Official Title of Study:

Phase 1/2a First-In-Human Study of BMS-986218 Monoclonal Antibody Alone and in Combination with Nivolumab in Advanced Solid Tumors

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Clinical Protocol CA022001

Phase 1/2a First-In-Human Study of BMS-986218 Monoclonal Antibody Alone and in Combination with Nivolumab in Advanced Solid Tumors

Short Title: Phase 1/2a Study of Monoclonal Antibody BMS-986218 Monotherapy and in Combination With Nivolumab in Patients With Advanced Solid Tumors

Protocol Amendment Number: 07

[redacted]
Clinical Trial Physician
Bristol Myers Squibb Company
3401 Princeton Pike, Lawrenceville, NJ 08648
Telephone (office): [redacted]
email: [redacted]

[redacted]
Clinical Scientist
Bristol Myers Squibb Company
3401 Princeton Pike , Lawrenceville, NJ 08648
Telephone (office): [redacted]
email: [redacted]

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

Bristol Myers Squibb Company
Route 206 & Province Line Road
Lawrenceville, NJ 08543
Avenue de Finlande 4
B-1420 Braine-l'Alleud, Belgium

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Protocol Amendment 07	29-Jul-2021	Added Part 2C and Part 2D evaluating the combination of anti-CTLA4-NF (BMS-986218) and nivolumab in non-small cell lung cancer (NSCLC) and microsatellite stable colorectal cancer (MSS CRC) participants, respectively. Incorporates Protocol Amendment 01 United States.
Protocol Amendment 01 United States	16-Apr-2021	Added tumor types in the Part 1A pharmacodynamic (PD) cohort: colorectal cancer microsatellite stable (CRC MSS), non-small cell lung cancer (NSCLC), and squamous cell carcinoma of the head and neck (SCCHN). Added dose levels or dose schedules to the PD cohort.
Protocol Amendment 06	22-Dec-2020	The changes include revising the protocol in response to feedback from Investigators [redacted] around pregnancy testing and contraception requirements; adding responses to the COVID-19 pandemic and aligning with nivolumab program standards, including updating the contraception language for women of child-bearing potential (WOCBP) participants and male participants, and their WOCBP partners.
Administrative Letter 05	08-Oct-2019	To notify of incorrect notation stating that Sections 3.2.2 and 3.2.3 were updated per Investigator's Brochure (IB). The sections were not updated.
Administrative Letter 04	03-Oct-2019	Note added to correct and provide clarifying directions to the schedule of activities table and only noted change to Table 2-4, when it affects Tables 2-2, 2-3, and 2-4
Revised Protocol 05	14-Aug-2019	The primary reasons for the changes to the protocol are: 1) Specify interim dose levels for Part 1A and Part 1B. 2) Include a subgroup of additional participants with advanced stage cutaneous melanoma in Part 1A. 3) Specify the doses and schedules for expansions in Part 2A and Part 2B. 4) Update safety information to align with current Investigator Brochure for BMS-986218.
Revised Protocol 04	25-Dec-2018	The primary reasons for the changes to the protocol are to: 1) Update pharmacokinetic and immunogenicity assessments sampling schedules to add and/or clarify blood and anti-drug antibody samples. 2) Clarify relevant systemic exposure of study drugs for male participant contraceptive guidance.
Revised Protocol 03	24-Oct-2018	Updated the study design as follows: • Part 1A: Inclusion of alternative every-2-weeks (Q2W) dosing schedule to study BMS-986218 in the context of rapid T-regulatory cell (Treg) depletion and recovery. • Part 1B: Inclusion of Bayesian Logistic Regression Model (BLRM) using the escalation with overdose control (EWOC) principle, and a starting dose 1 at dose level below the current safety cleared monotherapy cohort (to allow initiation of this study part prior to declaring the RP2D and evaluation of different doses in combination in select tumor types) • Part 2A: Inclusion of several dose levels and/or schedules to study BMS-986218 monotherapy and ipilimumab monotherapy in a randomized setting in participants with cutaneous melanoma

Document	Date of Issue	Summary of Change
		• Part 2B: Inclusion of several dose levels and/or schedules to study BMS-986218 monotherapy in a randomized setting in participants with non-small cell lung cancer (NSCLC). Other key changes: [redacted] clarified expectations and timing of scheduled activities; updated eligibility criteria; [redacted]
Administrative Letter 03	07-Aug-2018	Updated study personnel
Administrative Letter 02	18-May-2018	Updated study personnel
Revised Protocol 02	14-Feb-2018	Expand enrollment in Part 1A to include up to 60 participants, extend the treatment period to 2 calendar years, modify eligibility criteria for participants with advanced PDAC, permit the use of concomitant palliative hormonal therapy, remove the option of re-treatment following progression, [redacted]
Revised Protocol 01	05-Apr-2017	Incorporates Amendment 01
Amendment 01	05-Apr-2017	Incorporates revisions to the inclusion/exclusion criteria, study schematic, timing of pharmacokinetic and pharmacodynamic collection, and rectified inconsistencies in cohort sample size and administrative updates.
Original Protocol	14-Feb-2017	Not Applicable

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 07:

The primary purpose of this amendment is to add Part 2C and Part 2D, BMS-986218 administered in combination with nivolumab in non-small cell lung cancer (NSCLC) and microsatellite stable colorectal cancer (MSS CRC) participants, respectively. This cohort expansion will evaluate preliminary efficacy and safety of BMS-986218 in combination with nivolumab. This amendment also includes the revisions from Protocol Amendment 01 United States which allows the inclusion of participants with MSS CRC, non-small cell lung cancer (NSCLC), and squamous cell carcinoma of the head and neck (SCCHN) tumor types as well as adding dose levels or dose schedules in the Part 1A pharmacodynamic (PD) cohort.

