3 study in participants with treatment-naive advanced NSCLC.[2] Participants with PD-L1 expression ≥ 1% were randomized in a 1:1:1 ratio to receive nivolumab alone, nivolumab plus ipilimumab, or chemotherapy; those with PD-L1 expression < 1% were randomly assigned in a 1:1:1 ratio to receive nivolumab (3 mg/kg Q2W) plus ipilimumab (1 mg/kg Q6W), nivolumab (360 mg Q3W) plus chemotherapy, or chemotherapy. The study met its primary endpoint with a statistically significant improvement in OS for nivolumab plus ipilimumab versus chemotherapy in participants with PD-L1 ≥ 1% (median 3-year OS = 17.1 versus 14.9 months, HR = 0.79, 97.5% confidence interval [CI]: 0.65 to 0.96). The survival benefit of nivolumab plus ipilimumab versus chemotherapy was also demonstrated in those with PD-L1 expression < 1% (median 3-year OS = 17.2 months versus 12.2 months, HR = 0.62, 97.5% CI: 0.47 to 0.81). Overall, nivolumab plus ipilimumab treatment resulted in prolonged OS in comparison to chemotherapy (median OS = 17.1 months versus 13.9 months) (see Table 5.4.2-1). There were no new safety findings with Grade 3 or 4 treatment-related AEs reported in 32.8% of participants receiving nivolumab plus ipilimumab versus 36.0% of participants receiving chemotherapy.[28]

This dual immunotherapy regimen is a novel chemo-sparing first-line treatment option for advanced NSCLC. The combination of nivolumab and ipilimumab is approved in the US for the treatment of adults with metastatic NSCLC expressing PD-L1 ≥ 1% and was recently approved in Japan for the treatment of patients with unresectable advanced or recurrent NSCLC independent of PD-L1. The combination is a National Comprehensive Cancer Network (NCCN) recommended

intervention (category 1) for adults with metastatic NSCLC expressing PD-L1 ≥ 50%, 1% - 49%, and < 1%.[29]

Table 5.4.2-1: Efficacy of Nivolumab + Ipilimumab vs Chemotherapy by Tumor PD-L1 Expression Level - CA209227 Part 1a and Part 1b

	PD-L1 < 1% (Part 1b)		PD-L1 ≥ 1% (Part 1a)		PD-L1 1% - 49% (Part 1a)		PD-L1 ≥ 50% (Part 1a)	
	Nivo + Ipi N = 187	Chemo N = 186	Nivo + Ipi N = 396	Chemo N = 397	Nivo + Ipi N = 191	Chemo N = 205	Nivo + Ipi N = 205	Chemo N = 192
OS								
HR (97.5% CI)	0.62 (0.47, 0.81)		0.79 (0.65, 0.96)		0.94 (0.73, 1.22)		0.70 (0.53, 0.93)	
Median	17.15	12.19	17.08	14.88	15.08	15.08	21.19	13.96
(95% CI), mo.	(12.85, 22.05)	(9.17, 14.32)	(14.95, 20.07)	(12.71, 16.72)	(12.16, 18.66)	(13.34, 17.54)	(15.51, 38.18)	(10.05, 18.60)
PFS per BICR (1° Definition)								
HR (97.5% CI)	0.75 (0.57, 0.99)		0.83 (0.69, 1.01)		1.15 (0.89, 1.50)		0.62 (0.47, 0.82)	
Median	5.06	4.70	5.06	5.55	4.01	5.49	6.74	5.59
(95% CI), mo.	(3.15, 6.37)	(4.21, 5.59)	(4.07, 6.31)	(4.63, 5.82)	(2.99, 5.52)	(4.37, 5.82)	(4.53, 11.01)	(4.57, 6.60)
ORR per BICR (CR + PR)								
Responders (%)	51 (27.3)	43 (23.1)	142 (35.9)	119 (30.0)	51 (26.7)	51 (24.9)	91 (44.4)	68 (35.4)
95% CI	(21.0, 34.3)	(17.3, 29.8)	(31.1, 40.8)	(25.5, 34.7)	(20.6, 33.6)	(19.1, 31.4)	(37.5, 51.5)	(28.7. 42.6)
DOR per BICR								
Median	17.97	4.83	23.16	6.24	12.22	7.59	31.84	5.75
(95% CI), mo.	(12.42, 28.65)	(3.71, 5.78)	(15.21, 32.16)	(5.59, 7.39)	(6.14, 16.07)	(6.24, 12.45)	(18.66, NA)	(4.47, 6.90)

Abbreviations: BICR, blinded independent central review; chemo, chemotherapy; CI, confidence interval; CR, complete response; CSR, clinical study report; DOR, duration of response; HR, hazard ratio; Ipi, ipilimumab; Nivo, nivolumab; Nivo + Ipi, nivolumab + ipilimumab; N, number; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PR, partial response.

Source: Table 7.1.1.1-1 (Part 1a), Table 7.1.2-1 (Part 1b), (Figure S.5.120.5.309 (PFS-BICR), Figure S.5.326.4 9 (ORR-BICR), Table S.5.500.12 (PD-L1 1% - 49% DOR), Table S.5.128.1 (PD-L1 ≥ 50% DOR), and Table S.5.126.1.1 (PD-L1 ≥ 50% ORR-BICR), Table S.5.500.24 (PD-L1 ≥ 50% OS), Table S.5.500.25 (PD-L1 ≥ 50% PFS) of CA209227 Part 1 Final CSR.

5.4.3 Rationale for Combination with BMS-986207, Nivolumab, and Ipilimumab in NSCLC

Despite clinical efficacy observed with nivolumab plus ipilimumab in NSCLC, resistance to treatment persists. TIGIT upregulation has been observed in cancer patients, in particular on T cells, and is co-expressed with markers of T cell exhaustion. Blockade of TIGIT with BMS-986207 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. Thus, BMS-986207 may be a novel therapeutic partner to overcome resistance by targeting both T and NK cells when used in combination with nivolumab and ipilimumab in NSCLC.

Combining anti-TIGIT and anti-PD-(L)1 agents have demonstrated clinical benefit in several studies.[5,6,27] In Phase 1/2a study CA020002, BMS-986207 in combination with nivolumab showed clinical benefit in participants with melanoma (n = 2 participants) and prostate cancer (n = 1 participant) that had best overall responses (BORs) consistent with PR (preliminary results). In a randomized Phase 2 study conducted in 1L Stage IV NSCLC participants comparing the anti-TIGIT agent tiragolumab plus atezolizumab versus placebo plus atezolizumab, clinically meaningful improvement was observed in the tiragolumab plus atezolizumab group with high PD-L1 (≥ 50% PD-L1) expression: ORR (66% versus 24%) and PFS (HR: 0.30, 95% CI: 0.15 to 0.61). The treatment regimen was well tolerated, with safety similar to that seen in the placebo plus atezolizumab treatment.[5] In addition, recent data presented from a Phase 1 study (NCT02964013) of vibostolimab, an anti-TIGIT antibody, plus pembrolizumab in participants with anti-PD-(L)1-naive NSCLC demonstrated promising anti-tumor activity (ORR 46% and median PFS 8.4 months in TPS ≥ 1%).[6] These data suggest combining TIGIT blockade with anti-PD-(L)1 can be safe, tolerable, and have clinical benefit.

In the proposed study, the combination of BMS-986207, nivolumab, and ipilimumab will be tested in 1L Stage IV NSCLC with participants stratified by PD-L1 expression and histology. Anti-TIGIT agents and anti-PD-(L)1 agents showed clinical benefit when used in combination, in particular in PD-L1 positive tumors. Nivolumab plus ipilimumab is efficacious in 1L Stage IV NSCLC, with ipilimumab providing a unique mechanism of action that adds benefit, especially for tumors with PD-L1 expression < 1%. The combination of BMS-986207, nivolumab, and ipilimumab is expected to have a synergistic effect in the 1L Stage IV NSCLC population based on the preclinical and clinical activity of the combinations (BMS-986207 plus nivolumab plus ipilimumab, nivolumab plus ipilimumab, anti-TIGIT plus anti-PD-(L)1, and anti-TIGIT plus anti-CTLA-4) and their complementary mechanisms of action.

5.4.4 Rationale for Up to 2-Year Duration of Treatment

The optimal duration of immunotherapy is an important question and continues to be investigated. Clinical trials across different tumor types in the nivolumab and ipilimumab development program indicate that most of the responses occur early, with a median time to response of 2-4 months, and emerging data suggests that benefit can be maintained in the absence of continued treatment. A retrospective pooled analysis of two melanoma studies suggest the majority of patients who discontinue nivolumab and/or ipilimumab for toxicity maintain disease control in the absence of

further treatment.[30] Furthermore, a limited duration of ipilimumab, including only 4 induction doses, resulted in long term survival in patients with metastatic melanoma, with a sustained plateau in survival starting around 2 years after the start of treatment.[31]

Accumulating data suggest that 2 years of PD-1 checkpoint inhibitor treatment may be sufficient for long term benefit. CA209003, a dose-escalation cohort expansion trial evaluating the safety and clinical activity of nivolumab in patients with previously treated advanced solid tumors (including 129 patients with NSCLC), specified a maximum treatment duration of 2 years. Among 16 patients with NSCLC who discontinued nivolumab after completing 2 years of treatment, 12 patients were alive > 5 years and remained progression-free without any subsequent therapy. In the CA209003 NSCLC cohort, the OS curve begins to plateau after 2 years, with an OS rate of 25% at 2 years and 18% at 3 years.[32] These survival outcomes are similar to Phase 3 studies in previously treated NSCLC, in which nivolumab treatment was continued until progression or unacceptable toxicity (2 year OS rates of 23% and 29%, and 3 year OS rates of 16%-18% for squamous and nonsquamous NSCLC respectively).[33]

Taken together, these data suggest that treatment beyond 2 years is unlikely to confer additional clinically meaningful benefit and that the risk of progression after discontinuing treatment at 2 years is low.

In contrast, a shorter duration of nivolumab of only 1 year was associated with increased risk of progression in previously treated patients with NSCLC, suggesting that treatment beyond 1 year is likely needed. In CA209153, patients with previously treated advanced NSCLC who completed 1 year of nivolumab therapy were randomized to either continue or stop treatment, with the option of retreatment upon progression. Among 163 patients still on treatment at 1 year and without progression, those who were randomized to continue nivolumab had significant improvement in PFS compared to those who were randomized to stop treatment, with median PFS (post-randomization) not reached versus 10.3 months, respectively; HR = 0.42 (95% CI, 0.25 to 0.71). With a median follow-up of 14.9 months post-randomization, there also was a trend for patients on continued treatment to live longer (OS HR = 0.63 [95% CI: 0.33, 1.20]). Of note, the PFS curves in both groups plateau approximately 1 year after randomization (ie, 2 years after treatment initiation), suggesting that there may be minimal benefit in extending treatment beyond a total of 2 years.[34]

Collectively, these data suggest that there is minimal if any benefit derived from continuing IO treatment beyond two years in advanced tumors. Even though immunotherapy is well tolerated, patients will be at risk for additional toxicity with longer term treatment. Therefore, in this study, treatment will be given for up to a maximum of 2 years from the start of study intervention.

5.4.5 Rationale for Permitting Continued Treatment in Select Cases of Progressive Disease

Accumulating clinical evidence indicates some participants treated with immune system-stimulating agents may develop progression of disease (by conventional response criteria) before demonstrating clinical response and/or SD. This phenomenon was observed in approximately 10%

of participants in the Phase 1 study of nivolumab and has been observed with ipilimumab monotherapy as well, suggesting that it is not a drug-specific occurrence.

Two hypotheses have been put forth to explain this phenomenon. 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, participants will be allowed to continue immunotherapy after initial investigator-assessed RECIST v1.1-defined progression if they are assessed to be deriving clinical benefit and tolerating study drug. Such participants must discontinue study therapy upon evidence of further progression as defined in Section 8.1.2.

5.4.6 Rationale for Stratification

To minimize the potential for imbalances across treatment arms, there will be 2 stratification factors utilized in this trial: histology (squamous versus nonsquamous) and tumors PD-L1 expression (< 1%, 1% - 49%, ≥ 50%).

The prognostic implications of histology are well established, even before the advent of immunotherapy, hence different chemotherapy regimens are indicated according to histology.

With regard to PD-L1 expression, previous clinical studies with nivolumab monotherapy have shown participants with PD-L1 positive tumors may have better outcomes with PD-1-based therapies than those with nonexpression. In the CheckMate 227 study, PD-L1 status may impact response to treatment with nivolumab plus ipilimumab (see Table 5.4.2-1). Participants in the current trial will therefore be stratified by PD-L1 status as the effect of PD-L1 expression on response to anti-PD-1, anti-CTLA-4, and anti-TIGIT combination therapies is not yet known.

5.4.7 Rationale for Blinding

Participants, investigators, and site staff will be blinded (single-blind) to BMS-986207 treatment assignment. The DMC and Sponsor will be unblinded to BMS-986207 treatment assignment. A single-blind will be implemented in order to:

- Minimize investigator bias (eg, avoid biased estimate of treatment effect)
- Curtail investigator bias in reporting, classification, and management of AEs
- Permit unblinded safety monitoring by Sponsor (see Section 10.5.1 and additional information will be provided in the SAP) that is in addition to the safety monitoring by the DMC. Treatment information access will not be used by the Sponsor to perform by-arm efficacy analyses.

Single-blinding will be maintained for participants who progress even after disease progression, unless needed by the investigator (eg, selection of subsequent therapies). See Section 7.3 for additional information.

5.4.8 Rationale for PFS as a Primary Endpoint

Treatment options that are clinically active are increasingly available in patients with unresectable or Stage IV or recurrent NSCLC and their use after disease progression on the current study may confound an OS endpoint. PFS is not confounded by post-study intervention therapies and has been demonstrated to correlate with OS in a recent analysis of IO NSCLC trials published at American Society of Clinical Oncology (ASCO) 2018.[35] The study, which explored immunotherapy treatments in NSCLC using the SMARTImmuno-Oncology repository, reported that median PFS correlated well with median OS in anti-PD-1 trials (correlation range: r = 0.82 - 0.84).

5.4.9 Rationale for Clinical Outcomes Assessments

The evaluation of the participant's experience in the evaluation of biopharmaceutical treatments is important to fully understand the impact of such products on how participants feel and function. Patient-reported outcomes (PROs) have been incorporated in oncology trials in order to more fully understand the participant's experience. In addition, there is an increased focus from the clinical community on the specific concepts that are influenced by therapeutic products, including disease-related symptoms, symptomatic AEs, and physical functioning. When used in tandem with traditional clinical measures, the Non-small Cell Lung Cancer-Symptom Assessment Questionnaire (NSCLC-SAQ) can provide additional context for safety and efficacy results. In the current trial, the participant's experience will be directly measured through the NSCLC-SAQ, the Functional Assessment of Cancer Therapy - General 7 item version (FACT-G7), 5 level EQ-5D (EQ-5D-5L) questionnaire, the Patient Global Impression of Severity (PGIS), and the Patient Global Impression of Change (PGIC). The Center for Drug Evaluation and Research has determined that the NSCLC-SAQ demonstrated adequate evidence of content validity and cross-sectional measurement properties (ie, internal consistency reliability, test-retest reliability, convergent validity, and known-groups validity) to measure symptoms of NSCLC in the context of the participant population being studied in this trial.

PRO data will be collected in this trial. PRO data from this trial will also be used to conduct additional psychometric analyses of the longitudinal properties of the NSCLC-SAQ including the use of the PGIS and PGIC as anchor measures when evaluating these additional psychometric analyses. These analyses will be described in a separate PRO Statistical Analyses Plan.

5.5 Justification for Dose

In this study, participants will receive BMS-986207 600 mg Q3W in combination with nivolumab 360 mg Q3W plus ipilimumab 1 mg/kg Q6W in participants with 1L NSCLC. Detailed justification for each drug is provided below (see Sections 5.5.1, 5.5.2, and 5.5.3).

5.5.1 BMS-986207

The safety of BMS-986207 was evaluated in participants with advanced solid tumors in study CA020002, with a maximum clinical dose tested at 1600 mg Q2W for monotherapy, 1600 mg Q4W in combination with nivolumab, and 1200 mg in combination with nivolumab plus ipilimumab. In monotherapy and in combination with nivolumab, no DLT was identified at any

doses, and there was no relationship between the incidence, severity, or causality of AEs and the BMS-986207 dose levels (see Sections 3.2.2.4 and 3.2.2.5). In combination with nivolumab plus ipilimumab, based on the BOIN design, BMS-986207 600 mg Q3W in combination with nivolumab plus ipilimumab was considered tolerable with no DLTs observed at this dose level (see Section 3.2.2.6).

The PK of BMS-986207 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 study 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. For participants who received combination treatment of BMS-986207 and nivolumab in Part 1B, the PK of BMS-986207 appears to be consistent with that reported for monotherapy in Parts 1A and 2A.[7]

BMS-986207 will be administered at a dose of 600 mg Q3W in combination with nivolumab and ipilimumab in participants with 1L Stage IV NSCLC. The selection of BMS-986207 600 mg Q3W regimen was based on the following rationale: (i) DLTs were observed at 1200 mg Q3W in combination with nivolumab 360 mg Q3W and ipilimumab 1 mg/kg Q6W in Study CA020002, resulting in de-escalation of BMS-986207 to 600 mg Q3W, which was well tolerated and did not result in DLTs (see Section 3.2.2.6); (ii) BMS-986207 exposures appear reasonably proportional across the dose range evaluated to date; (iii) available tumor penetration data from the Phase 1 study suggest that the 600 mg dose is predicted to have > 80% intratumoral TIGIT receptor occupancy at trough level, which may provide positive clinical benefit; (iv) the every-3-weeks dosing regimen allows for aligning the schedule of BMS-986207 with the combination of nivolumab Q3W and ipilimumab Q6W in 1L Stage IV NSCLC.

5.5.2 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.

Nivolumab is also approved in combination with ipilimumab for the treatment of various cancers, including melanoma, RCC, CRC, and HCC with dosing regimen of 1 mg/kg Q3W or 3 mg/kg Q3W for 4 doses, depending on tumor type, then 240 mg Q2W or 480 mg Q4W. In addition, nivolumab 360 mg Q3W and 3 mg/kg Q2W are approved for the treatment of 1L Stage IV NSCLC in combination with ipilimumab 1 mg/kg Q6W plus 2 cycles of chemotherapy and with ipilimumab, respectively. Nivolumab 360 mg Q3W in combination with ipilimumab 1 mg/kg Q6W is also approved for the treatment of 1L mesothelioma.[23] Based on quantitative clinical pharmacology and linear pharmacokinetics of nivolumab, nivolumab exposure is expected to be similar between 3 mg/kg Q2W and 360 mg Q3W. A Q3W regimen will offer a less frequent and more convenient option for participants and health care providers for participants to receive BMS-986207, nivolumab, and ipilimumab on the same dose day.

Since the primary efficacy evaluation in this study will be in participants with 1L Stage IV NSCLC, nivolumab will be administered as 360 mg Q3W infused over approximately 30 minutes, one of

the approved combination regimen for this indication, in combination with ipilimumab and BMS-986207 or with ipilimumab and BMS-986207 placebo.

5.5.3 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.

In addition, a less frequent but continuous ipilimumab regimen (1 mg/kg Q6W) was 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. In 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 standard of care 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.[25]

Based on the clinical experience, low-dose ipilimumab 1 mg/kg Q6W infused over approximately 30 minutes will be used in combination with nivolumab plus BMS-986207 or its placebo for participants with 1L NSCLC in this study.

6 STUDY POPULATION

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

6.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1) Signed Written Informed Consent

a) Participants must have signed and dated an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved written informed consent form (ICF) in accordance with regulatory, local, and institutional guidelines. This must be obtained before the performance of any protocol-related procedures that are not part of normal patient care.

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

2) Type of Participant and Target Disease Characteristics

a) Histologically confirmed metastatic 1L Stage IV NSCLC of squamous or nonsquamous histology (as defined by the 8th International Association for the Study of Lung Cancer Classification).

b) A FFPE tumor tissue block (preferred, equivalent to 20 sections) or a minimum of 20 unstained slides* of tumor tissue 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 prior to randomization. Samples may be from core biopsy, punch biopsy, excisional biopsy or surgical specimen. Fine needle aspirates or other cytology samples are NOT acceptable. Central laboratory must confirm receipt of evaluable tumor tissue as described in the Laboratory Manual prior to randomization. Assessment of tumor-cell PD-L1 expression by IHC also must be performed by central laboratory using pre-treatment tissue sample, and results must be reported to IRT prior to randomization.

Note: Please refer to Section 9.8 for additional details on tumor tissue requirements

*If despite best efforts, a minimum of 20 slides is not obtainable, submission of fewer slides may be acceptable in some circumstances following discussion with Sponsor or designee.

c) Participants should not have received any systemic anti-cancer therapy after the date that the submitted tumor tissue was obtained.

d) No prior systemic anti-cancer treatment (including EGFR, ROS-1, BRAF, and ALK inhibitors) given as primary therapy for advanced or metastatic NSCLC.

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

f) Prior adjuvant or neoadjuvant chemotherapy for early-stage lung cancer is permitted if completed at least 6 months prior to enrollment.

g) Prior palliative radiotherapy to non-central nervous system (CNS) lesions must have been completed at least 2 weeks prior to treatment. 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.

h) Measurable disease per RECIST v1.1.

i) Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 at screening and confirmed prior to randomization.

j) Participants must have a life expectancy of at least 3 months at the time of first dose.

3) Age of Participant

a) Participant must be at least 18 years old or local age of majority at the time of signing the informed consent.

4) Reproductive Status

- Investigators shall counsel women of childbearing potential (WOCBP) participants, and male participants who are sexually active with WOCBP, on the importance of pregnancy prevention and the implications of an unexpected pregnancy.
- The investigator shall evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.
- Local laws and regulations may require the use of alternative and/or additional contraception methods.

a) Female Participants:

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

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

iii) WOCBP must have a negative highly sensitive serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study intervention.

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

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

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

v) 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

b) Male Participants:

i) Male participants should maintain their usual practice with regard to contraception (if any); however, no specific contraceptive measures are required. Please see Appendix 4 for further information on contraception methods.

6.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1) Medical Conditions

a) Mutation status

i) Participants 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 nonsquamous histology must have been tested for EGFR mutation status; use of an FDA (or local

Health Authority)-approved test is strongly encouraged. Participants with nonsquamous histology and unknown or indeterminate EGFR status are excluded.

ii) ALK translocations which are sensitive to available targeted inhibitor therapy are excluded. All participants with nonsquamous histology must have been tested for ALK mutation status; use of an FDA-approved or local Health Authority test is strongly encouraged. Participants with nonsquamous histology and unknown ALK status are excluded.

iii) ROS-1 translocations which are sensitive to available targeted inhibitor therapy are excluded. All participants with nonsquamous histology must have been tested for ROS-1 translocation status. Participants with nonsquamous histology and unknown ROS-1 status are excluded.

iv) Known BRAF V600E mutations which are sensitive to available targeted inhibitor therapy are excluded. If BRAF mutation status is unknown or indeterminate, participant may enroll.

b) Untreated CNS metastases. Participants are eligible if CNS metastases have been treated and participants have neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment). In addition, participants must have been either off corticosteroids, or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent) for at least 2 weeks prior to randomization. Imaging performed within 28 days prior to randomization must document radiographic stability of CNS lesions and be performed after completion of any CNS directed therapy.

c) Participants with leptomeningeal metastases (carcinomatous meningitis).

d) Concurrent malignancy (present during screening) requiring treatment or history of prior malignancy active within 2 years prior to randomization (ie, participants with a history of prior malignancy are eligible if treatment was completed at least 2 years before randomization and the participant has no evidence of disease). Participants with history of prior early stage basal/squamous cell skin cancer or non-invasive or in situ cancers that have undergone definitive treatment at any time are also eligible.

e) Participants with an active, known or suspected autoimmune disease. Participants with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

f) Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) within 14 days or other immunosuppressive medications within 30 days of randomization. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

g) Prior organ or tissue allograft

h) Participants with interstitial lung disease.

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

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

ii) Uncontrolled angina within the past 3 months

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

iv) 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)

v) Cardiovascular disease-related requirement for daily supplemental oxygen therapy

vi) QT interval corrected for heart rate using Fridericia's formula (QTcF) prolongation > 480 msec, except for right bundle branch block

vii) History of myocarditis, regardless of etiology

j) Known human immunodeficiency virus (HIV) positive with an AIDS defining opportunistic infection within the last year, or a current CD4 count < 350 cells/µL. Participants with HIV are eligible if:

i) They have received antiretroviral therapy (ART) for at least 4 weeks prior to treatment assignment or randomization as clinically indicated while enrolled on study

ii) They continue on ART as clinically indicated while enrolled on study

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

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

k) Participants with serious or uncontrolled medical disorders.

l) Participants who have not recovered from the effects of major surgery or significant traumatic injury at least 14 days before first treatment.

m) Known medical condition that, in the investigator's opinion, would increase the risk associated with study participation or study drug administration or interfere with the interpretation of safety results.

n) 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.

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

i) Acute symptoms must have resolved and based on investigator assessment in consultation with the Sponsor/Medical Monitor (or designee), there are no sequelae that would place the participant at a higher risk of receiving study intervention.

2) Reproductive Status

a) Women who are pregnant or breastfeeding

3) Prior/Concomitant Therapy

a) Prior treatment with anti-TIGIT, anti-PD-1, anti-PD-(L)1, anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4) antibody or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways.

b) Use of immunosuppressive agents, other than systemic corticosteroids, within 30 days of randomization

c) Use of immunosuppressive doses of systemic corticosteroids within 14 days of randomization

d) Any concurrent anti-neoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive non-palliative radiation therapy, or standard or investigational agents for treatment of NSCLC).

e) Treatment with any live/attenuated vaccine within 30 days of first study intervention.

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

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

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

h) Prior radiation therapy within 2 weeks prior to first study treatment. Participants must have recovered (ie, Grade ≤ 1 or at baseline) from radiation-related toxicities prior to first study intervention.

4) Physical and Laboratory Test Findings

a) WBC < 2000/µL

b) Neutrophils < 1500/µL

c) Platelets < 100 x 10^3/µL

d) Hemoglobin < 9.0 g/dL

e) Serum creatinine > 1.5 x upper limit of normal (ULN), unless creatinine clearance ≥ 40 mL/min (measured or calculated using the Cockcroft-Gault formula)

f) AST/ALT: > 3.0 x ULN

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

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

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

5) Allergies and Adverse Drug Reaction

a) History of allergy or hypersensitivity to study drug components

6) Other Exclusion Criteria

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

b) Any other serious or uncontrolled medical disorder, active infection, physical exam finding, laboratory finding, altered mental status, or psychiatric condition that, in the opinion of the investigator, would limit a participant's ability to comply with the study requirements, substantially increase risk to the participant, or impact the interpretability of study results.
c) Any other sound medical, psychiatric, and/or social reason as determined by the investigator

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

6.3 Lifestyle Restrictions

Not applicable. No restrictions are required.

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but who are not subsequently randomized in the study/included in the analysis population.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, as applicable, and to respond to queries from regulatory authorities. Minimal information includes date of consent, demography, screen failure details, eligibility criteria, and any serious AEs.

6.4.1 Retesting During Screening

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

Retesting of laboratory parameters and/or other assessments within any single Screening period will be permitted (in addition to any parameters that require a confirmatory value).

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

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

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

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

In the instance of a SARS-CoV-2 infection during screening, the screening period may be extended beyond the protocol-specified timeframe with the Sponsor/Medical Monitor (or designee) 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 Sponsor/Medical Monitor (or designee) (eg, safety labs, SpO2, chest computed tomography [CT scan]) should be repeated.

7 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

Study intervention includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational/Auxiliary [Medicinal] Product (Non-IP/Non-IMP/AxMP) as indicated in Table 7.1-1.

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

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

7.1 Study Interventions Administered

The selection and timing of dose for each participant is as follows:

Table 7.1-1: Study Interventions

ARM Name	**Nivolumab + Ipilimumab + BMS-986207**	**Nivolumab + Ipilimumab + Placebo**[a]
Intervention Name	Nivolumab + Ipilimumab + BMS-986207	Nivolumab + Ipilimumab + Placebo
Type	Nivolumab: biologic	Nivolumab: biologic

Table 7.1-1: Study Interventions

ARM Name	Nivolumab + Ipilimumab + BMS-986207	Nivolumab + Ipilimumab + Placebo[a]
	Ipilimumab: biologic	Ipilimumab: biologic
	BMS-986207: biologic	Placebo
Dose Formulation	Nivolumab: solution for injection	Nivolumab: solution for injection
	Ipilimumab: solution for injection	Ipilimumab: solution for injection
	BMS-986207: lyophilized powder for injection	Placebo: solution for injection
Unit Dose Strength(s)	Nivolumab: 100 mg/vial (10 mg/mL)	Nivolumab: 100 mg/vial (10 mg/mL)
	Ipilimumab: 50 mg/vial (5 mg/mL); 200 mg/vial (5 mg/mL)	Ipilimumab: 50 mg/vial (5 mg/mL); 200 mg/vial (5 mg/mL)
	BMS-986207: 160 mg/vial	Placebo: NA
Dosage Level(s)	Nivolumab: 360 mg Q3W	Nivolumab: 360 mg Q3W
	Ipilimumab: 1 mg/kg Q6W	Ipilimumab: 1 mg/kg Q6W
	BMS-986207: 600 mg Q3W	Placebo[a:] Q3W
Route of Administration	IV infusion	IV infusion
Use	Experimental	Background intervention
IMP and Non-IMP/AxMP	IMP	IMP
Sourcing	Nivolumab: provided centrally by the Sponsor	Nivolumab: provided centrally by the Sponsor
	Ipilimumab: provided centrally by the Sponsor	Ipilimumab: provided centrally by the Sponsor
	BMS-986207: provided centrally by the Sponsor	Placebo: provided locally by the trial site
Packaging and Labeling[b]	Study intervention will be provided in vials. Each vial will be labeled as required per country requirement.	Study intervention will be provided in vials. Each vial will be labeled as required per country requirement.
Current/Former Name(s) or Alias(es)	Nivolumab: anti-PD-1, BMS-936558, MDX1106, ONO-4538	Nivolumab: anti-PD-1, BMS-936558, MDX1106, ONO-4538
	Ipilimumab: anti-CTLA-4, BMS-734016, MDX010, MDX-CTLA4	Ipilimumab: anti-CTLA-4, BMS-734016, MDX010, MDX-CTLA4
	BMS-986207: anti-TIGIT, TIGIT	Placebo[a]: NA

Abbreviations: AxMP, auxiliary medicinal product; BOIN, Bayesian optimal interval; CTLA-4, cytotoxic T-lymphocyte associated protein 4; IMP, Investigational Medicinal Product; IV, intravenous; NA, not applicable; PD-1, programmed cell death 1; Q3W, every 3 weeks; Q6W, every 6 weeks; TIGIT, T cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain.

[a] 0.9% sodium chloride for injection or 5% dextrose for injection can be used for BMS-986207 placebo.

[b] Nivolumab, ipilimumab, and BMS-986207 will be delivered to the pharmacy as open-label. BMS-986207 will be administered in a single-blind fashion.

During the treatment phase, participants will receive 1 of the treatment regimens by arm described in Table 7.1-1. BMS-986207 will be administered in a blinded manner, while nivolumab plus ipilimumab will be unblinded. Dose reductions are not permitted for study intervention.

Participants will receive nivolumab at a dose of 360 mg over an approximately 30 minute infusion twice each treatment cycle until progression, unacceptable toxicity, withdrawal of consent, completion of 2 calendar years (24 months) of treatment, or the study ends, whichever occurs first. If needed, flush the intravenous line with an appropriate amount of diluent (eg, 0.9% Sodium Chloride or 5% Dextrose in water) to ensure that the complete dose is administered over approximately 30 minutes. Begin study intervention within 3 calendar days of randomization.

Use body weight for dosing calculations. It is not necessary to re-calculate subsequent doses if the participant weight is within 10% of the baseline weight or the weight used to calculate the previous dose. Round all doses to the nearest milligram per institutional standard.

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

Please refer to the current IBs and/or Pharmacy Manual for further details regarding storage, preparation, handling, and administration of nivolumab, ipilimumab, and/or BMS-986207 or its placebo.[7,8,9]

BMS-986207 or its placebo will always be given as the last treatment after nivolumab and/or ipilimumab. Thus, an approximately 30-minute infusion of nivolumab will be followed by a 30-minute observation period, followed by a 30-minute infusion of ipilimumab and a 30-minute observation period (on Day 1 of each cycle only), followed by an approximately 30-minute infusion of BMS-986207 or its placebo. For participants < 22 kg, the infusion time for BMS-986207 600 mg or its placebo will be approximately 90 minutes.

There will be no intra-participant dose escalations or reductions of nivolumab or BMS-986207 or its placebo allowed. For Q3W dosing, participants may be dosed no less than 19 days from the previous dose. Premedications are not recommended for the first dose of study interventions.

Monitor participants carefully for infusion reactions during study intervention administration. If an acute infusion reaction is noted, manage participants according to Section 7.4.4.

Doses of study drug(s) may be interrupted, delayed, skipped, or discontinued depending on how well the participant tolerates the treatment (see Section 7.4). Day 1 dosing visits for each cycle are not skipped.

Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agents.

Use separate infusion bags and filters when administering nivolumab, ipilimumab or BMS-986207 on the same day.

7.2 Method of Study Intervention Assignment

After the participant's initial eligibility is established and informed consent has been obtained, the participant must be enrolled into the study via the IRT to obtain a participant number. Specific instructions for using IRT will be provided to the investigational site in a separate document. The investigator or designee will register the participant for enrollment by following the enrollment procedures established by BMS.

Once it is determined that the participant meets the eligibility criteria following enrollment, participant will be randomized through the IRT, and stratified by tumor histology and PD-L1 expression. The following information is required for participant randomization:

- Evaluable tumor tissue confirmed by central laboratory
- Tumor histology: squamous versus nonsquamous
- Tumor PD-L1 expression (< 1%, 1% - 49% and ≥ 50%)

If a participant has confirmation of evaluable tumor tissue but indeterminate PD-L1 expression by central laboratory, the participant may be eligible if local PD-L1 results are available and after consultation with the Sponsor/Medical Monitor (or designee). The exact procedures for using the IRT will be detailed in the IRT manual. Further information regarding tissue biopsy collection will be detailed in the Laboratory Manual.

7.3 Blinding

The participants, investigators, and site staff will be blinded (single-blind) to treatment assignment. The administration of nivolumab and ipilimumab is not blinded since it is given in both treatment cohorts. The administration of BMS-986207 or its placebo will be blinded. Access to treatment assignment will be restricted from all participants and site personnel prior to primary database lock with the exception of an unblinded pharmacist/designee that must be assigned by the site. Each investigative site must assign an unblinded pharmacist/designee to provide oversight of drug supply and other unblinded study documentation.

The DMC and Sponsor will not be blinded to treatment assignment. The specific treatment administered to a participant will be assigned using an IRT. Treatment information access will be used by the Sponsor to monitor safety in an unblinded manner as the study is ongoing, but not to perform any by-arm efficacy analyses. In addition, access to treatment assignment will be provided to the DMC as specified per the DMC charter. Additional information regarding blinding, including Sponsor personnel with access to treatment information for safety monitoring, will be provided in the SAP.

Blinding of study intervention assignment is critical to the integrity of this clinical study. However, in the event of a pregnancy, medical emergency, or unexpected death in an individual participant in which knowledge of the IP is critical, the blind for that participant may be broken by the investigator. The participant's safety takes priority over any other considerations in determining if a treatment assignment should be unblinded.

Before breaking the blind of an individual participant's treatment, the investigator should determine that the unblinded information is necessary (ie, that it will alter the participant's immediate management). In many cases, particularly when the event is clearly not related to the IP, the problem may be properly managed by assuming that the participant is receiving the IP. It is highly desirable that the decision to unblind treatment assignment be discussed with the Sponsor/Medical Monitor (or designee), but the investigator always has ultimate authority for the decision to unblind. The actual task of unblinding can be delegated by the investigator to a designee assigned the task on the Delegation of Authority. The Principal Investigator or appointed designee should only initiate individual participant unblinding after the decision to unblind the participant has been documented. The method of unblinding is by IRT transaction. Please consult the IRT manual for further information on how to unblind a participant.

In cases of accidental unblinding, contact the Sponsor/Medical Monitor (or designee) and ensure every attempt is made to minimize additional disclosure and the impact of unblinding.

Any request to unblind a participant for nonemergency purposes should be discussed with the Sponsor/Medical Monitor (or designee).

7.4 Dosage Modification

Intra-participant dose escalation/reduction of BMS-986207 (or its placebo), nivolumab, or ipilimumab (except per weight-based dosing; see Section 7.1) is not permitted in this study in order to allow better evaluation of the safety and efficacy at individual dose levels and schedules. Separate assessments of study interventions will be used in considering criteria for dose delay, resumption, and discontinuation (see Sections 7.4.1, 7.4.2, and 8.1.1).

AEs will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.

7.4.1 Dose Delay Criteria for Nivolumab, Ipilimumab, and BMS-986207

The criteria for dose delay, resumption, and discontinuation in Table 7.4.2-1 applies to ipilimumab, nivolumab, and BMS-986207 or its placebo. Since this study is single-blinded, the criteria in Table 7.4.2-1 for BMS-986207 or its placebo will be the same as that for nivolumab.

Dose delay criteria apply for all drug-related AEs, regardless of whether the event is attributed to BMS-986207, nivolumab or ipilimumab. Delay administration of all study interventions (BMS-986207, nivolumab, and ipilimumab) if any of the delay criteria in Table 7.4.2-1 are met. Delay all study medication dosing for any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

For participants who require delay of study interventions, re-evaluate weekly, or more frequently, if clinically indicated and resume dosing when criteria to resume treatment are met (see Section

7.4.2). Continue tumor assessments per protocol even if dosing is delayed. See Section 8.1 for further information regarding permanent discontinuation of study interventions.

7.4.2 Criteria to Resume Treatment

Participants may resume treatment with study intervention if they have completed AE management (ie, corticosteroid taper) or are on ≤ 10 mg prednisone or equivalent, and meet the requirements per Table 7.4.2-1.

Prior to re-initiating treatment in a participant with a dosing delay lasting > 8 weeks, the Sponsor/Medical Monitor (or designee) must be consulted and treatment decision agreed upon. Continue tumor assessments per protocol even if dosing is delayed. Continue periodic study visits to assess safety and laboratory studies every 3 weeks or more frequently if clinically indicated during such dosing delays.

When criteria to resume treatment are met, resume all study interventions (BMS-986207 or its placebo, nivolumab and ipilimumab) on the same day unless the investigator determines that one of the agents must be discontinued due to toxicity attributed to that agent alone. Since this study is blinded, criteria for dose delay, resumption, and discontinuation in Table 7.4.2-1 for BMS-986207 or its placebo will be the same as that for nivolumab. Thus, if nivolumab is resumed, BMS-986207 or its placebo will also resume. Treatment with BMS-986207 or its placebo will not resume without nivolumab.

Dose delay is required for participants with confirmed SARS-CoV-2 infection. 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 Sponsor/Medical Monitor (or designee). 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 intervention in a participant with a dosing delay lasting > 8 weeks due to SARS-CoV-2 infection, the Sponsor/Medical Monitor (or designee) must be consulted.

Table 7.4.2-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Nivolumab, Ipilimumab, and BMS-986207

Drug-Related AE per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Gastrointestinal			
Colitis or Diarrhea	Grade 2	Delay dose	Dosing may resume when AE resolves to baseline
	Grade 3	Permanently discontinue Ipilimumab	Nivolumab + BMS-986207 may be resumed when AE resolves to baseline. If Grade 3 diarrhea or colitis recurs while on nivolumab + BMS-986207, permanently discontinue
	Grade 4	Permanently discontinue	
Renal			
Serum Creatinine Increased	Grade 2 or 3	Delay dose	Dosing may resume when AE resolves to Grade ≤ 1 or baseline value
	Grade 4	Permanently discontinue	
Pulmonary			
Pneumonitis	Grade 2	Delay dose	Dosing may resume after pneumonitis has resolved to ≤ Grade 1.
	Grade 3 or 4	Permanently discontinue	
Hepatic			
AST, ALT, or T.bili increased	AST or ALT > 3x and ≤ 5x ULN or T.Bili > 1.5x and ≤ 3x ULN, regardless of baseline value	Delay dose or permanently discontinue	If the abnormality is not associated with new signs/symptoms of liver inflammation, dosing may resume when laboratory values return to baseline. If AST or ALT elevation and symptomatic liver inflammation (eg, right upper quadrant tenderness, jaundice), then permanently discontinue.
	AST or ALT > 5 x ULN or T.bili > 3 x ULN, regardless of baseline value	Delay dose or permanently discontinue	In most cases of AST or ALT > 5 x ULN, study intervention will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study intervention, a discussion between the

Table 7.4.2-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Nivolumab, Ipilimumab, and BMS-986207

Drug-Related AE per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
			investigator and the Sponsor/Medical Monitor (or designee) must occur and approval from Sponsor/Medical Monitor (or designee) prior to resuming therapy.
	Concurrent AST or ALT > 3 x ULN and T.bili > 2 x ULN, regardless of baseline value	Permanently discontinue	
Endocrinopathy			
Adrenal Insufficiency	Grade 2 adrenal insufficiency	Delay dose	Dosing may resume after adequately controlled with hormone replacement.
	Grade 3 or 4 adrenal insufficiency or adrenal crisis	Delay dose or permanently discontinue	Mandatory discussion with and approval from the Sponsor/Medical Monitor (or designee) needed prior to resuming therapy. If adrenal insufficiency resolves or is adequately controlled with physiologic hormone replacement, participant may not require discontinuation of study drug.
Hyperglycemia	Hyperglycemia requiring initiation or change in daily management (Grade 2 or 3)	Delay dose	Dosing may resume if hyperglycemia resolves to Grade ≤ 1 or baseline value, or is adequately controlled with glucose-controlling agents.
	Grade 4	Delay dose or permanently discontinue	Mandatory discussion with and approval from the Sponsor/Medical Monitor (or designee) needed prior to resuming therapy. If hyperglycemia resolves, or is adequately controlled with glucose-controlling agents, participant may not require discontinuation of study drug.
Hypophysitis/Hypopituitarism	Symptomatic Grade 1-3 that is also associated with corresponding abnormal lab and/or pituitary scan	Delay dose	Dosing may resume if endocrinopathy resolves to be asymptomatic, or is adequately controlled with only physiologic hormone replacement.