The synopsis has been revised as applicable to align with the protocol changes.

This protocol amendment applies to all participants.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 07		
Section Number & Title	**Description of Change**	**Brief Rationale**
Synopsis	All changes in the body are included in the synopsis as applicable.	To align the changes in the body with the synopsis.
Section 2: Schedule of Activities; **Table 2-1**	Updated the note for Medical History and the note for Concomitant Medications to include information regarding COVID-19 vaccination. Revised the note for the collection of tumor tissue procedure. [redacted]	To ensure COVID-related vaccine history is captured and noted as a concomitant medication. To provide clarity on the tissue requirements. [redacted]
Section 2: Schedule of Activities; **Table 2-2**	Added the Combination Cohort Expansions (Part 2C and Part 2D) to the On-Treatment tables and added assessment timepoints as applicable. [redacted]	To include assessments for Part 2C and Part 2D. [redacted]
Section 2: Schedule of Activities; **Table 2-3**	[redacted] Removed the 12-week tumor imaging assessment for the body imaging procedure.	[redacted] Table 2-3 is for Part 1A of the study, this assessment applied

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 07		
Section Number & Title	**Description of Change**	**Brief Rationale**
	[redacted]	to Part 2A, therefore it is not applicable. [redacted]
[redacted]		
Section 3.2.1: BMS-986218	BMS-986218 Part 1A administration was updated to include 100 and 150 mg doses Q4W and 35 and 50 mg doses for Q2W.	To provide updated clinical dosing information.
Section 3.2.2: Nivolumab	Removed outdated information and added updated data.	To provide updated nivolumab clinical information.
Section 3.3: Benefit-Risk Assessment	Revised bullet item 2 regarding observation following first 3 infusions of BMS-986218. Updated COVID-19 text.	To clarify the observation period for participants after each infusion. To provide guidance on COVID-19 testing and vaccines.
Section 4: Objectives and Endpoints	Removed laboratory abnormalities from the first primary endpoint for safety, tolerability and DLTs when BMS-986218 is administered as monotherapy and in combination with nivolumab. Added a primary safety and efficacy objective for Part 2B, Part 2C, and Part 2D. Added Part 1A and Part 1B to the secondary efficacy objective.	Laboratory abnormalities are removed from primary endpoint as they will be reported as adverse events. To include objectives for all parts of the study.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 07		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 5.1: Overall Design; **Figure 5.1-1 Study Design Schematic;** **Section 5.1.2.1: The BMS- 986218 Monotherapy Escalation (Part 1A);** **Section 5.1.2.4: The Randomized BMS-986218 Monotherapy Cohort Expansion in Cutaneous Melanoma (Part 2A), the BMS-986218 Cohort Expansion Monotherapy (Part 2B), and the BMS-986218 Cohort Expansion - Combination Therapy (Part 2C and Part 2D)**	Added MSS CRC, NSCLC, and SCCHN tumor types to Part 1A in addition to cutaneous melanoma and named the cohort "Part 1A PD Cohort." Added language to allow additional dose levels and enrollment of more participants at the new dose levels or dose schedules. Updated the schematic and text to include additional tumor types in Part 1A PD cohort and Part 2C and Part 2D. Updated the table notes accordingly. Updated dose selection text for Part 2C and Part 2D cohorts.	To allow additional participants with selected tumor types to be enrolled in the Part 1A PD cohort. To include Part 2C and Part 2D participants to sections as appropriate. To explain how dose selection will occur for Part 2C and Part 2D.
Section 5.1.4: Data Monitoring Committee and Other External Committees	Updated the Bristol-Myers Squibb (BMS) department name 'Global Pharmacovigilance and Epidemiology (GPVE)' to 'WorldWide Patient Safety (WWPS)'. Updated the BMS department name 'Medical Surveillance Team (MST)' to 'Safety Management Team (SMT)'.	To align the names to the current BMS department names.
Section 5.2: Number of Participants	Updated the number of participants for each study part.	To provide each study part and the corresponding number of participants.
Section 5.4 7: Rationale for Tumor Selection	Added rationale for including tumor type selection in the PD cohort to evaluate the potential therapeutic effect of BMS-986218.	To provide clarity on rationale for selection of tumor types for the PD cohort.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 07		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.5.2: Rationale for Dose Selection and Dosing Schedule; **Table 5.5.2-1 Dosing Schedule by Study Part**	Updated the table to include the Part 2C doses for NSCLC and Part 2D doses for MSS CRC.	To include doses for Part 2C and Part 2D.
Section 6.1: Inclusion Criteria 2) Type of Participants and Target Disease Characteristics c) iv), (1), c) vi) and added vii) **Section 6.1: Inclusion Criteria 2) Type of Participants and Target Disease Characteristics k) i), (1)** **Inclusion Criteria 2) Type of Participants and Target Disease Characteristics l)**	Removed two criteria; no longer applicable per Protocol Amendment 01 US and added criteria regarding previous therapies. Updated inclusion criteria of transitional cell (urothelial) carcinoma (TCC) of urinary bladder to urothelial carcinoma. Added NCLSC inclusion criteria for Part 2C. Added MSS CRC inclusion criteria for Part 2D participants.	The criteria are now included in 2) c) vii. Criteria was clarified to allow all urothelial carcinomas. To add criteria for Part 2C and Part 2D cohorts.
Section 6.1: Inclusion Criteria 4) Age and Reproductive Status c)	Clarified duration of contraception for monotherapy and combination therapy for women of childbearing potential. Added a reference to Appendix 4. Also clarified that male participants receiving monoclonal antibodies (mAbs), are not required to practice contraception because mAbs do not collect in seminal fluid.	For clarification of contraception and duration of contraceptive requirements based on current safety information.
Section 6.2: Exclusion Criteria 3) Medical History and Concurrent Diseases h)	Clarified the exclusion for SARS-CoV-2 vaccines that require 2 doses.	To provide clarification.
Section 7.1: BMS-986218; **Section 7.1.2: Nivolumab;** **Section 7.1.3: Ipilimumab**	Removed text that is also included in the pharmacy manual.	To reduce redundant text.
Section 7.3: Schedule of Dose for Each Investigational Product **Table 7.3-1**	Clarified the infusion times for each study treatment and added Part 2C and Part 2D; updated the table note.	The lower doses are now able to be administered as standard IV infusions. To provide clear guidance for each study treatment and to include Part 2C and Part 2D.
Section 7.4: Method of Treatment Assignment	Added the method of treatment assignment for Part 2C and Part 2D.	To include Part 2C and Part 2D treatment assignment.
Section 8.1 Discontinuation from Study Treatment	Removed "Grade 4 amylase or lipase elevation."	To correct an inconsistency in the protocol.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 07		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 9.2.1: Time Period and Frequency for Collecting AE and SAE Information	Removed outdated information on where to find the Reference Safety Information.	Information is outdated and no longer applicable.
Section 9.2.5: Pregnancy	Updated to align with male participants not required to use contraception and removed repetitive text.	For clarification of contraception and duration of contraceptive requirements based on current safety information.
Section 9.5: Pharmacokinetic and Immunogenicity Assessments; **Table 9.5-2: table note 'b'** **Table 9.5-3: table note 'b'** **Table 9.5-4: table note 'b'**	Extended the time of EOI PK sample draw from within 5 minutes to within 15 minutes after the end of the flush. Removed information on infusion of drug without a flush.	EOI PK sampling window updated to allow time for ECG collection. Information is not needed.
Table 9.5-5: table title and table note 'b'	Added Part 2C and Part 2D to the table title and changed the time of EOI PK sampling window from within 5 minutes to within 15 minutes after the end of the flush (table note 'b').	To include participants in Part 2C and Part 2D for pharmacokinetic sampling. EOI PK sampling window updated to allow time for ECG collection.
[redacted]		

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 07		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 10.1.1: Monotherapy Dose Escalation (Part 1A); **Section 10.1.2: The Safety Evaluation of Combination Doses of BMS-986218 with Nivolumab (Part 1B);** **Section 10.1.3: The Randomized BMS-986218 Monotherapy Cohort Expansion in Cutaneous Melanoma (Part 2A);** **Section 10.1.4: The BMS-986218 Cohort Expansion - Monotherapy (Part 2B);** **Section 10.1.5: The BMS-986218 Combination - Therapy Cohort Expansion in NSCLC (Part 2C);** **Section 10.1.6: The BMS-986218 Combination - Therapy Cohort Expansion in MSS CRC (Part 2D)** **Section 10.3.1: Efficacy Analyses;** [redacted] **Section 10.3.9: Interim Analysis**	Revised the sample size calculation for Part 1A and Part 1A PD cohort. Defined the participants as 'dose-limiting toxicity evaluable' and 'response evaluable' as applicable. Added the sample size calculation for Part 2C and Part 2D . Added Part 2C and Part 2D. Added details of the planned interim analyses.	To provide updated sample size calculations. To define the 'evaluable' participants. To include the Part 2C and Part 2D participants. To describe the planned interim analysis.
Section 10.3.2 Safety Analyses; **Table 10.3.2-1 Safety - Statistical Analyses**	Replaced 'Laboratory abnormalities' with 'Toxicity Changes from Baseline'	Laboratory abnormalities are removed from primary endpoint as they will be reported as adverse events.
APPENDIX 2: STUDY GOVERNENCE CONSIDERATIONS	Information on remote monitoring will be included in the monitoring plan. Removed information on the process when on-site drug destruction is not allowed.	To address the details of remote monitoring if it is utilized. The process is not applicable for the sites participating in this study.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 07		
Section Number & Title	**Description of Change**	**Brief Rationale**
APPENDIX 4: WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION	Updated information regarding hormone replacement therapy, the highly effective contraceptive methods that are user dependent and independent, unacceptable methods of contraception and added less than highly effective contraceptive methods that are user dependent.	These updates are to align with the BMS standards of contraceptive methods.
APPENDIX 8: COUNTRY SPECIFIC REQUIREMENTS	Updated HIV exclusion language for Argentina	Clarification of a country requirement for Argentina .
APPENDIX 11 STATISTICAL METHODS	Expanded the BLRM simulation results performed at the beginning of the study to the additional planned doses that were added in Part 1A mono therapy escalation and Part 1B combo therapy escalation from previous protocol amendments. The BLRM mono therapy prior was slightly updated to reflect the changes in expectation for reference dose, and the combo therapy prior incorporated mono therapy DLT information for combo therapy simulations.	To update BLRM simulations for the additional doses in Part 1A and Part 1B from previous protocol amendments.
All as applicable	The abbreviation 'PD' is now 'pharmacodynamic' not 'progressive disease'. Updated the Bristol-Myers Squibb (BMS) department name 'Global Pharmacovigilance and Epidemiology (GPVE)' to 'WorldWide Patient Safety (WWPS)'. Updated the BMS department name 'Medical Surveillance Team (MST)' to 'Safety Management Team (SMT)'. Minor formatting and typographical corrections throughout.	The cohort is named 'Part 1A PD Cohort' and 'PD' represents pharmacodynamic. To update to the current department name. Minor, therefore have not been summarized.