Table 7.4.2-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Nivolumab, Ipilimumab, and BMS-986207

Drug-Related AE per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
	Grade 4	Delay dose or permanently discontinue	Mandatory discussion with and approval from the Sponsor/Medical Monitor (or designee) needed prior to resuming therapy. If endocrinopathy resolves or is adequately controlled with physiologic hormone replacement, participant may not require discontinuation of study drug.
Hyperthyroidism or Hypothyroidism	Grade 2 or 3	Delay dose	Dosing may resume if endocrinopathy resolves to be asymptomatic, or is adequately controlled with only physiologic hormone replacement or other medical management.
	Grade 4	Delay dose or permanently discontinue	Mandatory discussion with and approval from the Sponsor/Medical Monitor (or designee) needed prior to resuming therapy. If endocrinopathy resolves or is adequately controlled with physiologic hormone replacement or other medical management, participant may not require discontinuation of study drug.
Skin			
Rash	Grade 2 rash covering > 30% body surface area or Grade 3 rash	Delay dose or permanently discontinue	Dosing may resume when rash reduces to ≤ 10% body surface area. If Grade 3 rash does not improve to ≤ Grade 1 after 2 weeks of treatment delay, then permanently discontinue.
	Suspected Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or drug reaction with eosinophilia and systemic symptoms (DRESS)	Delay dose	Dosing may resume if SJS, TEN, or DRESS is ruled out and rash reduces to is ≤ 10% body surface area
	Grade 4 rash or confirmed SJS,TEN, or DRESS	Permanently discontinue	

Table 7.4.2-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Nivolumab, Ipilimumab, and BMS-986207

Drug-Related AE per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Neurological			
Guillain-Barre Syndrome (GBS)	Any Grade	Permanently discontinue	
Myasthenia Gravis (MG)	Any Grade	Permanently discontinue	
Encephalitis	Any Grade encephalitis	Delay dose	After workup for differential diagnosis, (ie, infection, tumor-related), if encephalitis is not drug related, then dosing may resume when AE resolves
	Any Grade drug-related encephalitis	Permanently discontinue	
Myelitis	Any Grade myelitis	Delay dose	After workup for differential diagnosis, (ie, infection, tumor-related), if myelitis is not drug related, then dosing may resume when AE resolves
	Any Grade drug-related myelitis	Permanently discontinue	
Neurological (other than GBS, MG, encephalitis, or myelitis)	Grade 2	Delay dose	Dosing may resume when AE resolves to baseline
	Grade 3 or 4	Permanently discontinue	
Myocarditis			
Myocarditis	Symptoms induced from mild to moderate activity or exertion	Delay dose	Dosing may resume after myocarditis has resolved. Mandatory discussion with and approval from the Sponsor/Medical Monitor (or designee) is needed prior to resuming therapy.
	Severe or life threatening, with symptoms at rest or with minimal activity or exertion, and/or where intervention indicated.	Permanently discontinue	

Table 7.4.2-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Nivolumab, Ipilimumab, and BMS-986207

Drug-Related AE per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Other Clinical AE			
Pancreatitis:	Grade 3 with symptoms	Delay dose	Note: Grade 3 increased amylase or lipase without signs or symptoms of pancreatitis does not require dose delay. Dosing may resume when participant becomes asymptomatic.
Amylase or Lipase increased	Grade 4	Permanently discontinue	
Uveitis, episcleritis, iritis[a]	Grade 2	Delay dose or permanently discontinue	Dosing may resume if AE responds to topical therapy (eye drops) and after AE resolves to Grade ≤ 1 or baseline. If participant requires oral steroids for AE, then permanently discontinue study drug.
	Grade 3 or 4	Permanently discontinue	
SARS-CoV-2	Confirmed infection	Delay dose	
Other Drug-Related AE (not listed above)	Grade 2 non-skin AE, except fatigue	Delay dose	Dosing may resume when AE resolves to Grade ≤ 1 or baseline value.
	Grade 3 AE - First occurrence lasting ≤ 7 days	Delay dose	Dosing may resume when AE resolves to Grade ≤ 1 or baseline value.
	Grade 3 AE- First occurrence lasting > 7 days	Permanently discontinue	
	Recurrence of Grade 3 AE of any duration	Permanently discontinue	
	Grade 4 or Life-threatening adverse reaction	Permanently discontinue	

Table 7.4.2-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Nivolumab, Ipilimumab, and BMS-986207

Drug-Related AE per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Other Lab abnormalities			
Other Drug-related lab abnormality (not listed above)	Grade 3	Delay dose	Exceptions: No delay required for: Grade 3 lymphopenia or Grade 3 anemia that responds to pRBC transfusion Permanent Discontinuation for: Grade 3 thrombocytopenia > 7 days or associated with clinically significant bleeding or Grade 3 hemolysis
	Grade 4	Permanently discontinue	Exceptions: The following events do not require discontinuation of study drug: • Grade 4 neutropenia ≤ 7 days • Grade 4 lymphopenia or leukopenia • Grade 4 isolated electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are responding to supplementation/appropriate management within 72 hours of their onset
Infusion Reactions (manifested by fever, chills, rigors, headache, rash, pruritus, arthralgia, hypotension, hypertension, bronchospasm, or other allergic-like reactions)			
Hypersensitivity reaction or infusion reaction	Grade 3 or 4	Permanently discontinue	Refer to Section 7.4.4 on treatment of related infusion reactions

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; DRESS, drug reaction with eosinophilia and systemic symptoms; GBS, Guillain-Barre Syndrome; MG, Myasthenia Gravis; pRBC, packed red blood cells; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SJS, Stevens-Johnson syndrome; T.bili, total bilirubin; TEN, toxic epidermal necrolysis; ULN, upper limit of normal.

[a] Inflammation of components within the eye (eg, episcleritis, uveitis) are uncommon events of nivolumab or ipilimumab monotherapy (< 1% of cases). Routine eye examinations should be performed in participants receiving immune checkpoint inhibitors.

7.4.3 Management Algorithms for Nivolumab plus Ipilimumab ± BMS-986207

IO agents are associated with AEs that can differ in severity and duration from AEs caused by other therapeutic classes. Nivolumab, ipilimumab, and BMS-986207 are considered IO agents and the management algorithms in Appendix 6 provide guidance on assessing and managing the following groups of AEs:

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

7.4.4 Treatment of Related Infusion Reactions

Since BMS-986207, nivolumab and ipilimumab 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, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. Report all Grade 3 or 4 infusion reactions within 24 hours as an SAE if it meets the criteria.

Treatment recommendations are provided below based on CTCAE v5 grading definitions 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 additional study drug administrations.

For Grade 2 symptoms: (Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, nonsteroidal anti-inflammatory drugs [NSAIDS], narcotics, IV fluids); 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 study medication 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 administered at least 30 minutes before nivolumab and/or ipilimumab 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 (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. Grade 4: Life-threatening consequences; urgent intervention 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. Monitor participant until the Investigator judges that the symptoms will not recur. Study drug will be permanently discontinued. Follow 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).

7.5 Preparation/Handling/Storage/Accountability

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

The product storage manager should ensure that the study intervention 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 intervention arise, the study intervention should not be dispensed, and BMS should be contacted immediately.

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

IP/AxMP documentation (whether supplied by BMS or not) must be maintained that includes all processes required to ensure the 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).

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study interventions are provided in the Appendix 2 and the Pharmacy Manual.

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

Refer to the current version of the product-specific IB and/or Pharmacy Manual for complete storage, handling, and preparation information.

7.6 Treatment Compliance

Treatment compliance will be monitored by drug accountability as well as the participant's medical record and electronic case report form (eCRF). This will be source data verified by the Unblinded Site Monitor through regularly scheduled monitoring visits.

7.7 Concomitant Therapy

7.7.1 Prohibited and/or Restricted Treatments

Medications taken within 4 weeks prior to study intervention administration must be recorded on the CRF.

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

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids (except as per Section 7.7.3)
- Any concurrent systemic anti-neoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents for treatment of NSCLC)
- Any non-palliative radiation therapy. Radiation therapy administered with palliative intent (ie, for pain, bleeding, spinal cord compression, brain metastasis, new or impending pathologic fracture, superior vena-cava syndrome, or obstruction) is permitted.
- Any complementary medications (eg, herbal supplements or traditional Chinese medicines) intended to treat the disease under study. Such medications are permitted if they are used as supportive care. Use of marijuana and its derivatives for treatment of symptoms related to cancer or cancer treatment are permitted if obtained by medical prescription or if its use (even without a medical prescription) has been legalized locally.
- Any live/attenuated vaccine (eg, varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella [MMR]) during treatment and until 100 days post last dose.
- Administration of investigational SARS-CoV-2 vaccines is not allowed during the study. Participants may receive authorized or approved SARS-CoV-2 vaccines while continuing on study intervention at the discretion of the Investigator.

- Treatment of active SARS-CoV-2 infections or high risk exposures, including use of investigational therapies, is allowed and should be discussed with the Sponsor/Medical Monitor (or designee).

7.7.2 Other Restrictions and Precautions

7.7.2.1 Imaging Restriction and Precautions

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

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

7.7.3 Permitted Therapy

Participants are permitted the use of the following treatments:

- Topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption)
- Adrenal replacement steroid doses > 10 mg daily prednisone are permitted.
- A brief (less than 3 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted
- Regular concomitant use of biphosphonates and receptor activator of nuclear kappa beta-ligand (RANK-L) inhibitors for prevention or reduction of skeletal-related events in participants with bone metastases is allowed if initiated prior to first dose of study intervention
- Prior palliative radiotherapy must have been completed at least 2 weeks prior to treatment

7.7.3.1 Palliative Local Therapy

Palliative local therapy, including palliative radiation therapy and palliative surgical resection, to symptomatic non-target bone lesions, skin lesions, or CNS lesions is permitted prior to discontinuation of study intervention for participants who do not have evidence of overall clinical or radiographic progression per RECIST v1.1. Palliative local therapy to lesions causing hemoptysis may also be permitted prior to discontinuation of study intervention in participants who do not have evidence of overall clinical or radiographic progression per RECIST v1.1,

provided that the lesions undergoing palliative local therapy are not the only sites of measurable disease and the case is discussed with and approved by the Sponsor/Medical Monitor (or designee).

Participants requiring palliative local therapy should be evaluated for objective evidence of disease progression prior to the initiation of such therapy, particularly if the most recent tumor assessment was more than 4 weeks prior to the start of local therapy. If progression per RECIST v1.1 is identified on any tumor assessments prior to the initiation of palliative local therapy, then participants must either discontinue study intervention or they must meet criteria to continue treatment beyond progression (Section 8.1.2) in order to resume immunotherapy after palliative local therapy. If radiographic progression per RECIST v1.1 is identified prior to the initiation of palliative local therapy, sites must request a BICR from the third-party radiology vendor (Section 5.1.5). However, the initiation of palliative local therapy need not be delayed to await the assessment by the BICR.

The potential for overlapping toxicities with radiotherapy and immunotherapy currently is not known; however, anecdotal data suggest that it is tolerable. As concurrent radiotherapy and the immunotherapy regimens evaluated in this study have not been formally evaluated, whenever palliative radiotherapy is required for a tumor lesion, then immunotherapy should be withheld for at least 1 week before, during, and 1 week after radiation. Participants should be closely monitored for any potential toxicity during and after receiving radiotherapy and AEs should resolve to Grade ≤ 1 prior to resuming immunotherapy.

7.8 Continued Access to Study Intervention After the End of the Study

At the conclusion of the study, if the study intervention is not available as an approved treatment in the local country, participants who continue to demonstrate clinical benefit will be eligible to receive BMS-supplied study intervention for maximum treatment duration as specified in Section 7.1. If the study intervention is not available as an approved and available treatment, study intervention will be provided via an extension of the study, a rollover study requiring approval by the responsible Health Authority and ethics committee, or through another mechanism at the discretion of BMS.

BMS reserves the right to terminate access to BMS-supplied study intervention if any of the following occur: a) the study is terminated due to safety concerns; b) the development of 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 medication from a government-sponsored or other health program. In all cases, BMS will follow local regulations.

8 DISCONTINUATION CRITERIA

8.1 Discontinuation From Study Intervention

Participants MUST discontinue IP (and Non-IP/AxMP at the discretion of the investigator) for any of the following reasons:

- Participant's request to stop study intervention. Participants who request to discontinue study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws

consent for any further contact with him/her or persons previously authorized by the participant to provide this information

- Any clinical AE, laboratory abnormality, or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant
- Termination of the study by BMS
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness. (Note: Under specific circumstances and only in countries where local regulations permit, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply, and BMS approval is required)
- Documented and confirmed disease progression as defined by RECIST v1.1 (Appendix 5) unless participants meet criteria for treatment beyond progression (Section 8.1.2).
- Any drug-related AE occurring at any time that meets criteria to permanently discontinue as outlined in Table 7.4.2-1.
- Pregnancy (refer to Section 9.2.5)
- Significant noncompliance with protocol (eg, procedures, assessments, medications, etc). The investigator should discuss such issues with the Sponsor/Medical Monitor (or designee).
- Any event that leads to delay in dosing lasting > 8 weeks from the previous dose requires discontinuation, with the following exceptions:
  - Dosing delays for prolonged steroid tapers to manage drug-related AEs are allowed (See Section 7.4.2)
  - Dosing delays lasting > 8 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the Sponsor/Medical Monitor (or designee)

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

All participants who discontinue study intervention 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 (eg, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

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

For all participants, global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration' in the source data and in the eCRF. Tumor assessments for participants who discontinue study intervention without radiographic progression, confirmed by BICR (Section 5.1.5), should continue as per protocol until radiographic progression is determined by BICR.

8.1.1 Discontinuation of Nivolumab, Ipilimumab or BMS-986207

Make separate assessments for discontinuation of study interventions. Since this study is blinded to participants, investigators, and site staff, criteria for dose discontinuation in Table 7.4.2-1 for BMS-986207 or its placebo will be the same as that for nivolumab.

Ipilimumab treatment must be permanently discontinued per criteria in Table 7.4.2-1. If discontinuation criteria are met for ipilimumab but not for nivolumab plus BMS-986207 or its placebo, treatment with nivolumab plus BMS-986207 or its placebo may continue. However, ipilimumab will not continue as monotherapy.

Nivolumab treatment must be permanently discontinued per criteria in Table 7.4.2-1. If a participant meets discontinuation criteria for nivolumab, then the participant will permanently discontinue all study interventions (nivolumab, BMS-986207 or its placebo, and ipilimumab).

If a participant meets criteria for discontinuation in Table 7.4.2-1 and the Investigator is unable to determine whether the event is related to ipilimumab, nivolumab, or BMS-986207 or its placebo, the participant must discontinue all study intervention and be taken off the treatment phase of the study.

Discontinue nivolumab plus BMS-986207 or its placebo and/or ipilimumab for 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, BMS-986207 and/or ipilimumab dosing.

The criteria for dose delays and discontinuations for nivolumab or ipilimumab cannot be altered, except in the case where the guidance will become more stringent due to the novel agent profile.

Any event that leads to delay in dosing lasting > 8 weeks from the previous dose requires discontinuation of study drug, with the following exceptions:

- Dosing delays to allow for prolonged steroid tapers to manage drug-related AEs are allowed.
- Dosing delays lasting > 8 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the Sponsor/Medical Monitor (or designee).

8.1.2 Treatment Beyond Disease Progression

Accumulating evidence indicates a minority of participants treated with immunotherapy may derive clinical benefit despite initial evidence of PD.[36]

Participants will be permitted to continue immunotherapy treatment beyond initial RECIST v1.1 defined PD, assessed by the investigator up to a maximum of 2 calendar years (24 months) from date of first dose as long as they meet the following criteria:

- Investigator-assessed clinical benefit
- Tolerance of study intervention
- Stable PS

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

Continue radiographic assessment/scan(s) in accordance with the Section 2 Schedule of Activities for the duration of the treatment beyond progression and submit to the central imaging vendor. Balance the assessment of clinical benefit with clinical judgment as to whether the participant is clinically deteriorating and unlikely to receive any benefit from continued treatment with nivolumab, ipilimumab and BMS-986207 or its placebo.

For the participants who continue study therapy beyond progression, further progression is defined as an additional 10% increase in tumor burden with a minimum 5 mm absolute increase from time of initial PD. This includes an increase in the sum of diameters of all target lesions and/or the diameters of new measurable lesions compared to the time of initial PD. Upon documentation of further progression, permanently discontinue treatment unless the clinical judgement of the investigator is that continuing treatment is in the participant's best interest.

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

8.1.3 Post-study Intervention Study Follow-up

In this study, PFS is a key endpoint of the study. Post-study follow-up is of critical importance and is essential to preserving participant safety and the integrity of the study. Participants who discontinue study intervention must continue to be followed (in this study or a rollover study) for collection of outcome and/or survival follow-up data as required and in line with Section 5 until death or the conclusion of the study.

If progression has not occurred before treatment discontinuation, tumor assessments should continue according to Table 2-3 (Section 2 Schedule of Activities).

Participants should undergo 100 days of safety follow-up post last dose of study drug.

BMS may request that survival data be collected on all treated/randomized participants outside of the protocol defined window (see Section 2). At the time of this request, each participant will be contacted to determine their survival status unless the participant has withdrawn consent for all contact or is lost to follow-up.

8.2 Discontinuation From the Study

Participants who request to discontinue study intervention 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.
- 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 intervention only or also from study procedures and/or post-treatment study follow-up, and entered on the appropriate CRF page.
- In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

8.2.1 Individual Discontinuation Criteria

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

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

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

9 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the Schedule of Activities (Section 2).
- Protocol waivers or exemptions are not allowed.
- All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.
- Adherence to the study design requirements, including those specified in the Schedule of Activities (Section 2), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Schedule of Activities (Section 2).
- Images will be submitted to a central imaging vendor for BICR at any time during the study. Prior to scanning the first participant, sites should be qualified and understand the image acquisition guidelines and submission process as outlined in the CA020016 Imaging Manual provided by the central imaging vendor.
- Perform additional measures, including non-study required laboratory tests, as clinically indicated or to comply with local regulations. Laboratory toxicities (eg, suspected drug induced liver enzyme evaluations) will be monitored during the follow-up phase via on-site/local labs until all study drug-related toxicities resolve, return to baseline, or are deemed irreversible.
- Evaluate participant immediately to rule out cardiac or pulmonary toxicity if participant shows cardiac or pulmonary-related signs (hypoxia, abnormal heart rate or changes from baseline) or symptoms (eg, dyspnea, cough, chest pain, fatigue, palpitations).

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

9.1 Efficacy Assessments for the Study

9.1.1 Imaging Assessment for the Study

Images will be submitted to a central imaging vendor for BICR at any time during the study. Prior to scanning the first participant, sites should be qualified and understand the image acquisition guidelines and submission process as outlined in the CA020016 Imaging Manual provided by the central imaging vendor.

Screening and on study images should be acquired as outlined in Section 2 Schedule of Activities. Tumor assessments at other timepoints may be performed if clinically indicated and should be submitted to the central imaging vendor as soon as possible. Unscheduled CT/MRI should be submitted to central imaging vendor. X-rays and bone scans that clearly demonstrate interval progression of disease, for example most commonly as unequivocal lesions that are unmistakably new since the prior CT/MRI, should be submitted to central imaging vendor. Otherwise, they do not need to be submitted centrally.

9.1.1.1 Methods of Measurement

Contrast-enhanced CT of the chest, abdomen, pelvis, and all other known and/or suspected sites of disease should be performed for tumor assessments. Images should be acquired with slice thickness of 5 mm or less with no intervening gap (contiguous). Every attempt should be made to image each participant using an identical acquisition protocol on the same scanner for all imaging timepoints. Tumor measurements should be made by the same investigator or radiologist for each assessment, whenever possible. Change in tumor measurements and tumor response to guide ongoing study intervention decisions will be assessed by the investigator using the RECIST v1.1 criteria.

If a participant has a contraindication for CT intravenous contrast, then a non-contrast CT of the chest and a contrast-enhanced MRI of the abdomen, pelvis, and other known/suspected sites of disease should be obtained.

If a participant has a contraindication for both MR and CT intravenous contrasts, then a non-contrast CT of the chest and a non-contrast MRI of the abdomen, pelvis, and other known/suspected sites of disease should be obtained.

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

Use of CT component of a positron emission tomography (PET)-CT scanner: Combined modality scanning such as with PET-CT is increasingly used in clinical care, and is a modality/technology that is in rapid evolution; therefore, the recommendations outlined here may change rather quickly with time. At present, low dose or attenuation correction CT portions of a

combined PET-CT are of limited use in anatomically-based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for anatomically-based RECIST v1.1 measurements. However, if a site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST v1.1 measurements. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

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

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

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

9.1.1.2 Imaging and Clinical Assessment

Tumor assessments should continue on the protocol defined imaging schedule regardless if dosing is delayed or discontinued. Changes in tumor measurements and tumor responses will be assessed by the same investigator or designee using RECIST v1.1 criteria. Investigators will report the number and size of new lesions that appear while on study. The timepoint of tumor assessments will be reported on the eCRF based on the investigator's assessment using RECIST v1.1 criteria (See Appendix 5 for specifics of RECIST v1.1 criteria to be used in this study). Assessments of PR and CR must be confirmed at least 4 weeks (28 days) after initial response. A BOR of SD requires a minimum of 35 days on study from randomization to the date of the first imaging assessment.

9.1.1.3 BICR Confirmation of Progression

Sites should submit all scans to the central imaging vendor on a rolling basis, throughout the duration of the study. BICR of scans will occur on a rolling basis, blinded to treatment arm, clinical data, and investigator assessment of submitted scans. When progression per RECIST v1.1 criteria is assessed by the investigator, the site will inform the central imaging vendor, in order for BICR assessment of progression to be performed. The BICR will be completed and the results provided to the site as specified in the imaging vendor documents, provided there are no pending imaging queries to the site. All details on the timelines and associated process requirements will be outlined in the Imaging Manual.

Participants whose progression is not confirmed by the BICR will be required to continue tumor assessments (if clinically feasible) according to the protocol-specified schedule, or sooner if clinically indicated. Also, if participants discontinue treatment without radiographic progression,

tumor assessments will continue according to the protocol-specified schedule, as noted in Section 2 (Schedule of Activities) until progression has been confirmed by BICR.