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[redacted]

[redacted]

1 SYNOPSIS

Protocol Title: Phase 1/2a First-In-Human Study of BMS-986218 Monoclonal Antibody Alone and in Combination with Nivolumab in Advanced Solid Tumors

Short Title: Phase 1/2a Study of Monoclonal Antibody BMS-986218 Monotherapy and in Combination With Nivolumab in Patients With Advanced Solid Tumors

Study Phase: 1/2a

Rationale:

This is a Phase 1/2a, first-in-human (FIH) study of BMS-986218, a non-fucosylated (NF) variant of the anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) monoclonal antibody (mAb), alone and in combination with nivolumab (anti-programmed cell death 1 [PD-1]), in humans with advanced solid tumors.

Anti-CTLA-4 (ipilimumab) and anti-PD-1 (nivolumab) are approved immunotherapies that define the field of checkpoint blockade. Ipilimumab is the first immunotherapy to show a survival advantage in late-stage metastatic melanoma and has also demonstrated a significant 25% reduction in risk of recurrence or death in the adjuvant treatment in melanoma. Blockade of CTLA-4 by ipilimumab has demonstrated anti-tumor activity in other malignancies, including lung, prostate cancer, and renal cell carcinoma (RCC). However, no significant activity was observed in bladder, colorectal, esophageal, pancreatic, gastric, hepatocellular, or breast cancer. Ipilimumab is also currently in clinical development in combination with nivolumab. The combination was associated with a greater benefit in melanoma compared to each single agent. Benefit with the combination has also been observed in non-small cell lung cancer (NSCLC) and RCC and is currently being evaluated in other tumor types. The activation of a pre-existing but attenuated immune response to cancer by checkpoint blockade is associated with an adverse event (AE) profile that is inherent to immune activation. Ipilimumab treatment-related AEs can involve multiple organ systems (digestive, skin, and endocrine) that require cessation of drug and treatment with steroids, which attenuate the AEs but do not maintain anti-tumor responses. The combination regimen is associated with an increased incidence of AEs compared to nivolumab monotherapy, but a similar overall AE profile. Developing a new anti-CTLA-4 antibody (Ab) with a more manageable AE profile and an increased depth and breadth of response would provide a significant improvement to anti-CTLA-4 therapy.

BMS-986218 (CTLA-4.4g1fa-nf) is a human mAb against CTLA-4. The sequence is derived from the original hybridoma 10D1. The amino acid sequence is the same as that of ipilimumab but differs solely in its glycosylation pattern. The Ab is expressed in a fucosyltransferase-8 knockout Chinese hamster ovary cell line. Compared to ipilimumab, the glycans attached to the heavy chain Ab do not contain fucose. As a consequence, the NF Ab harbors a higher affinity for Fcγ receptors and improves antibody-dependent cellular cytotoxicity (ADCC) in addition to the CTLA-4 blocking activity of ipilimumab. T-regulatory cells (Tregs) are highly infiltrating in tumors, where they play an important role in impairing anti-tumor immune response by dampening effector cytolytic T-cell function. Tregs in tumors express higher levels of CTLA-4, and some studies have shown that part of the mechanism of action of ipilimumab is related to Treg depletion triggered by ADCC mediation once ipilimumab binds to CTLA-4-positive Tregs, but this aspect is controversial and ipilimumab may not be a strong ADCC-mediating Ab. Pre-clinical studies with anti-CTLA-4-NF show enhanced ADCC compared to ipilimumab, correlating with more profound Treg depletion in the tumor (but not the periphery). Therefore, it is expected that anti-CTLA-4-NF will result in a more efficacious therapy by combining CTLA-4 blocking with the depletion of Tregs expressing CTLA-4.

Based on this differentiated mechanism of action, this study will evaluate the safety and preliminary efficacy of BMS-986218 alone and in combination with nivolumab in tumors where ipilimumab did not demonstrate sufficient clinical activity and in tumors where high Treg infiltration is correlated with worse prognosis (eg, NSCLC, RCC, cutaneous melanoma), or in participants with progressive or recurrent disease after prior immunotherapy with an anti-PD-1 or anti-programmed death ligand 1 (PD-L1) containing regimen.

Study Population:

Participants must be at least 18 years old and have histologic or cytologic confirmation of a solid tumor that is advanced (metastatic, recurrent, and/or unresectable) with measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 or per Prostate Cancer Working Group 3 (PCWG 3) criteria for prostate, and have at least 1 lesion [redacted].

Objectives and Endpoints:

The objectives and endpoints for the primary, secondary, [redacted] of this study are shown in Table 1-1.

Table 1-1: Objectives and Endpoints

Objectives	Endpoints
Primary	
• To characterize the safety, tolerability, and DLTs and to determine the MTD/RP2D of BMS-986218 administered as monotherapy and in combination with nivolumab in participants with advanced solid tumors • To evaluate the efficacy and safety of BMS-986218 monotherapy relative to ipilimumab in participants with advanced cutaneous melanoma previously treated with anti-PD-1/PD-L1 immunotherapy (Part 2A only) • To evaluate the efficacy and safety of BMS-986218 alone and in combination with nivolumab in NSCLC (Part 2B and Part 2C) • To evaluate the efficacy and safety of BMS-986218 alone and in combination with nivolumab in MSS CRC (Part 2D)	• Incidence of AEs, SAEs, AEs meeting protocol-defined DLT criteria, AEs leading to discontinuation, and death • ORR, mDOR, and PFSR at 24, 36, and 48 weeks by RECIST v1.1
Secondary	
• To evaluate the preliminary efficacy of BMS-986218 alone and in combination with nivolumab in advanced solid tumors (Part 1A and Part 1B)	• ORR, mDOR, and PFSR at 24, 36, and 48 weeks by RECIST v1.1 or PCWG 3
• To characterize the PK and immunogenicity of BMS-986218 when administered alone and in combination with nivolumab	• Summary measures of PK parameters and incidence of ADA to BMS-986218
[redacted]	