All study intervention decisions will be based on the investigator's assessment of tumor images and not on the BICR assessment.

9.1.2 Clinical Outcomes Assessments

The evaluation of PROs is an increasingly important aspect of clinical efficacy and safety in oncology trials. Such data provide an understanding of the impact of treatment from the participant's perspective and offer insights into participant experience that may not be captured through physician reporting.

Participants will be asked to complete the NSCLC-SAQ, the FACT-G7, the 5 Level EQ-5D Questionnaire (EQ-5D-5L), the PGIS and the PGIC at designated study visits. When possible, participants should complete the PRO measures prior to any other study related procedure or assessments during study visits. Assessments will be completed prior to dosing on Day 1 of each cycle from Cycle 1 (with the exception of the PGIC which will be completed at each cycle from Cycle 2; see Section 2 Schedule of Activities). PRO measures will be completed electronically during the study and at Safety and Survival Follow-up.

The PROs should be completed in the following order:

1) NSCLC-SAQ
2) FACT-G7
3) EQ-5D-5L
4) PGIS
5) PGIC (except for C1D1 when it is not completed)

9.1.2.1 NSCLC-SAQ

The NSCLC-SAQ is a 7-item PRO measure intended for use in advanced NSCLC clinical trials to support medical product labelling.[37] The NSCLC-SAQ uses a 7-day recall period and verbal rating scale. It was developed in accordance with the US FDA PRO Guidance and scientific best practices, and the resulting qualitative interview data provide evidence of content validity. The NSCLC-SAQ total score measures overall severity of the following NSCLC symptoms: cough, pain, dyspnea, fatigue, and appetite. The NSCLC-SAQ has been qualified for exploratory use to measure symptoms of NSCLC in drug development programs. Further evaluation is needed on the instrument's longitudinal measurement properties and the interpretation of clinically meaningful within-patient change in score. After the NSCLC-SAQ's longitudinal measurement properties and the interpretation of clinically meaningful within-patient change have been evaluated, the NSCLC SAQ total score is intended to support labeling claims related to change in overall symptoms of NSCLC.

9.1.2.2 FACT-G7

The FACT-G7 is a valid, brief measure particularly of the physical and functional facets of quality of life, and is derived from the FACT-G.[38] It may enable rapid quality-of-life assessments in patients with advanced cancer. The FACT-G7 contains 7 items and comprises of physical well-being (PWB; X items), emotional well-being (EWB; X items) and functional well-being (FWB; X items). Scores for the PWB, FWB, and EWB subscales can be combined to produce a FACT-G7 total score, which provides an overall indicant of generic health-related quality of life (HRQoL). The recall period is 1 week. Each question is assessed on a 5-point Likert scale: 0 = not at all, 1 = a little bit, 2 = somewhat, 3 = quite a bit, and 4 = very much. Psychometric properties of the FACT-G7 have been evaluation with good validity and reliability.[39]

9.1.2.3 EQ-5D-5L

Patients' reports of general health status will be assessed using the 5-level EQ-5D (EQ-5D-5L). The EQ-5D-5L has 2 components, the EQ-5D-5L descriptive system and the EQ-5D visual analog scale (VAS).

The EQ-5D-5L descriptive system comprises of the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The participant is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number that expresses the level selected for that dimension. A total of 3,125 possible health states are defined in this way. Each state is referred to in terms of a 5-digit code. For example, state 11111 indicates no problems on any of the 5 dimensions, while state 12345 indicates no problems with mobility, slight problems with washing or dressing, moderate problems with doing usual activities, severe pain or discomfort, and extreme anxiety or depression. EQ-5D-5L health states, defined by the EQ-5D-5L descriptive system, may be converted into a single summary index by applying a formula that attaches values (also called weights) to each of the levels in each dimension. The index can be calculated by deducting the appropriate weights from 1, the value for full health (ie, state 11111). This is referred to as the EQ-5D-5L utility index. Value sets have been derived for the EQ-5D-5L in several countries. The United Kingdom (UK) Measurement and Valuation of Health study value set is generally considered the base case scoring function for the purposes of publication. EQ-5D-5L utility index scores will be calculated based on UK values with utility index scores ranging from -0.285 (worst imaginable health state) to 1 (full health). Currently there are no published minimally important differences for change scores for the EQ-5D-5L in a cancer population.

The EQ-5D-5L VAS records the respondent's self-rated health on a scale from 0 = "Worst imaginable health state" to 100 = "Best imaginable health state," where higher scores represent better self-rated health.

9.1.2.4 PGIS and PGIC

The PGIS and PGIC will be included as additional exploratory endpoints. The PGIS is a single item that assesses participants' perceptions of overall severity of cancer symptoms for the last

7 days with response options ranging from "none" to "very severe." The PGIC assesses participants' perceptions of overall change in symptom severity since before treatment and assesses whether or not participants feel such a change is meaningful. Response options for this item range from "much worse" to "much improved." Data collected from the PGIS and PGIC will be used as anchor measures for use in assessing the psychometric properties and the threshold for meaningful change for the NSCLC-SAQ.

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, or a surrogate).

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

Use CTCAE v5 definitions and grading for safety reporting of all AE and SAEs on the case report form.

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

Refer to Appendix 3 for SAE reporting.

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

All SAEs must be collected from the time of signing the consent, including those thought to be associated with protocol-specified procedures, and within 100 days following discontinuation of dosing. For participants randomized to treatment and never treated with study drug, collect SAEs for 30 days from the date of randomization.

Collect all nonserious AEs (not only those deemed to be treatment-related) continuously during the treatment period and for a minimum of 100 days following discontinuation of study intervention. The collection of non-serious AEs (with the exception of non-serious AEs related to SARS-CoV-2 infection) should begin at initiation of study intervention.

The investigator must report any SAE that occurs after these time periods and that is believed to be related to study intervention or protocol-specified procedure (eg, a follow-up skin biopsy, tissue biopsy).

- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the appropriate section of the CRF module.
- All SAEs will be recorded and reported to Sponsor or designee within 24 hours, as indicated in Appendix 3.

- The investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of updated information being available.
- All SAEs, and all AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection must be collected from the date of the participant's written consent until 100 days following discontinuation of dosing.

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 intervention or study participation, the investigator must promptly notify the Sponsor.

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

9.2.2 Method of Detecting AEs and SAEs

AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a participant. Care should be taken not to introduce bias when collecting AEs and/or SAEs. Inquiry about specific AEs should be guided by clinical judgement in the context of known AEs, when appropriate for the program or protocol.

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

9.2.3 Follow-up of AEs and SAEs

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

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

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

9.2.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of SAEs is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a product under clinical investigation are met.
- An investigator who receives an investigator safety report describing SAEs or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

The Sponsor or designee must report AEs to regulatory authorities and ethics committees according to local applicable laws and regulations. A SUSAR (suspected, unexpected serious adverse reaction) is a subset of SAEs and must 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 intervention, it is subsequently discovered that a participant is pregnant or may have been pregnant at the time of study exposure, including during at least for 5 months after study product administration, the investigator must immediately notify the BMS Medical Monitor/designee of this event and 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.

Not applicable for WNOCBP - 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 eCRF, 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 intervention discontinued or interrupted
- Any laboratory test result abnormality that required the participant to receive specific corrective therapy

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

9.2.7 Potential Drug-induced Liver Injury

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

Potential DILI is defined as:

- Aminotransaminases (AT [ALT or AST]) elevation > 3 times ULN

AND

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

AND

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

9.2.8 Other Safety Considerations

Any significant worsening of conditions noted during interim or final physical examinations, ECG, x-ray filming, or any other potential safety assessment required or not required by the protocol should also be recorded as a nonserious AE or SAE, as appropriate, and reported accordingly.

9.3 Overdose

For this study, any dose of immunotherapy greater than the planned dose within a 24-hour time period will be considered an overdose. Overdoses that meet the regulatory definition of SAE will be reported as an SAE (see Appendix 3).

In the event of an overdose, the Investigator should:

- Contact the Sponsor/Medical Monitor (or designee) immediately
- Closely monitor the participant for AEs/SAEs and laboratory abnormalities
- Obtain a plasma sample for PK analysis if requested by the Sponsor/Medical Monitor (or designee) (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 will be made by the investigator in consultation with the Sponsor/Medical Monitor (or designee) based on the clinical evaluation of the participant.

9.4 Safety

Planned time points for all safety assessments are listed in the Schedule of Activities.

9.4.1 Physical Examinations

Refer to Schedule of Activities Section 2.

9.4.2 Vital signs

Refer to Schedule of Activities Section 2.

9.4.3 Electrocardiograms

Refer to Schedule of Activities Section 2.

9.4.4 Clinical Safety Laboratory Assessments

- Investigators must document their review of each laboratory safety report.
- Local laboratory tests may be used to guide clinical decisions and determine eligibility for dosing once eligibility to participate in this study has been confirmed by central laboratory results.
- An on site/local laboratory will perform the analyses and will provide reference ranges for these tests.
- During screening and treatment, unless otherwise indicated results of clinical laboratory tests must be reviewed prior to dosing.

Table 9.4.4-1: Clinical Laboratory Assessments

Hematology	
Hemoglobin	
Hematocrit	
Total leukocyte count, including differential	
Platelet count	
Chemistry	
AST ALT Total bilirubin Direct bilirubin (reflex only if total bilirubin is elevated) ALP LDH Creatinine BUN or serum urea Glucose Amylase - screening only	Lipase - screening only Total protein Albumin Sodium Potassium Chloride Calcium Phosphorus TSH, free T3 and free T4 - screening TSH, with reflexive fT3 and fT4 if TSH is abnormal - on treatment
Urinalysis - screening 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	
Hepatitis B/C, (HBV sAG, HCV antibody or HCV RNA) - screening only	

Table 9.4.4-1: Clinical Laboratory Assessments

HIV-1 and -2 antibody (screening only, and as mandated by local requirement)
Other Analyses
Pregnancy test (WOCBP only: serum or urine - minimum sensitivity 25 IU/L or equivalent units of HCG).
FSH screening - only required to confirm menopause in women < age 55 years

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; FSH, follicle-stimulating hormone; HBV sAG, hepatitis B virus surface antigen; HCV, hepatitis C virus; HCG, human chorionic gonadotropin; HIV, human immunodeficiency virus; LDH, lactate dehydrogenase; RNA, ribonucleic acid; T3, triiodothyroninie; T4, thyroxine; TSH, thyroid stimulating hormone; WOCBP, women of childbearing potential.

9.4.5 Imaging/Other Safety Assessment

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

9.5 Pharmacokinetics and Immunogenicity Assessments

Samples for PK and immunogenicity assessments for BMS-986207, nivolumab, and ipilimumab will be collected for participants at the time points indicated in Table 9.5-1. All on-treatment PK and immunogenicity time points are intended to align with days on which study intervention is administered. If it is known that a dose is going to be delayed, then collect the predose sample just prior to the delayed dose. However, if a predose sample is collected, but the dose is subsequently delayed, do not collect an additional predose sample.

Draw blood samples from a site other than the infusion site (ie, contralateral arm) on days of infusion for all pre-dose and end of infusion-PK (EOI-PK) samples. Please ensure accurate documentation of the time and date of sample collection. If the infusion was interrupted, the interruption details will also be documented on the CRF.

End of infusion (EOI) samples for nivolumab, ipilimumab and BMS-986207 should be collected immediately following the last drug infusion (preferably within 5 minutes after end of infusion) on the contralateral arm (ie, the arm not for the infusion). Since the EOI-PK sample is drawn with the intent of accurately estimating the maximum concentration 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.

Ctrough and EOI concentrations (Ceoi) of BMS-986207, nivolumab and ipilimumab will be reported. In addition, concentration-time data may be used in an integrated population PK analysis along with data from other studies, which will be the subject of a separate report.

Concentration and ADA analyses for each study drug will be performed by validated bioanalytical method(s). Immunogenicity samples positive for anti-nivolumab, anti-ipilimumab, and anti-BMS-986253 may be analyzed for neutralizing antibodies by validated methods.

Bioanalytical samples designated for assessments (eg, immunogenicity, PK, or biomarker) from the same collection time point may be used interchangeably for analyses, if required (including, but not limited to, insufficient volume for complement assessment, to follow-up on suspected immunogenicity related AE, etc).

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

Treatment assignments will be released to the bioanalytical laboratory in order to minimize unnecessary analysis and/or reanalysis of PK/ADA samples. Placebo samples will not be analyzed.

Further details of sample collection, processing, and shipment will be provided in the laboratory/procedure manual.

Table 9.5-1: Pharmacokinetic and Immunogenicity Sampling Schedule for BMS-986207, Nivolumab, and Ipilimumab

Study Day of Sample Collection (1 Cycle = 6 weeks)	Event	Time Relative to Nivolumab Dose (hr:min)	BMS-986207 PK Serum Sample	Nivolumab PK Serum Sample	Ipilimumab PK Serum Sample	BMS-986207 IMG (ADA) Serum Sample	Nivolumab IMG (ADA) Serum Sample	Ipilimumab IMG (ADA) Serum Sample
Cycle 1 Day 1	Predose[a]	00:00	X	X	X	X	X	X
	End of infusion[b]	See note[b]	X	X	X			
Cycle 1 Day 8		168:00	X	X	X			
Cycle 1 Day 15		336:00	X	X	X			
Cycle 1 Day 22	Predose[a]	00:00	X	X	X	X	X	
Cycle 1 Day 29[c]		168:00	X	X	X			
Cycle 2 Day 1	Predose[a]	00:00	X	X	X	X	X	X
Cycle 2 Day 22	Predose[a]	00:00	X	X	X			
Cycle 3 Day 1	Predose[a]	00:00	X	X	X	X	X	X
	End of infusion[b]	00:00	X	X	X			
Cycle 4 Day 1	Predose[a]	00:00	X	X	X	X	X	X
Every 4 cycles starting at Cycle 5 Day 1 until Cycle 17 (C5D1, C9D1, C13D1, C17D1)	Predose[a]	00:00	X	X	X	X	X	X

Abbreviations ADA, anti-drug antibody; C, cycle; Cmax, maximum concentration; D, day; EOI, end of infusion; IMG, immunogenicity; IV, intravenous; PK, pharmacokinetic.

[a] All predose samples for nivolumab, ipilimumab and BMS-986207 should be taken prior to the start of nivolumab infusion. If it is known that a dose is going to be delayed, then collect the predose sample just prior to the delayed dose. However, if a predose sample is collected, but the dose is subsequently delayed, do not collect an additional predose sample.

[b] EOI samples for nivolumab, ipilimumab, and BMS-986207 should be collected immediately following the last drug infusion (preferably within 5 minutes after EOI) on the contralateral arm (ie, the arm not for the infusion). Since the EOI-PK sample is drawn with the intent of accurately estimating the 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 EOI. 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 EOI is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.

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

9.6 Immunogenicity Assessments

See Section 9.5.

9.7 Genetics

Genetic assessments include deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) analysis, as described in Section 9.8 (Biomarkers).

9.8 Biomarkers

Biomarkers are increasingly playing a key role in the development of cancer therapeutics. By evaluating treatment-induced changes in molecular markers measured in tissue and body fluids, the activity of experimental agents may be assessed and the details of their mechanisms of action may be elucidated. To explore potential predictive markers for clinical response to BMS-986207 in combination with nivolumab and ipilimumab, 4 types of specimens will be obtained from all participants for biomarker testing: (i) whole blood, (ii) serum, (iii) plasma, and (iv) tumor tissue. The sample subtypes and testing plans associated with each specimen type are described in the sections below and in Table 9.8-1. Blood and tumor tissue samples will be collected in this study at baseline and on treatment to identify markers associated with clinical activity and mechanism of action of BMS-986207 in combination with nivolumab and ipilimumab. Complete instructions on the collection, processing, handling, and shipment of all samples described herein will be provided to sites in a separate Laboratory Manual.

Table 9.8-1: Biomarker Sampling Schedule

Study Day of Sample Collection[a] (1 Cycle = 6 weeks)	Tumor Biopsy[b]	Serum Biomarkers	Whole Blood PBMC	Whole Blood Immunophenotyping	Whole Blood DNA	Plasma for ctDNA
Screening	X	X	X			X
Cycle 1 Day 1		X	X	X	X	X
Cycle 1 Day 8		X	X	X		
Cycle 1 Day 15		X		X		
Cycle 1 Day 22		X		X		
Cycle 1 Day 29	X	X	X			
Cycle 2 Day 1		X	X	X		X
Every 4 cycles starting at Cycle 5 Day 1 until Cycle 17 (C5D1; C9D1; C13D1; C17D1)						X
Progression (optional)[c]	X	X	X			X
End of Treatment or Follow-up Visit 1						

Abbreviations: C, cycle; ctDNA, circulating tumor deoxyribonucleic acid; D, day; DNA, deoxyribonucleic acid; PBMC, peripheral blood mononuclear cells.

[a] All collections in the table are mandatory except for collections at the time of progression, when they are optional, but strongly encouraged. All collections should be taken prior to the start of drug infusion. Detailed instructions for the collection, processing, and shipping of each sample will be provided in the Laboratory Manual.

[b] Participant consent for archival biopsy or fresh biopsy collection at screening and fresh biopsy collection at C1D29 is mandatory, while it is optional at progression, but strongly encouraged. On-treatment tumor biopsy to be performed at C1D29 (± 5 days).

[c] Unscheduled visit included to allow for biopsy and biomarker collection at progression.

9.8.1 Tumor Tissue Specimens

Consent for pre-treatment and on-treatment tumor biopsy samples is required for enrollment. Pre-treatment tumor samples are required from all participants, prior to randomization. A FFPE tumor tissue block (preferred, equivalent to 20 sections) or a minimum of 20 unstained slides of tumor tissue 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 prior to randomization Samples may be from core biopsy, punch biopsy, excisional biopsy, or surgical specimen. Fine needle aspirates or other cytology samples are NOT acceptable. If despite best efforts, a minimum of 20 slides is not obtainable, submission of fewer slides may be acceptable in some circumstances following discussion with Sponsor or designee. Central laboratory must confirm receipt of evaluable tumor tissue as described in the Laboratory Manual prior to randomization. Assessment of tumor-cell PD-L1 expression by IHC also must be performed by central laboratory using pre-treatment tissue sample and results must be reported to IRT prior to randomization. Participants with inadequate sample are not eligible for treatment. Participants with indeterminate PD-L1 may be eligible if they have local PD-L1 results after discussion with Sponsor/Medical Monitor (or designee). On-treatment biopsies are mandatory if medically feasible on Cycle 1 Day 29. Detailed biopsy collection instructions will be available in the Laboratory Manual.

9.8.2 Biomarker Assessments in Tumor

Pre-treatment tumor samples will be assessed for PD-L1 expression using the Dako PD-L1 IHC 28-8 pharmDx validated assay. PD-L1 stained tissue sections will be assessed by a pathologist and membranous PD-L1 expression will be scored in tumor and immune cells per Laboratory Manual standard. Indeterminate PD-L1 tumor expression is defined as membrane staining that is obscured by high cytoplasmic staining or melanin content. Tumor tissue samples may be assessed by immunohistochemistry or other methods to determine the abundance of TILs and expression of immunoregulatory proteins by the tumor cell, TILs or surrounding stroma cells. Analytes may include, but are not limited to, TIGIT, DNAM-1, PVR, PD-L1, PD-1, CD8, and granzyme B (GzmB). Pharmacodynamic changes in TIL prevalence and the presence (and/or abundance) of immunoregulatory and other proteins may be examined. Baseline and pharmacodynamic measures may also be correlated to clinical outcomes. Sample analyses of messenger RNA (mRNA) may be completed using RNA isolated from tumor tissue. Targeted or whole transcriptome RNA sequencing, or similar methodologies may be used to assess gene expression signatures, such as, but not limited to, those associated with immune-related signaling, for potential association with clinical outcomes. DNA may also be isolated from the tumor tissue sample. Whole genome or whole exome sequencing may be performed using this DNA material to investigate potential associations between somatic mutations and copy number variation with efficacy measures. Tumor samples may be assessed for the expression of other immune related genes, RNAs and/or proteins, as well as the presence of immune cell populations using a variety of methodologies. Tumor tissue may also be used to investigate levels of TIGIT and BMS-986207 to assess receptor occupancy.

9.8.3 Biomarker Assessments in Peripheral Blood

Whole blood, serum and plasma samples will be collected at the times indicated in Table 9.8-1 for the measurement of DNA, RNA, and protein biomarkers. A variety of biomarkers that may be associated with the treatment efficacy or pharmacodynamic activity will be investigated in peripheral blood specimens taken from all participants prior to and during treatment. These blood samples may be assessed for changes in quantity or phenotype of immune cell subsets, changes in soluble factors such as cytokines and chemokines, changes in immune cell functionality, changes in gene expression, circulating tumor DNA (ctDNA) and as germline control for TMB or determination of genetic changes within the tumor. These biomarkers may be used to assess pharmacodynamic changes and potential associations with efficacy. Additional biomarker assessments may also be performed if samples are available.

9.8.3.1 Exploratory Serum Biomarkers

Serum-based biomarkers are currently under investigation for their potential to predict or correlate with efficacy to immunotherapy. Serum samples may be assessed by enzyme-linked immunosorbent assay, seromics, ctDNA measurements, metabolomics, and/or other relevant multiplex-based protein assay methods for immune-related factors that may be associated with efficacy or AEs; such factors may include, but are not limited to, assessments of cytokines induced by IFN-γ signaling (eg, T-cell chemoattractants CXCL9 and CXCL10), chemokines, inflammatory factors, cytolytic markers (eg, granzyme A/B, perforin), ctDNA, and other soluble factors.

Additional or alternative methods for the profiling of serum markers may be based on the analysis of circulating anti-tumor antibodies. Furthermore, proteomic signatures of association with clinical response may be identified via proteome profiling of serum peptides at baseline and during treatment.

9.8.3.2 Whole Blood for Immunophenotyping

Flow cytometry will be used to assess baseline and serial on-treatment alterations in composition/activation status of immune-cell subsets present in the whole blood samples. Lymphocyte subsets to be assayed may include, but not be limited to, CD8+ and CD4+ T-cell subsets, central memory, effector memory cells, Treg cells and populations of those cells as defined by the expression of activation, exhaustion, or signaling markers, such as Ki67, cytolytic markers, and/or PD-1. Monocytes/macrophages and dendritic cell populations may also be monitored in a similar fashion, with a focus on characterizing subsets defined by the expression of lineage-specific markers.

9.8.3.3 Peripheral Blood Mononuclear Cells

Whole-blood samples will also be collected for isolation and cryopreservation of peripheral blood mononuclear cells (PBMCs). Blood samples may be used for immunophenotyping or characterization of the immune cell subsets in the circulation, including, but not limited to, T cells, B cells, NK cells, myeloid-derived suppressor cells, or subpopulations of the aforementioned immune cell types. These cryopreserved samples may be used for functional activation tests or for

additional assays if new biology suggests analysis beyond the immunophenotyping described above.

9.8.3.4 Whole Blood DNA

Whole blood collected from participants prior to study intervention initiation may be used to generate genomic DNA. Genomic DNA from whole blood may be used as a comparator for participants with tumors examined by whole-exome or genome-mutation analysis. Whole-exome or whole-genome sequencing methods may be used for this analysis.

9.8.3.5 Plasma for circulating tumor DNA

Circulating tumor DNA (ctDNA) is a valid surrogate tumor biomarker for monitoring tumor burden and responses to immunotherapies. Plasma ctDNA is more convenient to test, faster to obtain and less invasive, minimizing procedure-related risks and offering the opportunity to perform serial monitoring. Plasma samples will be collected at the time points indicated in Table 9.8-1. Circulating tumor DNA (ctDNA) may be isolated from the plasma and may be assessed for association with TMB. Genomic profiles of ctDNA may be used to obtain information on tumor heterogeneity and to capture the emergence of resistant clones to therapy.

9.9 Additional Research

This protocol will include residual sample storage for additional research (AR).

For All sites:

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

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

Additional research is intended to expand the R&D capability at Bristol-Myers Squibb, and will support as yet undefined research aims that will advance our understanding of disease and options for treatment. This may also include genetic/genomic exploration aimed at exploring disease pathways, progression and response to treatment etc.

Sample Collection and Storage

- Residual biomarker samples from peripheral blood and tumor tissue collections (see Table 9.9-1) will also be retained for additional research purposes

Samples kept for future research will be stored at the BMS Biorepository in New Jersey, USA or an independent, BMS-approved storage vendor.

The manager of these samples will ensure they are properly used throughout their usable life and will destroy the samples at the end of the scheduled storage period, no longer than fifteen (15) years after the end of the study or the maximum allowed by applicable law.

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

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

Further details of sample collection and processing will be provided to the site in the procedure manual.

Table 9.9-1: Residual Sample Retention for Additional Research Schedule

Sample Type	Timepoints for which residual samples will be retained
PK/IMG	All
Tumor Biopsy	All
Blood Biomarker Samples	All

Abbreviations: IMG, immunogenicity; PK, pharmacokinetic.

9.10 Other Assessments

Not applicable.

9.11 Health Economics or Medical Resource Utilization and Health Economics

Health economics/medical resource utilization and health economics parameters will not be evaluated in this study.

10 STATISTICAL CONSIDERATIONS

10.1 Statistical Hypotheses

It is expected that the PFS in participants with 1L Stage IV NSCLC and PD-L1 expression ≥ 1% randomized to the BMS-986207 with nivolumab plus ipilimumab (Arm A) will be improved as compared to the PFS in participants receiving nivolumab plus ipilimumab (Arm B).

10.2 Sample Size Determination

The sample size of the study is calculated to have a sufficient probability of making the correct decision and have a low probability of making an incorrect decision under the pre-defined go criteria of primary efficacy endpoint of PFS in the PD-L1 ≥ 1% subgroup. Using a Bayesian augmented control (BAC) design, a portion of the control cohort for Study CA020016 will be

borrowed from participants treated with nivolumab plus ipilimumab in Study CheckMate 227 whose baseline prognostic factors are similar to the current randomized population. Based on the results in the CheckMate 227 study, it is assumed that the median PFS in Arm B is 5 months with a constant HR of 0.605 of Arm A vs Arm B for the PD-L1 ≥ 1% subgroup. The pre-defined go criteria at the end of the trial is probability (Pr) (HR < 1) > 0.9 and Pr (HR < 0.7) > 0.5. With the above assumption, 64 PFS events will need to be observed across the 2 arms, and there is 72.2% probability of making a go decision for a scenario at the interim analysis occurring at about 70% of the events, and 78.1% probability of making a go decision at the final analysis. This assumes 12 months for accrual and a minimum of 10 months follow up, for a total of 105 randomized participants with PD-L1 ≥ 1% expression, with approximately 180 participants randomized under current assumptions of prevalence in the primary subgroup. The participants will be randomized to the BMS-986207 with nivolumab plus ipilimumab (Arm A) and the nivolumab plus ipilimumab (Arm B) in a 2:1 ratio.

The sample size of the study is planned to ensure a sufficient probability of making the correct decision and a low probability of making an incorrect decision under the pre-defined go criteria for the primary objective and is based on assumptions of expected prevalence of PD-L1 expression in the different PD-L1 subgroups. To ensure the randomized population is representative of the NSCLC population and to allow for appropriate subgroup analyses, total enrollment may be adjusted to ensure at least 105 randomized participants with tumor cell PD-L1 expression ≥ 1%, at least 75 randomized participants with tumor cell PD-L1 expression 1% - 49%, and at least 75 randomized participants with tumor cell PD-L1 expression < 1%, based on central laboratory results. The operating characteristics based on simulation under various scenarios are listed in Table 10.2-1 and Table 10.2-2. The simulation is conducted with FACTS 6.2 software (Berry Consultants, LLC).[40]

Table 10.2-1: Operating Characteristics of Design Performance Under Different Sample Size, Borrowed Events, and Assumed True Hazard Ratios in the PD-L1 Expression ≥ 1% Population

Historical Control		Current Control (mPFS)	Assumed True HR	N = 105 (2:1)		N = 90 (2:1)	
Historical Control (mPFS)	Borrowed Effective Events			Go%	No-go%	Go%	No-go%
5 months	14	5 months	1	2.1%	90.0%	3.9%	88.4%
			0.7	49.1%	24.4%	51.9%	24.6%
			0.6	79.3%	6.3%	77.9%	8.8%
	1		1	5.6%	84.4%	7.5%	81.9%
			0.7	49.0%	28.2%	50.8%	28.4%
			0.6	74.9%	10.7%	73.0%	13.1%

Abbreviations: HR, hazard ratio; mPFS, median progression-free survival; PD-L1, programmed death-ligand 1.

Table 10.2-2: Operating Characteristics of Design Performance Under Different Sample Size, Borrowed Events, and Assumed True Hazard Ratios in the All Randomized Population

Historical Control		Current Control (mPFS)	Assumed True HR	N = 180 (2:1)		N = 150 (2:1)	
Historical Control (mPFS)	Borrowed Effective Events			Go%	No-go%	Go%	No-go%
5 months	30	5 months	1	0.3%	93.1%	0.6%	92.0%
			0.7	48.7%	11.1%	50.6%	15.7%
			0.6	86.6%	1.4%	84.9%	2.2%
	1		1	1.6%	90.3%	2.8%	87.9%
			0.7	48.2%	21.4%	50.1%	23.9%
			0.6	80.4%	4.6%	79.5%	7.1%

Abbreviations: HR, hazard ratio; mPFS, median progression-free survival.

10.3 Analysis Sets

For the purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign informed consent and are registered in IRT
Treated	All participants who received any amount of study intervention
Randomized	All participants who were randomized using IRT
Randomized PD-L1 $\geq$ 1%	All participants who were randomized using IRT with $\geq$ 1% PD-L1 tumor expression
Safety-evaluable	All randomized participants who have received study intervention (all 3 components) and have completed the safety-evaluation period of 12 weeks, or who discontinued any study intervention due to toxicity prior to completing the safety-evaluation period.
PK	All participants who received at least 1 dose of study intervention and had any available concentration-time data
Immunogenicity	All treated participants who have baseline and at least 1 post-baseline pre-infusion immunogenicity assessment

Abbreviations: IRT, interactive response technology; PD-L1, programmed death-ligand 1; PK, pharmacokinetic.

10.4 Statistical Analyses

The SAP will be developed and finalized before database lock and will describe the selection of participants to be included in the analyses and procedures for accounting for missing, unused, and spurious data. Below is a summary of planned statistical analyses of the primary and secondary

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

10.4.1 General Considerations

10.4.1.1 Propensity Score Method to Select Control Data from Historical Trial

One downside of using historical control data augmentation for the current control arm in randomized controlled trials is potential discrepancies in prognostic factors between the historical data and the current control arm. One approach to minimize the bias is to use the Propensity Score Method to select historical data that are similar in terms of the observable pre-treatment characteristics with participants in the current study. All participants treated with nivolumab plus ipilimumab in CheckMate 227 and Study CA020016 will be combined and fit by logistic regression model using prognostic factors (eg, histology, PD-L1 expression, tobacco use, performance status, age, and gender) as independent variables, and the group assignment to the historical or the current study (0 = historical trial, 1 = the current study) as response variable. The 1:1 Greedy Nearest Neighbor Matching algorithm will be used to select about 180 participants from the CheckMate 227 study who are similar to the randomized participants from Arm B in Study CA020016 at the levels of baseline covariates mentioned above (see Appendix 10).

10.4.1.2 Bayesian Augmented Control Design

Hazard ratio between treatment and control arm will be estimated by a Bayesian exponential likelihood model with BAC arm as follows:

$$\lambda_i = \lambda e^{\theta I_i}$$

where

- λi is the hazard rate corresponding to the treatment arm for the ith participant;
- λ is the hazard rate for the current control arm.
- *Ii* is an indicator variable equal to 1 if the ith participant in the group received the current experimental arm and 0 otherwise;
- θ is the log hazard ratio (HR) between the current experimental arm and the current control arm

We assign a weak normal prior to log HR assuming no treatment effect as a priori. The prior for control hazard rate λ is assumed to follow a gamma (α, β) distribution where alpha is used to gauge the borrowed effective number of events from historical data and alpha/beta is the hazard rate estimated from the selected historical control data after propensity score matching from the CheckMate 227 study (see Appendix 10).[41] The detailed implementation is discussed in the SAP.

10.4.1.3 Sensitivity Analyses

Sensitivity analyses will be conducted using frequentist log-rank test for HR of control and treatment arms for PFS without augmentation by historical control data.

10.4.2 Primary Endpoint(s)

Table 10.4.2-1: Primary Endpoints

Primary Endpoint	Description	Timeframe
PFS by BICR in the PD-L1 ≥ 1% population is defined as the time from randomization to the date of the first documented tumor progression by BICR or death from any cause.	The PFS curve will be estimated using the Kaplan-Meier product-limit method. A primary analysis will be based on the BAC study. A sensitivity analysis will be based on log-rank test stratified by the PD-L1 expression (< 1%, 1% - 49%, ≥ 50%) and histology will be used to compare PFS based on RECIST v1.1 by BICR between the 2 treatment arms. HR and corresponding 2-sided 95% CI for PFS primary endpoint analysis and 95% CI will be estimated using a Cox proportional hazard model, with treatment arm as a single covariate, stratified by above PD-L1 expression and histology to assist in interpretation of the PFS analysis.	Time from randomization and every 6 weeks after randomization for the first 48 weeks, then every 12 weeks, until progression (by BICR), death, study discontinuation or initiation of subsequent therapy

Abbreviations: BAC, Bayesian augmented control; BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; PD-L1, programmed death-ligand 1; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

10.4.3 Secondary Endpoint(s)

Table 10.4.3-1: Secondary Endpoints

Secondary Endpoint	Description	Timeframe
ORR is defined as the proportion of participants with a confirmed BOR of CR or PR by RECIST v1.1.	The ORR and its corresponding 95% exact CI will be calculated by Clopper-Pearson method for each arm, based on BICR and on investigator by RECIST v1.1. The ORR difference will also be estimated by 95% CI and in each subgroup.	Time from randomization and every 6 weeks after randomization for the first 48 weeks, then every 12 weeks, until progression, death, study discontinuation or initiation of subsequent therapy
DOR is defined for participants who have a confirmed CR or PR as the date from first documented CR or PR per RECIST v1.1 to the date of the documentation of disease progression or death due to any cause, whichever is earlier.	The median DOR will be estimated using the Kaplan-Meier method with corresponding 95% CI.	From the time of first documentation of objective response, until progression, death, study discontinuation or initiation of subsequent therapy

Table 10.4.3-1: Secondary Endpoints

Secondary Endpoint	Description	Timeframe
PFS is defined for all randomized participants as the date from randomization to the date of the documentation of disease progression by BICR or death due to any cause, whichever is earlier.	The PFS curve will be estimated using the Kaplan-Meier product-limit method. If testing occurs, a log-rank test stratified by the PD-L1 expression (< 1%, 1% - 49%, ≥ 50%) and histology will be used to compare PFS based on RECIST v1.1 by BICR between the 2 treatment arms in the all randomized population. The HR and corresponding 2-sided 95% CI in these populations will be estimated using a Cox proportional hazard model, with treatment arm as a single covariate, stratified by PD-L1 expression and histology. PFS in each treatment arm will be estimated in the PD-L1 defined subgroups.	Time from randomization and every 6 weeks after randomization for the first 48 weeks, then every 12 weeks, until progression (by BICR), death, study discontinuation or initiation of subsequent therapy
OS is defined as the time from randomization to the time of death due to any cause	The OS curve will be estimated using the Kaplan-Meier techniques in the PD-L1 ≥ 1% and all randomized populations. A 2-sided 95% CI for median OS in each treatment arm will be computed via the log-log transformation method. If testing occurs, a log-rank test stratified by the PD-L1 expression (< 1%, 1% - 49%, ≥ 50%) and histology will be used to compare OS between the 2 treatment arms. The HR and corresponding 2-sided 95% CI for OS in these populations will be estimated using a Cox proportional hazards model, with treatment arm as a single covariate, stratified by PD-L1 expression and histology.	Time from randomization until death for any cause
The incidence of AEs, SAEs, TRAEs, AEs leading to discontinuation, and deaths in the randomized population	Descriptive statistics of AEs will be presented using NCI CTCAE v5. On-study incidence of AEs, SAEs, and TRAEs, and AEs leading to discontinuation will be tabulated using worst grade per NCI CTCAE v5 criteria by System Organ Class and Preferred Term.	Time from first dose, up to 100 days after the last treatment of study drug

Abbreviations: AE, adverse event; BICR, blinded independent central review; BOR, best overall response; CI, confidence interval; CR, complete response; DOR, duration of response; HR, hazard ratio; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, severe adverse event; TRAE, treatment-related adverse event.

10.4.4 Exploratory Endpoint(s)

Table 10.4.4-1: Exploratory Endpoints

Exploratory Endpoint	Description	Timeframe
Pharmacokinetics		
Ctrough and Ceoi	Summary statistics to assess attainment of steady state: geometric means and coefficients of variation, by treatment and by day, Ctrough plots versus time	Time from first study intervention up to last treatment of study drug or discontinuation, or Cycle 17, whichever occur first.
Immunogenicity		
Incidence of ADA to BMS-986207, nivolumab, and ipilimumab Baseline ADA-positive participant is defined as a participant who has an ADA-detected sample at baseline ADA-positive participant is a participant with at least 1 ADA-positive sample relative to baseline after initiation of the treatment Summary measures of ADA titers and kinetics (onset and duration) Assessments of ADA effect on efficacy, safety, and PK	Frequency distribution of baseline ADA-positive participants and ADA-positive participants after initiation of the treatment for each of BMS-986207, nivolumab, and ipilimumab. Summary statistics/plots of ADA titers. Table of ADA onset and duration. Summary table/plot of ORR and occurance of select AEs by ADA status. Plots of PK parameters/exposures by ADA status may be generated as part of a population PK analysis and reported separately.	Time from first study intervention up to last treatment of study drug or discontinuation, or Cycle 17, whichever occur first.
Biomarker Analysis		
Summary measures of change (or % change) from baseline in various biomarkers in the tumor and peripheral blood	Summary statistics/plots by planned study day and dose in each arm. Plots of the time course of biomarkers by treatment arm	Time from first study intervention up to last treatment of study drug or discontinuation, or Cycle 17, whichever occur first.
Clinical Outcomes Assessments Analysis		
NSCLC-SAQ total score based on the PGIS and PGIC as anchor measures	Summary statistics of change in NSCLC-SAQ total score based on the PGIS and PGIC as anchor measures tabulated by treatment arm and time points	Time from randomization until death, loss to follow-up, withdrawal of consent, or conclusion of the study, whichever comes first, for a period of up to 4 years from randomization.

Table 10.4.4-1: Exploratory Endpoints

Exploratory Endpoint	Description	Timeframe
NSCLC-SAQ total score and FACT-G7	Mean change from baseline in NSCLC-SAQ total score and FACT-G7 by treatment arm	Time from randomization until death, loss to follow-up, withdrawal of consent, or conclusion of the study, whichever comes first, for a period of up to 4 years from randomization.
EQ-5D-5L utility index and EQ VAS scores	Mean change from baseline in EQ-5D-5L utility index and EQ VAS scores by treatment arm	Time from randomization until death, loss to follow-up, withdrawal of consent, or conclusion of the study, whichever comes first, for a period of up to 4 years from randomization.

Abbreviations: ADA, anti-drug antibody; AE, adverse event; Ceoi, end of infusion concentration; Ctrough, observed serum trough concentration; EQ VAS, EuroQol visual analog scale; FACT-G7, Functional Assessment of Cancer Therapy - General - 7 item version; NSCLC-SAQ, Non Small Cell Lung Cancer Symptom Assessment Questionnaire; ORR, objective response rate; PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Severity; PK, pharmacokinetic.

10.4.5 Other Analyses

Other analyses may include analyses of assessments which are not defined as endpoints, that need to be prespecified and not necessarily be reported in the clinical study report (CSR), such as, but not limited to, exploratory PK and biomarkers .

PK and biomarker exploratory analyses will be described in the SAP finalized before database lock. Population PK and exposure response analyses may also be conducted and would be the subject of a separate report. Additional pharmacodynamic analyses may be done and will be presented separately from the main CSR.

Analyses related to estimation of the meaningful change threshold for the NSCLC-SAQ will be described in a separate PRO psychometric analysis plan.

10.5 Interim Analyses

10.5.1 Safety Continuous Monitoring

A Bayesian continuous monitoring framework will be utilized to monitor for toxicity for a safety-evaluation period of 12 weeks of treatment and detect safety signals that may lead to changes in study conduct.[42] In addition to the study DMC, a SMT consisting of BMS research and development representatives (including clinical development, drug safety and statistics) and external representatives (including selected investigators) will regularly meet to evaluate the

accumulating unblinded safety data of participants of the study. If the specified safety boundary (number of AEs) is exceeded in Arm A, the DMC will be contacted for additional evaluations of unblinded data as needed.

For this type of monitoring, the proportion of TRAEs of Grade 3 to Grade 4 is used to provide formal monitoring boundaries. These boundaries were established using a prior distribution of Beta(0.66, 1.37), which is a weak informative prior reflecting the approximate proportion of Grade 3 to Grade 4 TRAEs in the nivolumab plus ipilimumab arm in Study CA209227 (ie, 33%). The posterior distribution at any time point is Beta(0.66 + n, 1.37 + [m-n]), where n is the number of participants observed with Grade 3 to Grade 4 TRAEs, and m is the total number of safety-evaluable participants. (For the definition of safety-evaluable participants, see Section 10.3).

The monitoring function for toxicity is defined as the posterior probability of (Grade 3 to Grade 4 TRAEs > 40% | cumulating data) > 0.85. This criterion implies that there is a greater than 85% predictive probability that the aggregate toxicity rate in Arm A is larger than 40%. It will be applied after at least 8 randomized participants in Arm A are safety-evaluable and can be performed on a continuous basis afterwards. The resulting boundaries are presented in Table 10.5.1-1. This monitoring boundary criterion is not binding.

If, anytime during the study (first 126 participants), this Grade 3 to Grade 4 TRAE proportion reaches the pre-specified threshold for toxicity, then, taking into account all available safety information, additional evaluation will be conducted to allow a complete by treatment arm safety assessment and risk benefit evaluation.

Table 10.5.1-1: Safety Continuous Monitoring Boundary for Arm A

Number of Safety-evaluable Participants in Arm A[a]	Toxicity Boundary (# Evaluable Participants with Event) for > 85 Probability of TRAE > 40%
8	5
9-10	6
11-12	7
13-14	8
15-16	9
17-19	10
20-21	11
22-23	12
24-25	13
26-28	14
29-30	15
31-32	16
33-35	17

Table 10.5.1-1: Safety Continuous Monitoring Boundary for Arm A

Number of Safety-evaluable Participants in Arm A[a]	Toxicity Boundary (# Evaluable Participants with Event) for > 85 Probability of TRAE > 40%
36-37	18
38-40	19
41-42	20
43-44	21
45-47	22
48-49	23
50-52	24
53-54	25
55-57	26
58-59	27
60	28

Abbreviation: TRAE, treatment-related adverse event.