Table 1-1: Objectives and Endpoints

Objectives	Endpoints
[redacted]	

Abbreviations: ADA = anti-drug antibody; BMS = Bristol-Myers Squibb; [redacted] DLT = dose-limiting toxicity; [redacted] mDOR = median duration of response; MSS CRC = microsatellite stable colorectal cancer; MTD = maximum tolerated dose; NSCLC = non-small cell lung cancer; ORR = objective response rate; [redacted] PCWG 3 = Prostate Cancer Working Group; PFSR = progression-free survival rate; [redacted] PK = pharmacokinetic(s); RP2D = recommended Phase 2 dose; SAEs = serious adverse events; [redacted]

Overall Design:

This is a Phase 1/2a, open-label study of BMS-986218, administered as a single agent and in combination with nivolumab, in participants with advanced solid tumors. The study is comprised of 2 parts: dose escalation and dose expansion.

- Part 1: The Dose Escalation Phase, where the dose of BMS-986218, given alone or in combination with nivolumab, is escalated to determine the maximum tolerated dose/recommended Phase 2 dose (MTD/RP2D).

- The BMS-986218 Monotherapy Dose Escalation (Part 1A) will escalate the dose of BMS-986218 to determine the MTD/RP2D. The study will first evaluate the safety and tolerability of BMS-986218 once every 4 weeks (Q4W), given alone, based on dose-limiting toxicities (DLTs), using a Bayesian Logistic Regression Model (BLRM) employing the escalation with overdose control (EWOC) principle. In addition, to further evaluate the safety and tolerability of BMS-986218, an alternative once-every-2-weeks (Q2W) dosing schedule will be explored to characterize the safety and PK of BMS-986218. The Q2W dosing schedule will start at a total dose level equivalent to a dose that has cleared safety in the Q4W dosing cohort (eg, 10 mg Q2W vs 20 mg Q4W). Subsequent Q2W doses will be guided by Q4W equivalent doses that have cleared safety, and will continue evaluating higher Q2W doses up to the MTD equivalent of the Q4W dosing cohort. Based on the preliminary PK from the Q4W dosing cohorts, at the steady state, the Q2W dosing schedule is projected to provide approximately the same AUCtau (tau = 4 weeks) as the Q4W dosing schedule, and approximately 70% Cmax as the Q4W dosing schedule. Intra-participant movement between treatment regimens/dosing schedules is not permitted. Additionally, participants with advanced stage cutaneous melanoma, microsatellite stable colorectal cancer (MSS CRC), NSCLC, or SCCHN will be treated with BMS-986218 on a Q2W or Q4W schedule in the Part 1A pharmacodynamic (PD) cohort.
- The Safety Evaluation of Combination Doses of BMS-986218 with Nivolumab (Part 1B) will evaluate the safety and tolerability of doses of BMS-986218 in combination with nivolumab. The combination of BMS-986218 with nivolumab will be evaluated using a BLRM employing the EWOC principle. Starting at least 1 dose level lower than the current monotherapy dose level of BMS-986218 demonstrating an acceptable safety profile, BMS-986218 will be studied in combination with a 480 mg Q4W flat dose of nivolumab. Determination of the MTD for the Safety Evaluation of Combination Doses of BMS-986218 with Nivolumab (Part 1B) will be guided by BLRM-copula.