[a] Additional thresholds for the monitoring of > 60 participants will be calculated by the Statistician.

10.5.1.1 Efficacy Interim Analysis

An interim analysis of PFS will also be done after approximately 70% of the total number of events are projected to have occurred. At this time, an interim analysis of ORR will also be done (anticipate approximately 126 participants will be randomized and followed for at least 2 post-baseline scans). The purpose of the interim analysis is for internal decisions outside the conduct of this trial. An independent statistician external to BMS will perform the analysis.

10.5.1.2 DMC Analysis

The DMC will have access to periodic unblinded interim reports of safety and efficacy to allow a benefit-risk assessment, based on data summaries as specified in the charter, at pre-planned meetings (eg, at least every 6 months or as specified in the charter). The DMC review will include early monitoring for tolerability of the triplet combination in the first 8 participants who are randomized to Arm A. This analysis will occur after the 8 participants have completed 6 weeks of treatment. Additional and any ad hoc analyses as requested based on emerging safety signals may also be performed to support additional ad hoc DMC meetings (eg, based on assessment of aggregate data by the BMS SMT). Results will not be shared with BMS prior to the final analysis, unless otherwise specified under pre-specified conditions described in the charter. An independent statistician external to BMS will perform the analyses. Details are included in the DMC charter.

The DMC will also conduct an efficacy interim anaysis as described in Section 10.5.1.1.

The DMC/Review Board charter will describe the statistical analysis and procedures related to DMC operations.

11 REFERENCES

[1] Esfahani K, Roudaia L, Buhlaiga N, et al. A review of cancer immunotherapy: from the past, to the present, to the future. Curr Oncol 2020;27(Suppl 2):S87-97.

[2] Hellmann MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus ipilimumab in advanced non–small-cell lung cancer. N Engl J Med 2019;381:2020-31.

[3] Opdivo intravenous infusion. Japan Prescribing Information. Ono Pharmaceutical Co, Ltd; Bristol-Myers Squibb KK;2020.

[4] Jiang C, Qu X, Ma L, et al. CD155 expression impairs anti-PD1 therapy response in non-small cell lung cancer. Clin Exp Immunol 2022;uxac020. Epub ahead of print.

[5] Rodriguez-Abreu D, Johnson ML, Hussein MA, et al. Primary analysis of a randomized, double-blind, phase II study of the anti-TIGIT antibody tiragolumab (tira) plus atezolizumab (atezo) versus placebo plus atezo as first-line (1L) treatment in patients with PD-L1-selected NSCLC (CITYSCAPE)[abstract]. J Clin Oncol 2020;38:(Suppl 15):9503.

[6] Niu J, Nagrial A, Voskoboynik M, et al. 1410P Safety and efficacy of vibostolimab, an anti-TIGIT antibody, plus pembrolizumab in patients with anti-PD-1/PD-L1-naive NSCLC. Ann Oncol 2020;31(Suppl 4):S891-2.

[7] BMS-986207 Investigators Brochure Version 5. Bristol-Myers Squibb Company. 2022. Document Control No. 930104342.

[8] Ipilimumab (BMS-734016) Investigator Brochure, Version 23. Bristol Myers Squibb Company. 2020. Document Control No. 930017531.

[9] Nivolumab (BMS-936558) Investigator Brochure, Version 19. Bristol Myers Squibb Company. 2020. Document Control No. 930038243.

[10] Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. In press 2021.

[11] Hanna NH, Schneider BJ, Temin S, et al. Therapy for stage IV non-small-cell lung cancer without driver alterations: ASCO and OH (CCO) joint guideline update. J Clin Oncol 2020;38:1608-32.

[12] Mok TSK, Wu YL, Kudaba I, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. Lancet 2019;393:1819-30.

[13] Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med 2016;375:1823-33.

[14] Reck M, Rodriguez-Abreu D, Robinson AG, et al. Updated analysis of KEYNOTE-024: pembrolizumab versus platinum-based chemotherapy for advanced non-small-cell lung cancer with PD-L1 tumor proportion score of 50% or greater. J Clin Oncol 2019;37:537-46.

[15] Keytruda injection. US Prescribing Information. Merck & Co, Inc.; 2020.

[16] Herbst RS, Giaccone G, de Marinis F, et al. Atezolizumab for first-line treatment of PD-L1-selected patients with NSCLC. N Engl J Med 2020;383:1328-39.

[17] Tecentriq injection. US Prescribing Information. Genentech, Inc.; 2020.

[18] Stanietsky N, Simic H, Arapovic J, et al. The interaction of TIGIT with PVR and PVRL2 inhibits human NK cell cytotoxicity. Proc Natl Acad Sci U S A 2009;106:17858-63.

[19] Joller N, Hafler JP, Brynedal B, et al. Cutting edge: TIGIT has T cell-intrinsic inhibitory functions. J Immunol 2011;186:1338-42.

[20] Wherry EJ, Kurachi, M. Molecular and cellular insights into T cell exhaustion. Nat Rev Immunol 2015;15:486-99.

[21] Johnston RJ, Comps-Agrar L, Hackney J, et al. The immunoreceptor TIGIT regulates antitumor and antiviral CD8(+) T cell effector function. Cancer Cell 2014;26:923-37.

[22] Li M, Xia P, Du Y, et al. T-cell immunoglobulin and ITIM domain (TIGIT) receptor/poliovirus receptor (PVR) ligand engagement suppresses interferon-γ production of natural killer cells via β-arrestin 2-mediated negative signaling. J Biol Chem 2014;289:17647-57.

[23] Opdivo US Prescribing Information. Bristol-Myers Squibb Company; 2021.

[24] Opdivo Annex 1 Summary of Product Characteristics. Bristol-Myers Squibb Pharma EEIG; 2020.

[25] Yervoy US Prescribing Information. Bristol-Myers Squibb Company; 2020.

[26] Yervoy Annex 1 Summary of Product Characteristics. Bristol-Myers Squibb Pharma EEIG; 2021.

[27] Ahn MJ, Niu J, Kim DW, et al. 1400P Vibostolimab, an anti-TIGIT antibody, as monotherapy and in combination with pembrolizumab in anti-PD-1/PD-L1-refractory NSCLC. Ann Oncol 2020;31(Suppl 4):S887.

[28] An open-label, randomized Phase 3 trial of nivolumab, or nivolumab plus ipilimumab, or nivolumab plus platinum doublet chemotherapy versus platinum doublet chemotherapy in subjects with chemotherapy-naive Stage IV or recurrent non-small cell lung cancer (NSCLC) (CA209227). Final clinical study report for part 1 of study CA209227. Bristol-Myers Squibb Company; 2019. Document Control No. 930142967.

[29] National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. Non-Small Cell Lung Cancer. Version 1.2021. Available from: URL:

http://www.nccn.org/professionals/physician_gls/pdf/nscl_blocks.pdf. Accessed December 14, 2020.

[30] Schadendorf D, Wolchok JD, Hodi SF, et al. Efficacy and safety outcomes in patients with advanced melanoma who discontinued treatment with nivolumab and ipilimumab because of adverse events: a pooled analysis of randomized Phase II and III trials. J Clin Oncol 2017;35:3807-14.

[31] Schadendorf D, Hodi SF, Robert C, et al. Pooled analysis of long-term survival data from Phase II and Phase III trials of ipilimumab in unresectable or metastatic melanoma. J Clin Oncol 2015;33:1889-94.

[32] Brahmer J, Horn L, Jackman D, et al. Five-year follow-up from the CA209-003 study of nivolumab in previously treated advanced non-small cell lung cancer: clinical characteristics of long-term survivors [abstract]. Proceedings of the American Association for Cancer Research (AACR) Annual Meeting; 2017 Apr 1-5; Washington, DC, USA.

[33] Felip E, Gettinger SN, Burgio MA, et al. Three-year follow-up from Checkmate 017/057: Nivolumab versus docetaxel in patients with previously treated advanced non-small lung cancer (NSCLC). Proceedings of the European Society of Medical Oncology (ESMO) Annual Meeting. 2017 Sep 8-12; Madrid, Spain. Poster 1301PD.

[34] Spigel DR, McLeod M, Hussein MA, et al. Randomized results of fixed-duration (1-yr) vs continuous nivolumab in patients (pts) with advanced non-small cell lung cancer (NSCLC) [abstract]. Ann Oncol 2017;28(suppl 5):v460-96.

[35] Dasgupta A, Dhingra N, Stinchcombe T, et al. Progression-free survival as surrogate endpoint for overall survival in NSCLC trials of anti PD-1 and anti PD-L1 agents and the impact of line of treatment [abstract]. J Clin Oncol 2018;36(Suppl):e21135.

[36] Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 2009;15:7412-20.

[37] McCarrier KP, Atkinson TM, DeBusk KP, et al. Qualitative development and content validity of the Non-small Cell Lung Cancer Symptom Assessment Questionnaire (NSCLC-SAQ), a patient-reported outcome instrument. Clinical Ther 2016;38:794-810.

[38] Yanez, B, Pearman T, Lis CG, et al. The FACT-G7: a rapid version of the functional assessment of cancer therapy-general (FACT-G) for monitoring symptoms and concerns in oncology practice and research. Ann Oncol 2013;24:1073-8.

[39] Mah K, Swami N, Le LW, et al. Validation of the 7-item Functional Assessment of Cancer Therapy‐General (FACT‐G7) as a short measure of quality of life in patients with advanced cancer. Cancer 2020;126:3750-7.

[40] FACTS 6.2: Fixed and Adaptive Clinical Trial Simulator. Berry Consultants. Available from: URL: www.berryconsultants.com.

[41] Smith CL, Thomas Z, Enas N, et al. Leveraging historical data into oncology development programs: Two case studies of phase 2 Bayesian augmented control trial designs. Pharm Stat 2020;19:276-90.

[42] Thall PF, Simon R. Practical Bayesian guidelines for phase IIB clinical trials. Biometrics 1994;50:337-49.

12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
1L	first-line
ADA	anti-drug antibody
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AR	additional research
ART	antiretroviral therapy
AST	Aspartate aminotransferase
AT	aminotransaminases
AxMP	auxiliary medicinal product
BAC	Bayesian augmented control
BICR	blinded independent central review
BMI	body mass index
BMS	Bristol-Myers Squibb Company
BOIN	Bayesian optimal interval
BOR	best overall response
BP	blood pressure
BRAF	b-rapidly accelerated fibrosarcoma proto-oncogene
C1D1	cycle 1 day 1
CD	cluster of differentiation
Ceoi	end of infusion concentration
cHL	classical Hodgkin Lymphoma
CI	confidence interval
Cmax	maximum observed concentration
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CR	complete response
CRC	colorectal cancer
CRS	cytokine release syndrome

Term	Definition
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
CTLA-4	cytotoxic T-lymphocyte associated protein 4
Ctrough	observed serum trough concentration
D	day
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DNAM-1	DNAX accessory molecule 1, also called CD226
DOR	duration of response
DRESS	drug reaction with eosinophilia and systemic symptoms
EC50	half-maximal effective concentration
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
ELISA	enzyme linked immunosorbent assay
EOI	end of infusion
EOT	end of treatment
EQ-5D-5L	5 Level EQ-5D Questionnaire
EQ VAS	EuroQol visual analog scale
EU	European Union
EU-CTR	European Union Clinical Trials Regulation
EWB	emotional well-being
FACT-G7	Functional Assessment of Cancer Therapy - General - 7 item version
Fc	fragment crystallizable
FDA	Food and Drug Administration
FDG-PET	fluorodeoxyglucose positron emission tomography
FFPE	formalin-fixed paraffin-embedded
FSH	follicle-stimulating hormone

Term	Definition
FWB	functional well-being
GBS	Guillain-Barre Syndrome
HBV	hepatitis B virus
HBV sAG	hepatitis B virus surface antigen
HCC	hepatocellular carcinoma
HCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	hazard ratio
HRT	hormone replacement therapy
HuMAb	human monoclonal antibody
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IFN-γ	interferon gamma
Ig	immunoglobulin
IHC	immunohistochemistry
IMAE	immune-mediated adverse event
IMG	immunogenicity
IMP	Investigational Medicinal Product
IO	immuno-oncology
IP	Investigational Product
Ipi	ipilimumab
IRB	Institutional Review Board
IRT	interactive response technology
IUS	intrauterine hormone-releasing system
IV	intravenous
KRAS	Kirsten rat sarcoma viral oncogene homolog
LAM	lactational amenorrhea method
mAb	monoclonal antibody
MG	Myasthenia Gravis
MRI	magnetic resonance imaging

Term	Definition
N	number
NCI	National Cancer Institute
NE	not evaluable
Nivo	nivolumab
NK	natural killer
NSCLC	non-small cell lung cancer
NSCLC-SAQ	Non Small Cell Lung Cancer Symptom Assessment Questionnaire
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PD-1	programmed death-1
PD-L1	programmed death-ligand 1
PD-L2	programmed death-ligand 2
PE	physical examination
PET	positron emission tomography
PET-CT	positron emission tomography-computed tomography
PFS	progression-free survival
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	pharmacokinetic
Pr	probability
PR	partial response
PRO	patient-reported outcome
PS	performance status
Pts	participants
PVR	poliovirus receptor
PWB	physical well-being
Q2W	every 2 weeks
Q3W	every 3 weeks
Q4W	every 4 weeks
Q6W	every 6 weeks

Term	Definition
Q12W	every 12 weeks
R&D	Research and Development
RCC	renal cell carcinoma
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
ROS-1	c-ros oncogene 1
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
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
SJS	Stevens-Johnson syndrome
SmPC	Summary of Product Characteristics
SMT	safety management team
TEN	toxic epidermal necrolysis
TIGIT	T cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain
TIL	tumor infiltrating lymphocyte
TMB	tumor mutational burden
TPS	tumor proportion score
TRAE	treatment-related adverse event
Treg	T-regulatory cell
TSH	thyroid stimulating hormone
UK	United Kingdom
ULN	upper limit of normal
US	United States
USPI	US Prescribing Information
VAS	visual analog scale
WOCBP	women of childbearing potential
WWPS	Worldwide Patient Safety

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

The terms "participant" and "subject" refer to a person who has consented to participate in the clinical research study. Typically, the term "participant" is used in the protocol and the term "subject" is used in the Case Report Form (CRF).

REGULATORY AND ETHICAL CONSIDERATIONS

This study will be conducted in accordance with:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws, regulations, and requirements

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

All potential serious breaches must be reported to the Sponsor or designee immediately. A potential serious breach is defined as a Quality Issue (eg, protocol deviation) that is likely to affect, to a significant degree, one or more of the following: (1) the rights, physical safety or mental integrity of one or more participants; (2) the scientific value of the clinical trial (eg, reliability and robustness of generated data). Items (1) or (2) can be associated with either GCP regulation(s) or trial protocol(s).

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

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

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, Investigator's Brochure, product labeling information, ICF, participant recruitment materials (eg, advertisements), and any other written information to be provided to participants.

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

The investigator is responsible for providing oversight of the conduct of the study at the site and adherence to requirements of the following where applicable:

- ICH guidelines,
- United States Code of Federal Regulations, Title 21, Part 50 (21CFR50)
- European Union Directive 2001/20/EC; or
- European Regulation 536/2014 for clinical studies (if applicable),
- European Medical Device Regulation 2017/745 for clinical device research (if applicable),
- the IRB/IEC
- and all other applicable local regulations.

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

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

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

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

Documentation of approval/favorable opinion signed by the chairperson or designee of the IRB(s)/IEC(s) and, if applicable, also by the local Health Authority, must be sent to Bristol-Myers Squibb (BMS).

If an amendment substantially alters the study design or increases the potential risk to the participant: (1) the ICF 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 participants currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new participants prior to enrollment.

FINANCIAL DISCLOSURE

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information, in accordance with 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 participants are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

The Sponsor or designee will provide the investigator with an appropriate sample ICF, which will include all elements required by the ICH GCP, and applicable regulatory requirements. The sample ICF will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

The investigator or his/her representative must:

- Obtain IRB/IEC written approval/favorable opinion of the written ICF and any other information to be provided to the participant prior to the beginning of the study and after any revisions are completed for new information.
- Provide a copy of the ICF and written information about the study in the language in which the participant is proficient prior to clinical study participation. The language must be nontechnical and easily understood.
- Explain the nature of the study to the participant and answer all questions regarding the study.
- Inform participant that his/her participation is voluntary. Participant will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- Allow time necessary for participant to inquire about the details of the study.

Obtain an ICF signed and personally dated by participant and by the person who conducted the informed consent discussion.

- Include a statement in participant's medical record that written informed consent was obtained before participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Re-consent participant to the most current version of the ICF(s) during his/her participation in the study, as applicable.

Revise the ICF 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 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 participants must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the participant's signed ICF, and, in the US, the participant's signed HIPAA Authorization.

The ICF must also include a statement that BMS and local and foreign regulatory authorities have direct access to participant records.

BMS COMMITMENT TO DIVERSITY IN CLINICAL TRIALS

The mission of BMS is to transform patients' lives through science by discovering, developing, and delivering innovative medicines that help them prevail over serious diseases.
BMS is committed to doing its part to ensure that patients have a fair and just opportunity to achieve optimal health outcomes.

BMS is working to improve the recruitment of a diverse participant population with the goal that the clinical trial becomes more reflective of the real-world population and the people impacted by the diseases studied.

DATA PROTECTION, DATA PRIVACY, AND DATA SECURITY

BMS collects and processes personal data of study participants, patients, health care providers, and researchers for biopharmaceutical research and development to advance innovative, high-quality medicines that address the medical needs of patients. BMS ensures the privacy, protection, and confidentiality of such personal data to comply with applicable laws. To achieve these goals, BMS has internal policies that indicate measures and controls for processing personal data. BMS adheres to these standards to ensure that collection and processing of personal data are limited and proportionate to the purpose for which BMS collects such personal data. This purpose is clearly and unambiguously notified to the individual at the time of collection of personal data. In the true spirit of science, BMS is dedicated to sharing clinical trial information and data with participants, medical/research communities, the media, policy makers, and the general public. This is done in a manner that safeguards participant privacy and informed consent while respecting the integrity of national regulatory systems. Clinical trial data, health-related research, and pharmacovigilance activities on key-coded health data transferred by BMS across national borders is done in compliance with the relevant data protection laws in the country and GCP requirements.

BMS protects Personal Information with adequate and appropriate security controls as indicated under the data protection laws. To align with the recommended security standards, BMS has adopted internal security standards and policies to protect personal data at every stage of its processing.

To supplement these standards, BMS enters into Clinical Trial Agreements (CTAgs) with confidentiality obligations to ensure proper handling and protection of personal data by third parties accessing and handling personal data.

BMS takes unauthorized access and disclosure of Personal Information very seriously. BMS has adopted the security standards that include National Institute of Standards and Technology Cybersecurity Framework for studies in the US. BMS aligns with these standards to continuously assess and improve its ability to protect, detect, and respond to cyber attacks and other unauthorized attempts to access personal data. These standards also aid in mitigating possible adverse effects. Furthermore, BMS Information Technology has defined 6 principles to protect our digital resources and information:

1) Responsibilities of IT Personnel
2) Securing the BMS Digital Infrastructure
3) Identity and Access Management
4) External Partner Connections
5) Cyber Threat Detection and Response
6) Internal Cyber Incident Investigation

SOURCE DOCUMENTS

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the electronic CRF (eCRF) that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained.

- The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definitions of what constitutes source data can be found in 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).

The investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original, and attributable, whether the data are handwritten 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 records/electronic health records, adverse event (AE) tracking/reporting, protocol-required assessments, and/or drug accountability records.

When paper records from such systems are used in place of an 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 INTERVENTION RECORDS

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

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

BMS or its 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 (EDC) tool, eCRFs 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 the electronic SAE form is not available, a paper SAE form can be used.

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

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

The completed CRF and SAE/pregnancy CRFs must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a sub-investigator and who is delegated this task on the Delegation of Authority Form. Sub-investigators in Japan may not be delegated the CRF approval task. The investigator must retain a copy of the CRFs, including records of the changes and corrections.

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

MONITORING

Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site, they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable.

In addition, the study may be evaluated by the 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 the 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 its 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 its designee will notify the investigator (or head of the study site in Japan) when the study records are no longer needed.

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

RETURN OF STUDY TREATMENT

For this study, study treatments (those supplied by BMS or 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 interventions supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor, unless study treatments containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics). Partially used study interventions and/or empty containers may be destroyed after proper reconciliation and documentation. But unused IMP must be reconciled by site monitor/Clinical Research Associate prior to destruction. If study treatments will be returned, the return will be arranged by the responsible Study Monitor.
Study treatments sourced by site, not supplied by BMS (or its vendors; eg, study treatments sourced from the site's stock or commercial supply or a specialty pharmacy)	It is the investigator's or designee's responsibility to dispose of all containers according to the institutional guidelines and procedures.

It is the investigator's or designee's responsibility to arrange for disposal of study interventions, 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 standard operating procedures and a copy provided to BMS upon request.

- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal (eg, 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 Study Monitor to review throughout the clinical trial period.

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

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

STUDY AND SITE START AND CLOSURE

The Sponsor/designee reserves the right to close the study site or to terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include, but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local Health Authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

DISSEMINATION OF CLINICAL STUDY DATA

In order to benefit potential study participants, patients, healthcare providers and researchers, and to help BMS honor its commitments to study participants, BMS will make information about clinical research studies and a summary of their results available to the public as per regulatory and BMS requirements. BMS will post study information on local, national or regional databases in compliance with national and international standards for disclosure. BMS may also voluntarily disclose information to applicable databases.

In the European Union (EU), after EU Clinical Trial Regulation 536/2014 is in effect, the summary of results and summary for laypersons will be submitted within 1 year [6 months for studies including pediatric population] of the end of trial in EU/European Economic Area and third countries.

CLINICAL STUDY REPORT

A Signatory Investigator must be selected to sign the Clinical Study Report (CSR).

For each CSR related to this protocol, the following criteria will be used to select the Signatory Investigator:

- External Principal Investigator designated at protocol development
- National Coordinating Investigator
- Study Steering Committee chair or their designee
- Participant recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Regional representation (eg, among top quartile of enrollers from a specified region or country)

SCIENTIFIC PUBLICATIONS

The data collected during this study are confidential and proprietary to the Sponsor or designee. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the Clinical Trial Agreement (CTAg) governing [study site or investigator] participation in the study. These requirements include, but are not limited to, submitting proposed publications to the Sponsor or designee at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTAg.

Scientific publications (such as abstracts, congress podium presentations and posters, and manuscripts) of the study results will be a collaborative effort between the study Sponsor and the external authors. No public presentation or publication of any interim results may be made by any Principal Investigator, sub-investigator, or any other member of the study staff without the prior written consent of the Sponsor.

Authorship of publications at BMS is aligned with the criteria of the International Committee of Medical Journal Editors (ICMJE, www.icmje.org). Authorship selection is based upon significant contributions to the study (ie, ICMJE criterion #1). Authors must meet all 4 ICMJE criteria for authorship:

1) Substantial intellectual contribution to the conception or design of the work; or the acquisition of data (ie, evaluable participants with quality data), analysis, or interpretation of data for the work (eg, problem solving, advice, evaluation, insights and conclusion); AND
2) Drafting the work or revising it critically for important intellectual content; AND
3) Final approval of the version to be published; AND
4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Those who make the most significant contributions, as defined above, will be considered by BMS for authorship of the primary publication. Sub-investigators will generally not be considered for authorship in the primary publication. Geographic representation will also be considered.

Authors will be listed by order of significant contributions (highest to lowest), with the exception of the last author. Authors in first and last position have provided the most significant contributions to the work.

For secondary analyses and related publications, author list and author order may vary from primary to reflect additional contributions.

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

All AEs/SAEs are to be graded using CTCAE v5.

ADVERSE EVENTS

Adverse Event Definition:

An adverse event (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a clinical investigation participant administered study treatment that does not necessarily have a causal relationship with this treatment.

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

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or results from other safety assessments (eg, electrocardiograms, 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/serious adverse event (SAE) unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae and should specify "intentional overdose" as the verbatim term.

Events NOT Meeting the AE Definition

- Medical or surgical procedure (eg, endoscopy, appendectomy); the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

DEFINITION OF SAE

If an event is not an AE per definition above, then it cannot be an SAE, even if serious conditions are met.

SERIOUS ADVERSE EVENTS

A 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 Bristol-Myers Squibb (BMS) clinical studies: • A visit to the emergency room or other hospital department < 24 hours that does not result in admission (unless considered an important medical or life-threatening event). • Elective surgery, planned prior to signing consent. • Admissions as per protocol for a planned medical/surgical procedure. • Routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy). • Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases. • Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason). • 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 [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm and 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 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 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 the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

- **Assessment of Intensity**

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event, and both AEs and SAEs can be assessed as severe.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Follow-up of AEs and SAEs

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

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

All SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

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

SAE Email Address: worldwide.safety@BMS.com

SAE Facsimile Number: *Will be provided by local site monitor.*

SAE Telephone Contact (required for SAE and pregnancy reporting): *Will be provided by local site monitor.*

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

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 7.7.1 PROHIBITED AND/OR RESTRICTED TREATMENTS of the protocol. [c] IUSs are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness. For information specific to this study regarding permissibility of hormonal contraception, refer to .Sections 6.1 INCLUSION CRITERIA and 7.7.1 PROHIBITED AND/OR RESTRICTED TREATMENTS of the protocol..

Less Than Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of > 1% per year when used consistently and correctly.*
• Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously. • Diaphragm with spermicide. • Cervical cap with spermicide. • Vaginal sponge with spermicide. • Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action. (This method of contraception cannot be used by WOCBP participants in studies where hormonal contraception is prohibited.)
Unacceptable Methods of Contraception
• Periodic abstinence (calendar, symptothermal, postovulation methods). • Withdrawal (coitus interruptus). • Spermicide only. • LAM.

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of pregnancy information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 9.2.5 and Appendix 3.

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

1 EVALUATION OF LESIONS

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

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

1.1 Measurable

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

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

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

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

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

1.2 Non-Measurable

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

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

1.3 Special considerations regarding lesion measurability

1.3.1 Bone lesions

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

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

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

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

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

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

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

2 RESPONSE CRITERIA

2.1 Evaluation of Target Lesions

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

2.1.1 Special Notes on the Assessment of Target Lesions

2.1.1.1 Lymph nodes

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

2.1.1.2 Target lesions that become 'too small to measure'

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

CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

2.1.1.3 Lesions that split or coalesce on treatment

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

2.2 Evaluation of Non-Target Lesions

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

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

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

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

2.2.1.1 When the patient also has measurable disease

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

2.2.1.2 When the patient has only non-measurable disease

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

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

2.2.2 New Lesions

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

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

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

1. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
2. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the

date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

2.3 Response Assessment

2.3.1 Evaluation of Best Overall Response

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

2.3.2 Time Point Response

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

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

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

CR, complete response; PR, partial response, SD, stable disease; PD, progressive disease; N, inevaluable.

Table 2.3.2-2: Time Point Response: Patients with Non-target Disease Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]

Table 2.3.2-2: Time Point Response: Patients with Non-target Disease Only		
Non-Target Lesions	**New Lesions**	**Overall Response**
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR, complete response; PD, progressive disease; NE, inevaluable.

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

2.3.3 Best Overall Response

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

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

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

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

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

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, inevaluable.

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

2.3.4 Confirmation Scans

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

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

REFERENCES

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

APPENDIX 6 MANAGEMENT ALGORITHMS

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.

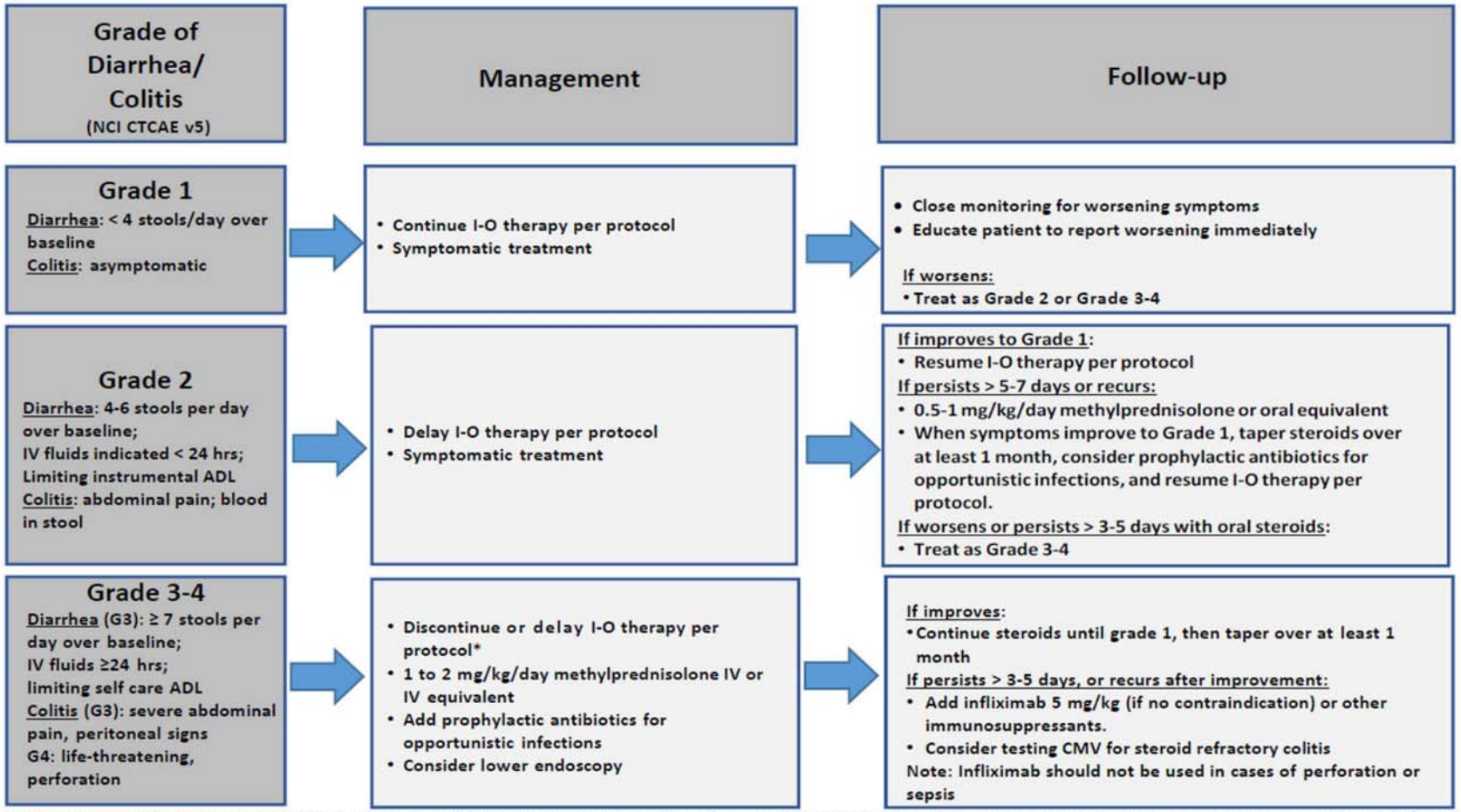
Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

All AEs/SAEs toxicity management are to be managed using CTCAE v5.

GI Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy.
Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



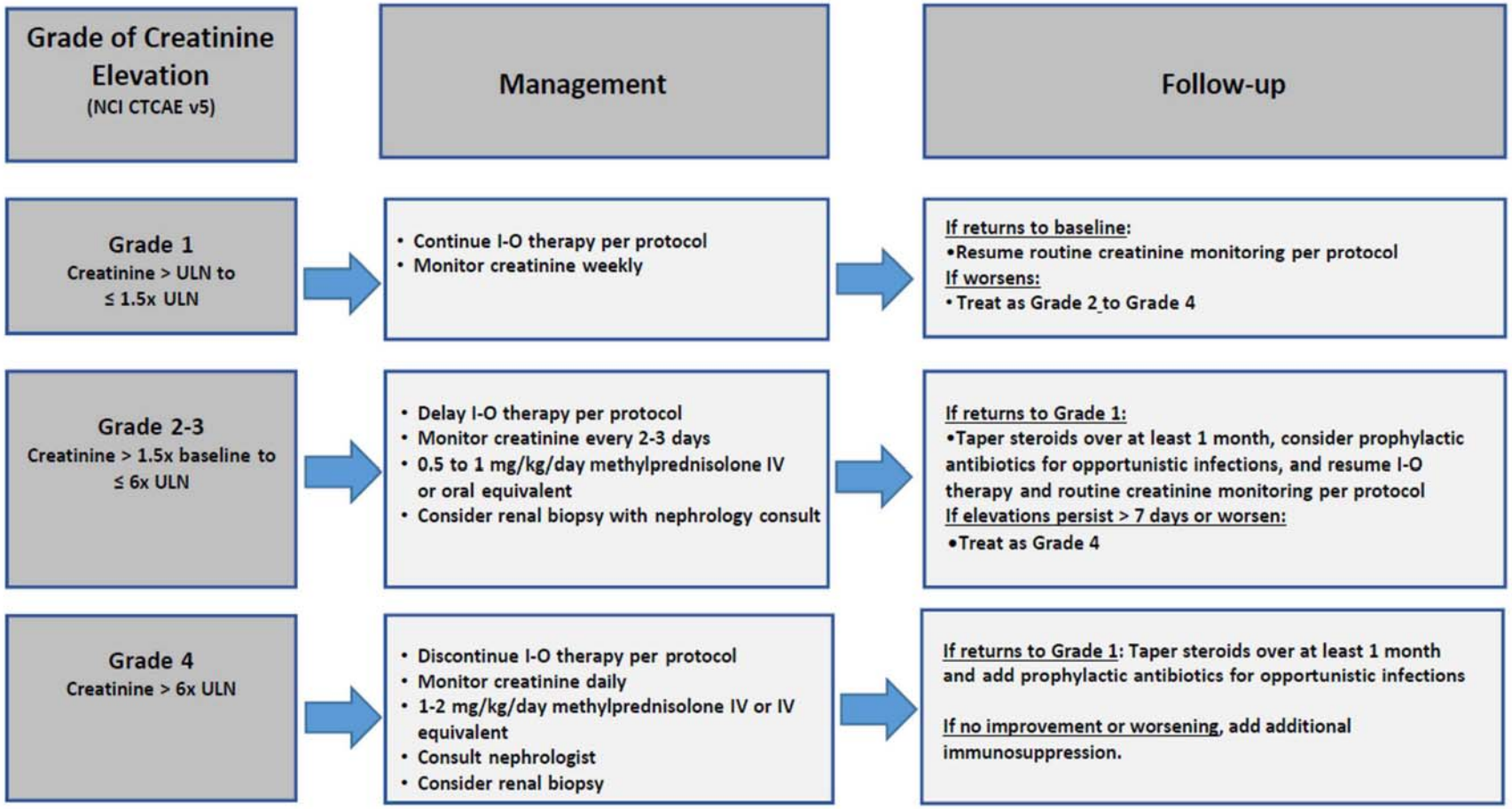
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

* Discontinue for Grade 4 diarrhea or colitis. For Grade 3 diarrhea or colitis, 1) Nivolumab monotherapy: Nivolumab can be delayed. 2) Nivolumab+ Ipilimumab combination: Ipilimumab should be discontinued while nivolumab can be delayed. Nivolumab monotherapy can be resumed when symptoms improve to Grade 1. Please refer to protocol for dose delay and discontinue criteria for other combinations.

28-Sep-2020

Renal Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

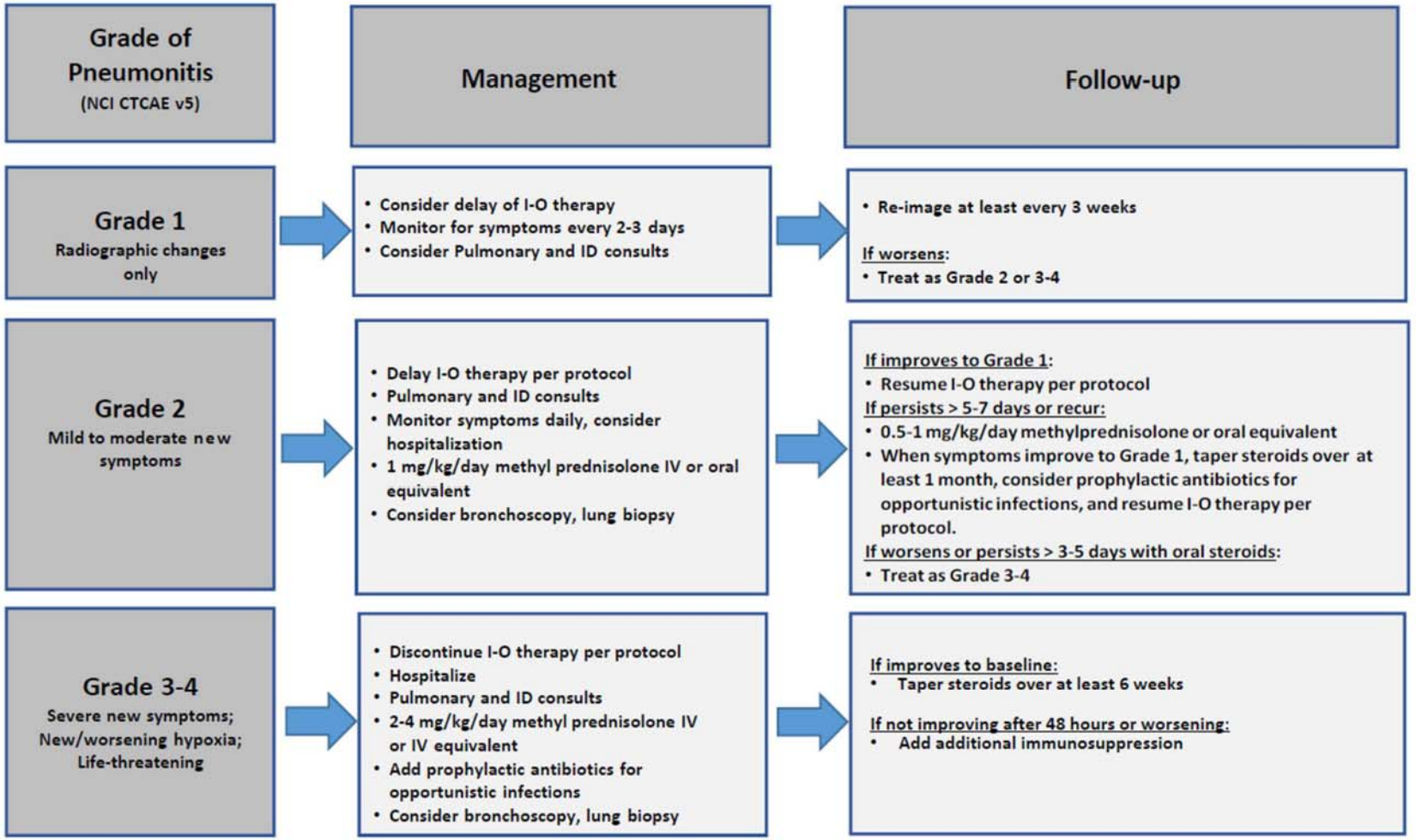


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

28-Sep-2020

Pulmonary Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.
Evaluate with imaging and pulmonary consultation.

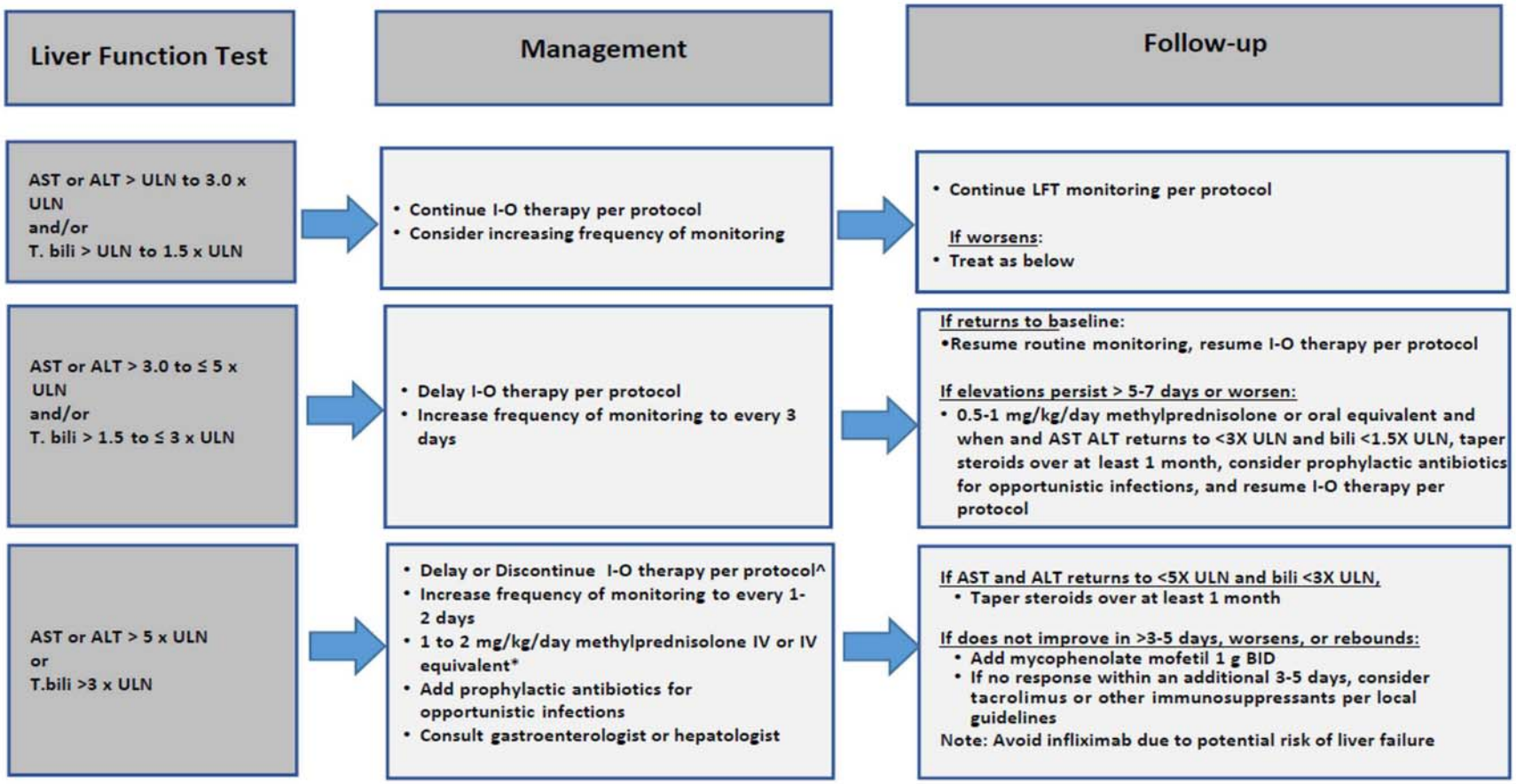


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

28-Sep-2020

Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.
Consider imaging for obstruction.