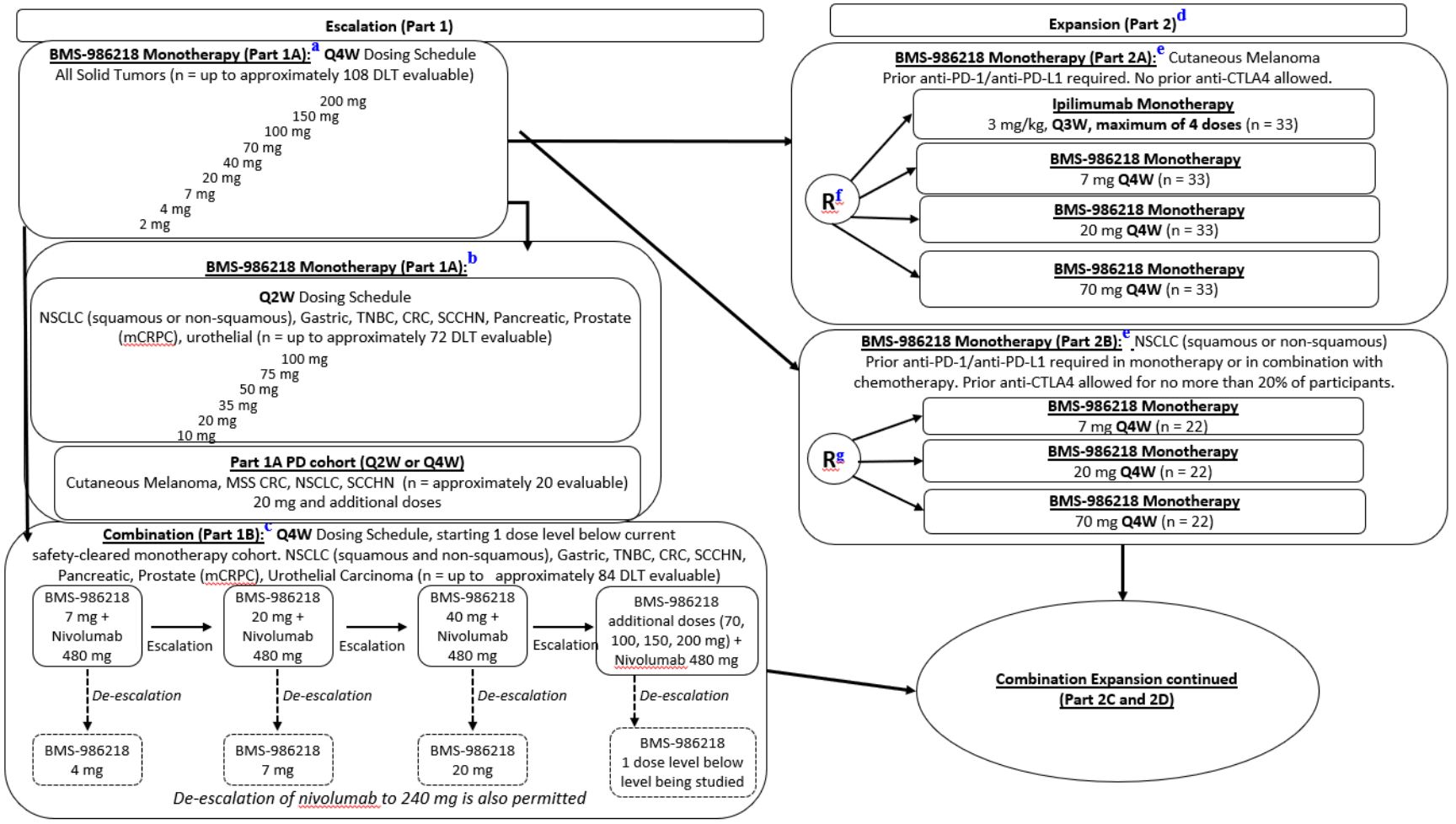
- Part 2: The Expansion Phase, where the cohort of participants is expanded to gather additional safety, tolerability, preliminary efficacy, pharmacokinetic (PK), and pharmacodynamic information in specific patient populations, regarding BMS-986218 alone and in combination with nivolumab.
  - The Randomized BMS-986218 Monotherapy Cohort Expansion in Cutaneous Melanoma (Part 2A) will evaluate the preliminary efficacy of BMS-986218 monotherapy relative to ipilimumab monotherapy in a cohort of cutaneous melanoma participants who have received prior immunotherapy with an anti-PD-1 or anti-PD-L1 containing regimen and must have progressive or recurrent disease after prior PD-1/PD-L1 directed therapy. Three dose levels for BMS-986218 from the Part 1A Q4W monotherapy escalation will be evaluated that have had at least 6 DLT evaluable participants and meet safety criteria: one at 7 mg Q4W, one at 20 mg Q4W, and one at 70 mg Q4W. Evaluating multiple different doses will aid in selecting the regimen that will ultimately provide the optimal benefit-risk ratio to future study participants. Participants must not have received prior anti-CTLA-4 therapy in the advanced or metastatic setting.
  - The Randomized BMS-986218 Monotherapy Cohort Expansion (Part 2B) will evaluate the preliminary efficacy of BMS-986218 in tumor types in which a high level of Treg infiltration correlates with poor prognosis. The tumor types to be evaluated will include NSCLC; other tumor types may be explored in the future. Participants should have received and then progressed on or relapsed/recurrence after anti-PD-1/PD-L1 directed therapy in monotherapy or in combination with chemotherapy. Prior anti-CTLA-4 therapy is allowed for no more than 20% of participants. Participants who have been intolerant to prior immunotherapy are excluded. Three dose levels or schedules for BMS-986218 from the Part 1A Q4W monotherapy escalation will be evaluated that have had at least 6 DLT evaluable participants and meet safety criteria: one at 7 mg Q4W, one at 20 mg Q4W, and one at 70 mg Q4W. The rationale for evaluating multiple dose levels is to optimize the benefit-risk ratio for the participant.
  - In the BMS-986218 Combination Therapy Cohort Expansion in NSCLC (Part 2C), the preliminary efficacy and safety of BMS-986218 in combination with nivolumab will be assessed in participants with NSCLC who have progressed or relapsed after anti-PD-1/PD-L1 therapy. Participants must not have received prior anti-CTLA-4 therapy in the advanced or metastatic setting. One or more doses to be evaluated in Part 2C will be selected from the range of doses assessed as tolerable in Part 1B, and which do not exceed the MTD or highest dose administered that has cleared safety. These dose(s) will be selected based on the totality of available safety, tolerability, efficacy, PK and PD data. The evaluation of efficacy in Part 2C will initially occur at one or more dose levels starting with up to 20 participants at each dose level. Additional participants up to 40 at a dose level may be evaluated following initial signal assessment. In Part 2C, participants will be treated Q4W for up to 2 calendar years regardless of treatment delays.