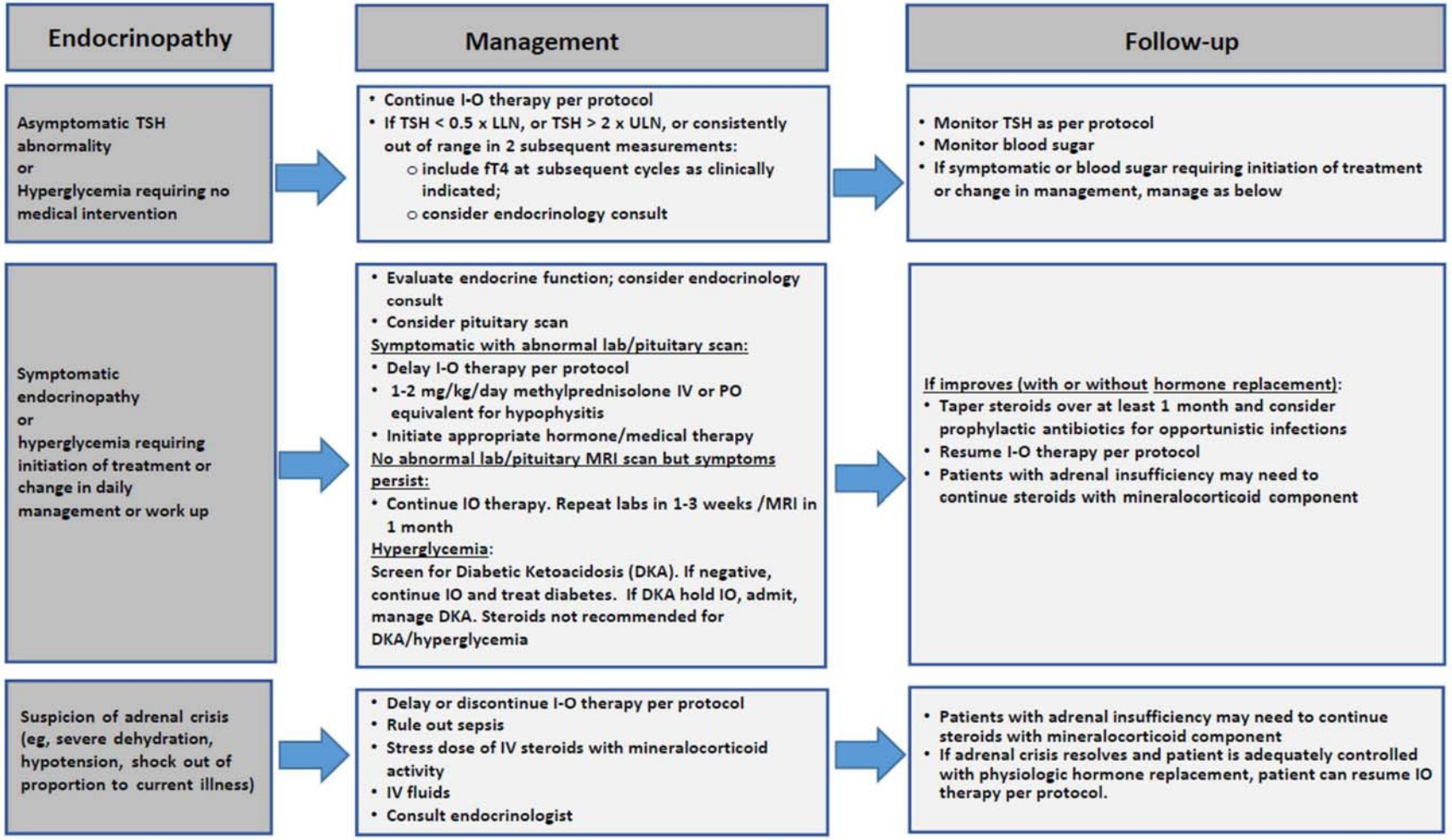


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
^ Please refer to protocol dose delay and discontinue criteria for specific details.
*The recommended starting dose for AST or ALT > 20 x ULN or bilirubin >10 x ULN is 2 mg/kg/day methylprednisolone IV.

28-Sep-2020

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.

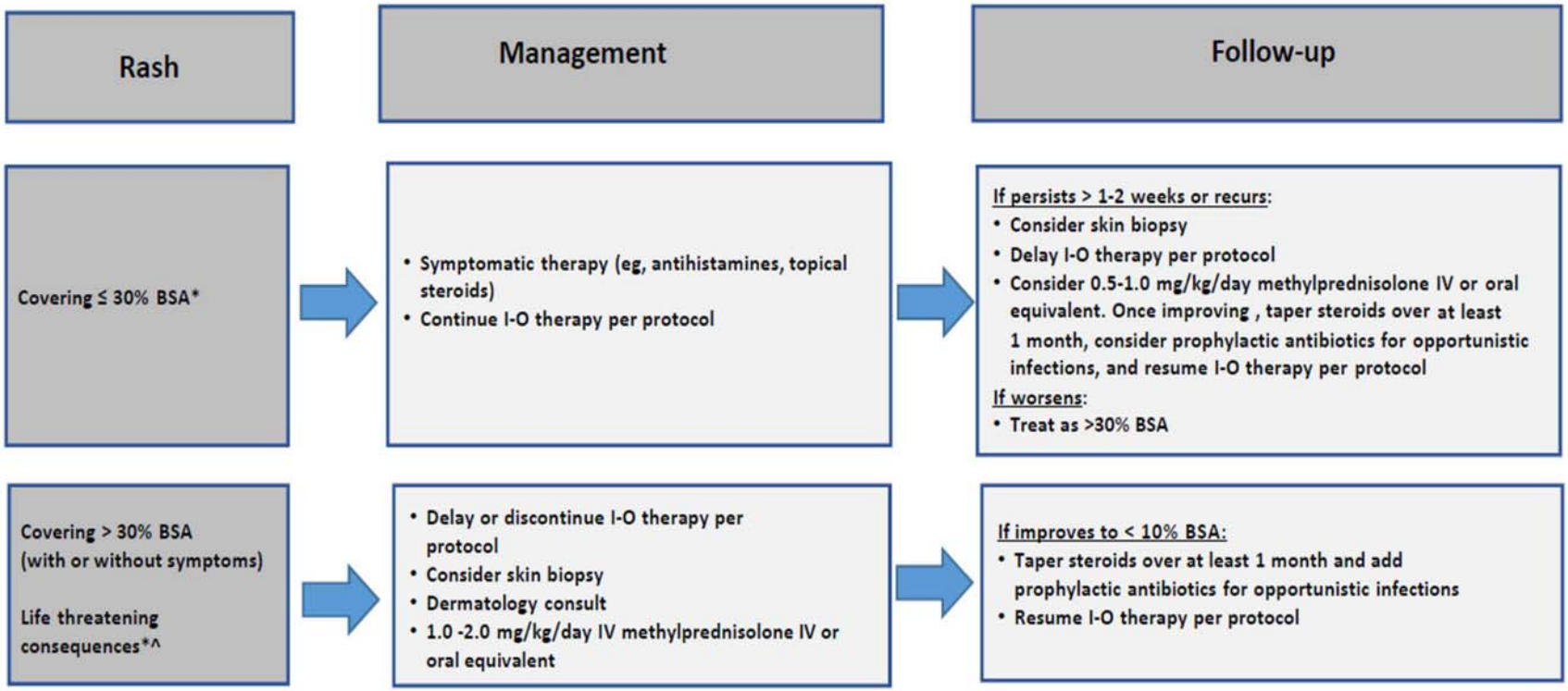


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

28-Sep-2020

Skin Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

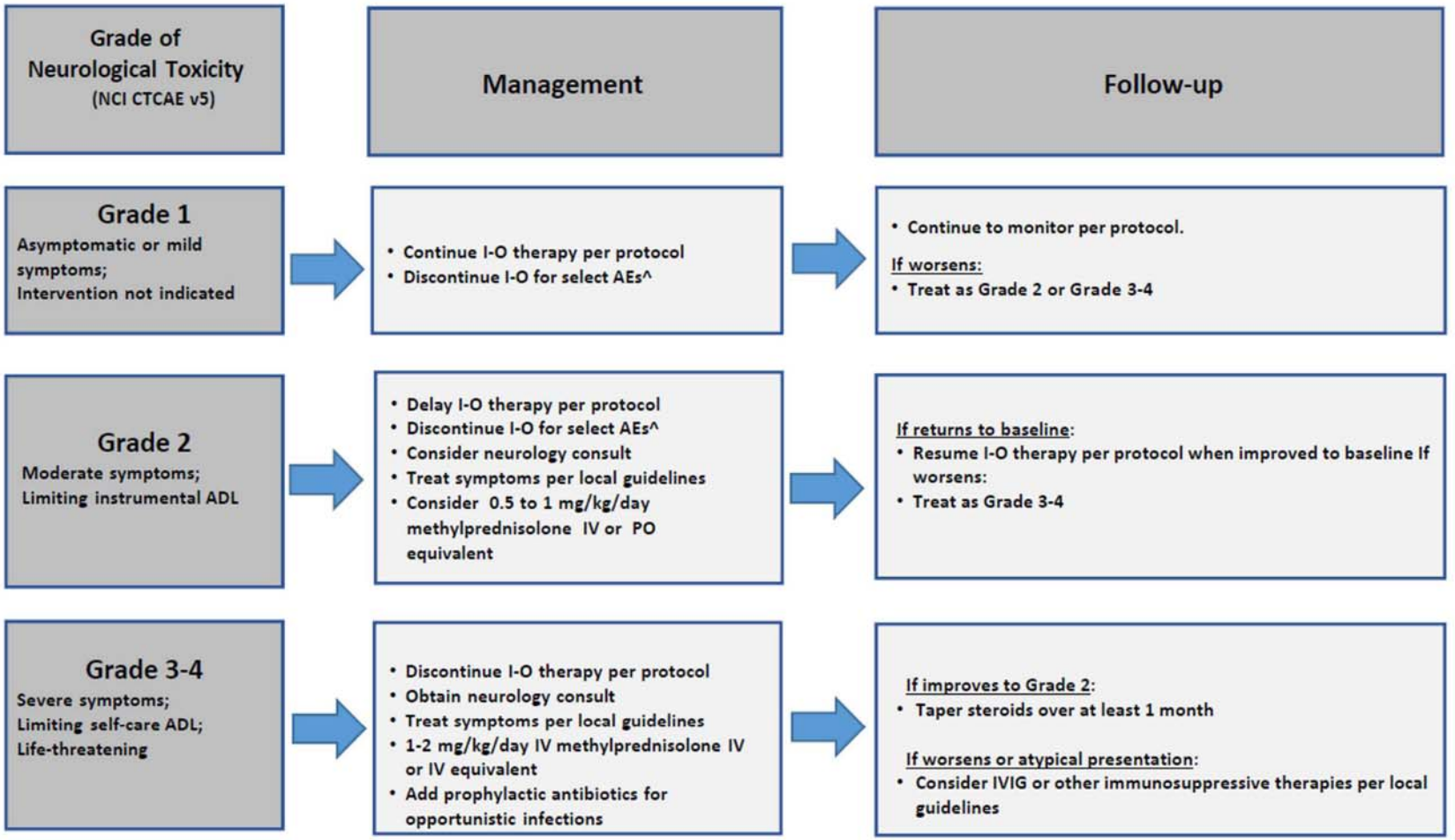
*Refer to NCI CTCAE v5 for term-specific grading criteria.

^If Steven-Johnson Syndrome (SJS),toxic epidermal necrosis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS, TEN, or DRESS is diagnosed, permanently discontinue I-O therapy.

28-Sep-2020

Neurological Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



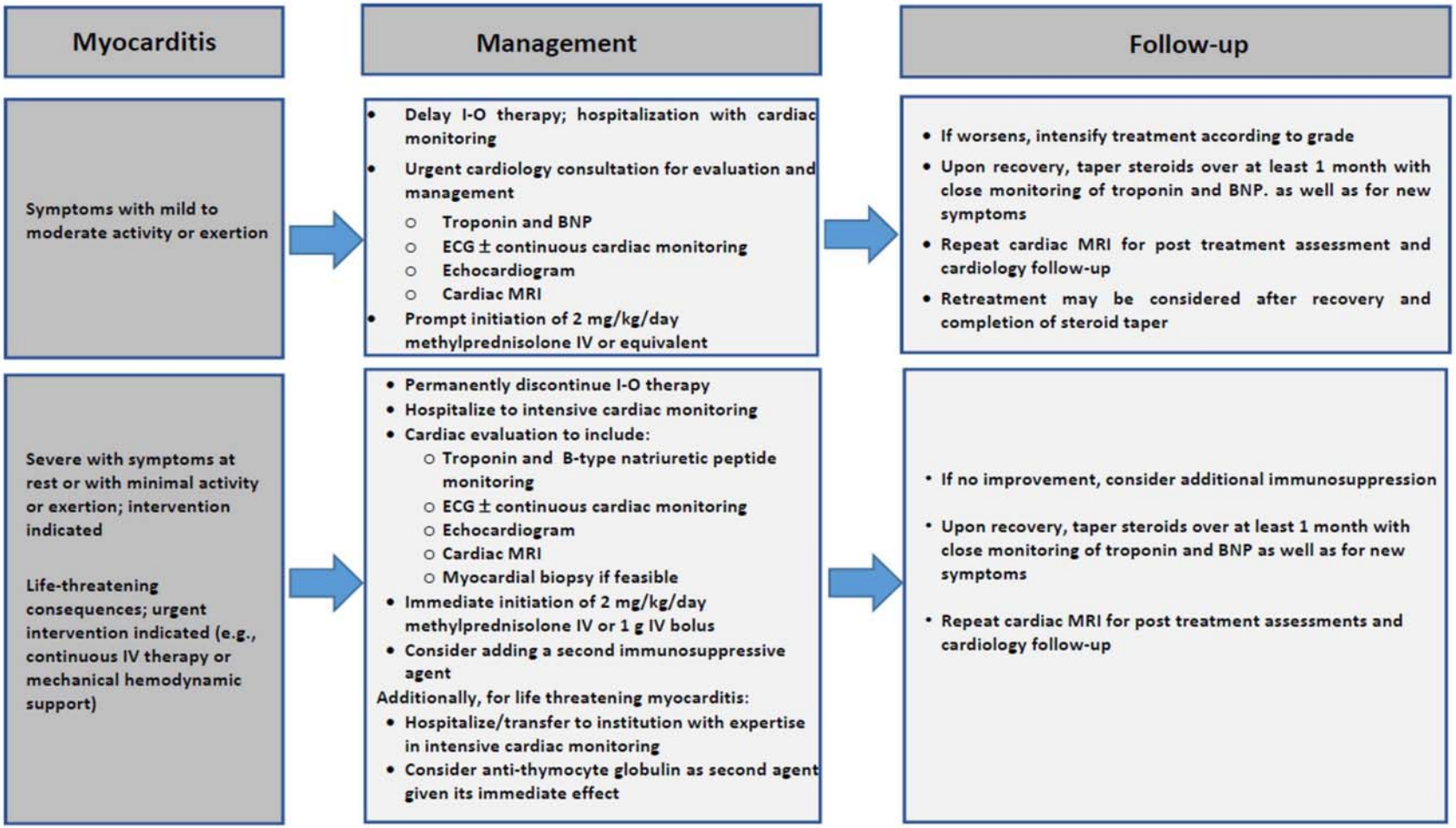
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

^Discontinue for any grade myasthenia gravis, Guillain-Barre syndrome, treatment-related myelitis, or encephalitis.

28-Sep-2020

Myocarditis Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.

28-Sep-2020

APPENDIX 7 EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

ECOG PERFORMANCE STATUS[a]	
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

[a] Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, and Carbone PP. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5: 649-655.

APPENDIX 8 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 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 DETAILS OF THE PROPENSITY SCORE MATCHING AND BAYESIAN AUGMENTED CONTROL (BAC) ANALYSIS

1.1 Propensity Score Matching

The use of historical control data as synthetic control for single-arm trial or augmentation for the current control arm in random controlled trials becomes promising in boosting the statistical power and estimate accuracy in the recent development of clinical trial design and practice. One downside of this method is potential discrepancies in prognostic factors between the historical data and the current active or control arm. With the availability of individual patient level data from historical controls, one approach to reduce biases is to use the Propensity Score Method to select historical data that are similar as participants from the active trials. The propensity score approach we employ in this protocol includes the following steps:

1. Selection of covariates or prognostic factors in multivariate logistic regression model

The variables for the propensity score modeling are selected based on prior clinical knowledge and their availability in the historical trial (CheckMate 227).

2. Propensity score matching

In the logistic regression model for the propensity scoring, the dependent variable is the indicator whether the patient belongs to the historical trial or the current trial, and the independent variables are the baseline covariates/prognostic factor mentioned above. The Greedy Nearest Neighbor Matching will be used to select about 180 control participants from the historical arms (1:1 matching ratio).[1] The matching caliper is set to 0.2 as appropriate so that participants are matched only if the difference in the logits of the propensity score for pairs of participants from the 2 groups is less than or equal to 0.2 times the pooled estimate of the common standard deviation of the logits of the propensity scores.

3. Assessment of Balance between Historical and Current Control

The frequency of all the binary covariates will be tabulated for the historical and current control participants before and after propensity score matching to access the improved balance.

1.2 Bayesian Modeling for Augmented Control with Historical Data

A Bayesian exponential-likelihood model has the following form:

$$\lambda_i = \lambda e^{\theta I_i}$$

where

- λi is the hazard rate corresponding to the treatment arm for the ith participant;
- λ is the hazard rate for the current control arm.
- *Ii* is an indicator variable equal to 1 if the ith participant in the group received the current experimental arm and 0 otherwise;
- θ is the log hazard ratio (HR) between the current experimental arm and the current control arm

For prior specification, we assign a normal prior to θ (log HR) where μ = 0 and σ = 100, assuming no priori treatment effects, and weakly informative prior with large variation:

$$\theta \sim N(\mu, \sigma^2)$$

The hazard rate for control arm is augmented by informative prior specified by Gamma distribution:

$$\lambda \sim Gamma(\alpha, \beta)$$

which can be re-parameterize to:

$$\lambda \sim Gamma(n, \frac{n}{\mu})$$

with

$$\alpha = n, \beta = \frac{n}{\mu}$$

where μ is the control hazard rate from the historical control selected by the Propensity Score Method assuming exponential distribution, and n is approximately the effective number of events this informative prior is equivalent to.[2,3]

REFERENCES:

1 Rosenbaum PR. Observational studies. New York: Springer-Verlag; 2002. (Available upon request)

2 Smith CL, Thomas Z, Enas N, et al. Leveraging historical data into oncology development programs: Two case studies of phase 2 Bayesian augmented control trial designs. Pharm Stat 2020;19:276-90.

3 FACTS 6.2: Fixed and Adaptive Clinical Trial Simulator. Berry Consultants. Available from: URL: www.berryconsultants.com.

APPENDIX 11 PROTOCOL AMENDMENT SUMMARY OF CHANGE HISTORY

Overall Rationale for Protocol Amendment 01, 19-May-2021

The purpose of this amendment is to clarify, at the request of the Health Authority (HA), the exclusion criteria for interstitial lung disease, resumption of dosing in limited circumstances after myocarditis, dose-limiting toxicity (DLT) criteria, and an additional serum sample collection at Cycle 1 Day 22 for BMS-986207.

Summary of Key Changes for Protocol Amendment 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 6.2: Exclusion Criteria	Modified the interstitial lung disease exclusion criterion 1)h to delete "that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity"	Updated exclusion criterion per HA request
Table 7.4.2-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Nivolumab, Ipilimumab, and BMS-986207	Added clarification text for myocarditis: "Mandatory discussion with and approval from the Medical Monitor is needed prior to resuming therapy"	Added to ensure appropriate benefit-risk considerations prior to resuming treatment.
	Added clarification text "clinically significant" bleeding for permanent discontinuation of therapy for Grade 3 thrombocytopenia	Clarified permanent discontinued criterion per HA request
Section 7.4.3: Dose-limiting Toxicities	Updated definition of dose-limiting toxicity (DLT) to include Grade 3 or greater febrile neutropenia and any additional Grade 3 events and exceptions to DLTs	Updated DLT criteria for patient safety, per HA request
Section 8.1: Discontinuation From Study Intervention	Updated drug-related adverse event bullet point based on revisions to DLT criteria	Updated criteria for permanent discontinuation based on changes to DLT criteria
Table 9.5-1: Pharmacokinetic and Immunogenicity Sampling Schedule for BMS-986207, Nivolumab, and Ipilimumab in Part 1 and Part 2 (Arms A and B)	Added ADA serum sample collection at Cycle 1 Day 22 (prior to second dose) for BMS-986207 and nivolumab	Added to capture early formation of antibodies to BMS-986207, per HA request
Appendix 10: Statistical Methodology	Updated Table 1.1-1 Operating Characteristics of the BOIN Design to better reflect the de-escalation setting in the safety lead-in with added condition to the standard BOIN design used previously for the	Provide additional information on the protocol BOIN design operating characteristics in response to HA request.

Summary of Key Changes for Protocol Amendment 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
	simulations. Added additional simulation cases.	
All	Minor typographical and formatting errors were corrected and edits were made for consistency and clarity	• Added KRAS mutation status, if known, to Table 2-1 (Screening Procedural Outline) • Updated footnote "a" from Table 5.1.2.1-1 (Lead-In Safety Evaluation Guidance Based on BOIN Design) to remove "≥" in front of "2 DLTs" to align with the table • Deleted Section 5.1.2.2 Dose-limiting Toxicities to avoid duplication of information already captured in Section 7.4.3 Dose-limiting Toxicities • Additional corrections made for clarity and consistency within the document were minor, therefore have not been summarized