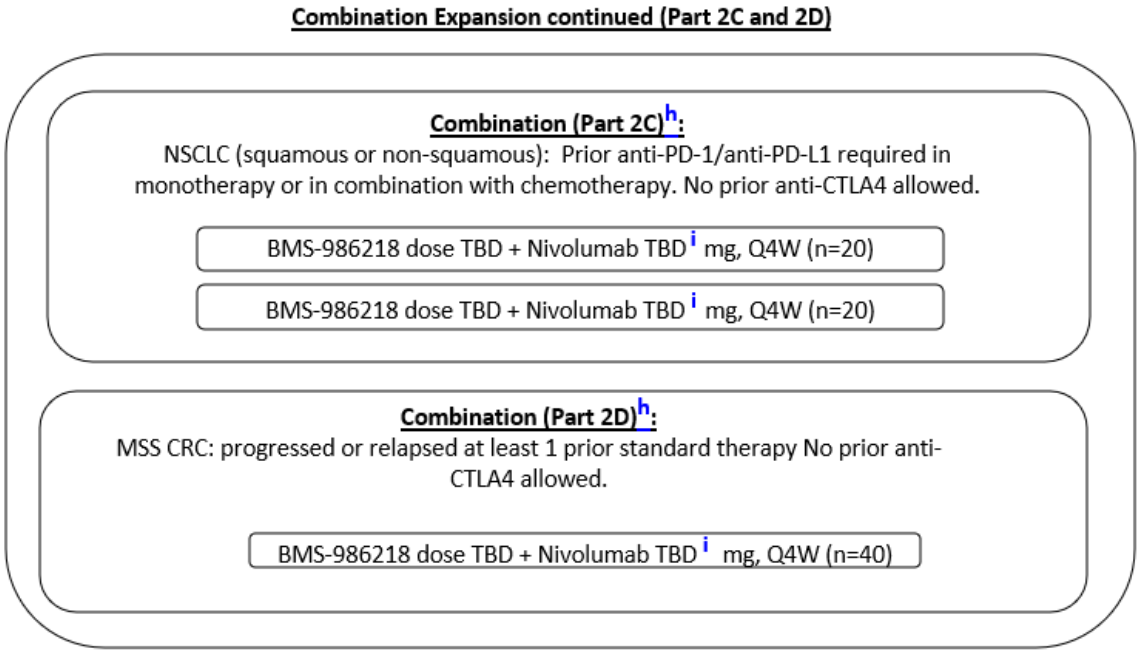
In the BMS-986218 Combination Therapy Cohort Expansion in MSS CRC (Part 2D), the preliminary efficacy and safety of BMS 986218 in combination with nivolumab will be assessed in participants with MSS CRC who have progressed or relapsed on at least 1 prior standard therapy. Participants must not have received prior anti-CTLA-4 therapy in the advanced or metastatic setting.. The dose to be evaluated in Part 2D will be selected from the range of doses assessed as tolerable in Part 1B, and which do not exceed the MTD or highest dose administered that has cleared safety. The dose will be selected based on the totality of available safety, tolerability, efficacy, PK, and PD data. Participants will be tested during screening for extended rat sarcoma (RAS) (neuroblastoma rat viral oncogene homolog [NRAS] and Kirsten rat sarcoma viral oncogene homolog [KRAS]) and v-raf murine sarcoma viral oncogene homolog B1 (BRAF) mutation status. The RAS status evaluation will be conducted with the goal of enrolling approximately 20 participants each with either mutation or wild-type with respect to extended RAS status. The Sponsor may elect to prioritize enrollment of participants based on mutation status. In Part 2D, participants will be treated Q4W for up to 2 calendar years regardless of treatment delays.

- The duration of the study will be approximately 5 years.

The study design is shown in Figure 1-1.

Figure 1-1: Study Design Schematic





[a] If Part 1 is open upon the decision to initiate Part 2, treatment in the 2 parts will occur in parallel. If supported by clinical and safety data, doses higher than 200 mg may be studied until MTD is reached, and further details will be provided in a subsequent protocol amendment at such time.

[b] If Part 1 is open upon the decision to initiate Part 2, treatment in the 2 parts will occur in parallel. If supported by clinical and safety data, doses higher than 100 mg may be studied until MTD equivalent is reached in participants, and further details will be provided in a subsequent protocol amendment at such time.

[c] If Part 1B is open upon the decision to initiate Part 2C and Part 2D, treatment in the 2 parts will occur in parallel. If supported by clinical and safety data, doses higher than 200 mg BMS-986218 may be studied until MTD is reached, and further details will be provided in a subsequent protocol amendment at such time.

[d] Tumor-specific eligibility criteria are detailed in Section 6.

[e] Additional participants may be treated or randomized to further evaluate emerging data or subgroups of interest if needed but not to exceed 40 participants per dose level in Part 2A and Part 2B.

[f] Participants will be randomized, which will include ipilimumab monotherapy and BMS-986218 at different dose levels.

[g] Participants will be treated or randomized.

[h] Dose(s) of BMS-986218 selected for Part 2C and Part 2D will be based on the totality of preliminary safety, tolerability, efficacy, PK and PD data.

[i] The nivolumab dose found to be tolerable in Part1B will be used in Part 2 combination expansions (Part 2C and Part 2D)

Abbreviations: CTLA = cytotoxic T-lymphocyte-associated protein 4; DLT = dose-limiting toxicity; mCRPC = metastatic castration-resistant prostate cancer; MSS CRC = microsatellite stable colorectal cancer; MTD = maximum tolerated dose; NSCLC = non-small cell lung cancer ; PD = pharmacodynamic; PD-L1 = programmed death-ligand 1; Q2W = every 2 weeks; Q3W = every 3 weeks; Q4W = every 4 weeks; R = randomized; SCCHN = squamous cell carcinoma of the head and neck; TNBC = triple-negative breast cancer.

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 (ICF). Within a given disease type, participants meeting all eligibility criteria will be enrolled in the study using an Interactive Response Technology (IRT) according to the part and treatment arm availability.

Treatment: The dosing regimens of BMS-986218 are Q4W and Q2W. Participants will be treated with BMS-986218 Q4W ± nivolumab Q4W for up to 2 calendar years, BMS-986218 Q2W for up to 2 calendar years, and/or ipilimumab Q3W for up to a maximum of 4 doses. Each cycle of the treatment period will be 4 weeks in length, with the exception of the treatment arms with Q3W dosing of ipilimumab in the Randomized BMS-986218 Monotherapy Cohort Expansion in Cutaneous Melanoma (Part 2A), for which each cycle of ipilimumab will be 3 weeks in length.

- BMS-986218 will be infused over 30 minutes during BMS-986218 Monotherapy Dose Escalation (Part 1A),. Ipilimumab and nivolumab will be infused over 30 minutes.
- When both BMS-986218 and nivolumab are given in combination, nivolumab will be infused first, followed by BMS-986218. The BMS-986218 infusion will start at least 30 minutes after completion of the nivolumab infusion.
- BMS-986218 infusions will require a 60-minute observation period following the completion of the infusion for the first 3 doses for each participant.
- For participants receiving combination doses of BMS-986218 with nivolumab, a 30-minute infusion of nivolumab will be followed by a 30-minute observation period, followed by a 30-minute infusion of BMS-986218 and a 60-minute observation period following the first 3 infusions for each participant.
- Ipilimumab infusions will require a 30-minute observation period following the completion of the infusion for the first 3 doses for each participant.
- Tumor progression and response endpoints will be assessed using RECIST v1.1 criteria for solid tumors and PCWG 3 criteria for prostate.

Follow-up:

- Safety Follow-up Period:
  - Upon completion of study therapy (up to a maximum of 2 calendar years for BMS-986218 Q4W ± nivolumab Q4W; up to a maximum of 2 calendar years for BMS-986218 Q2W; up to a maximum of 4 doses for ipilimumab Q3W), or once the decision is made to discontinue the participant from treatment (ie, at end of treatment [EOT]), all participants will enter the safety follow-up period.
  - For participants who complete all scheduled cycles of therapy, the EOT visit will be the same visit as the last scheduled and completed on-treatment visit, and will be the start of the safety follow-up period. For participants who do not complete all scheduled cycles of therapy, the EOT visit will be the most recent on-treatment visit (with all available safety and response data), and will not need to be repeated. Accordingly, for these participants, this visit will be considered the start of the safety follow-up period.
  - After the EOT visit, all participants will be evaluated for any new AEs for at least 100 days after the last dose of study treatment. Follow-up visits should occur at Days 30, 60, and 100 (± 7 days for each visit) after the last dose, or the date of discontinuation (± 7 days). All participants will be required to complete the 3 clinical safety follow-up visits, regardless of whether new anti-cancer therapy is started, except those participants who withdraw consent for study participation.
- Response Follow-up Period:
  - At the time of the EOT visit or at the time of study treatment discontinuation, all participants will continue to have radiologic and clinical tumor assessments every 8 weeks (Q8W; ± 1 week) until subsequent tumor-directed therapy is initiated, or until 48 weeks after discontinuation of study treatment/EOT visit, and then every 12 weeks (Q12W; ± 2 weeks) for a total of 2 years. Radiologic assessments for participants who have ongoing clinical benefit and remain free of subsequent therapy may continue to be collected after participants complete the survival follow-up period of the study. Scans will be submitted to an imaging core laboratory for review by blinded independent central review (BICR) at a later date or at any time during the study at the Sponsor's discretion.

- Survival Follow-up Period:
  - In parallel with the safety follow-up period, all participants will start the survival follow-up period. Participants will be followed up by telephone Q12W (± 2 weeks) from EOT for up to 4 years following the first dose of study treatment or until death, loss to follow-up, withdrawal of consent, or conclusion of the study, whichever comes first. EQ-5D-3L data can be collected by telephone during the Survival Follow-up Period. The duration of the survival follow-up is up to 4 years following the first dose of study treatment. Additional survival follow-up time may continue for up to 5 years from the first dose of the study drug. Tumor assessment scans, for participants who have ongoing clinical benefit beyond the 4-year period following first dose of study treatment, may continue to be collected as part of standard-of-care treatment.

Number of Participants:

The approximate total number of evaluable participants will be up to 684. Up to approximately 284 evaluable participants may be treated in the escalation phase, with 200 evaluable participants for the BMS-986218 Monotherapy Escalation (Part 1A) and 84 evaluable participants for the Safety Evaluation of Combination Doses of BMS-986218 with Nivolumab (Part 1B).

Approximately 20 evaluable participants will be treated in the Part 1A pharmacodynamic (PD) cohorts. In addition, in order to evaluate more than one dose level or schedule, up to 40 additional evaluable participants may be treated in the Part 1A PD cohorts (from participants initially planned for other Part 1 cohorts), provided the total number of participants in Part 1 is not exceeded.

The remaining 400 evaluable participants represent the potential number of participants in BMS-986218 cohort expansions who may be either randomized (Part 2A and Part 2B) or treated (Part 2C and Part 2D). For the Randomized BMS-986218 Monotherapy Cohort Expansion in Cutaneous Melanoma (Part 2A), approximately 132 evaluable participants may be treated, with 33 participants per arm required. For the BMS-986218 Monotherapy Cohort Expansion (Part 2B), approximately 66 evaluable participants with NSCLC may be treated, with 22 evaluable participants per arm required. In Part 2A and Part 2B, additional participants may be treated or randomized to further evaluate emerging data or subgroups of interest if needed, but not to exceed a total of 40 evaluable participants per arm. If additional participants are treated or randomized in Part 2A and Part 2B, then up to 160 response-evaluable participants (= 40 subjects × 4 arms) and 120 response-evaluable participants (= 40 subjects × 3 arms) can be randomized in Part 2A and Part 2B, respectively. For the BMS-986218 Combination Therapy Cohort Expansion in NSCLC (Part 2C), approximately 40 response-evaluable participants will be treated. If more than one dose level is evaluated, additional participants (up to 40 response-evaluable participants per dose level) may be enrolled, up to 80 response-evaluable participants (= 40 participants × 2 arms). In Part 2D BMS-986218 Combination Therapy Cohort Expansion in MSS CRC, approximately 40 response-evaluable participants will be treated, with the goal of treating approximately 20 participants each with either mutation or wild-type with respect to extended RAS status.

Study Treatment:

Table 1-2: Study Treatment for CA022001

Medication	Potency	IP/Non-IP
BMS-986218 Injection	20 mg/mL	IP
Nivolumab Injection	10 mg/mL	IP
Ipilimumab Injection	5 mg/mL	IP

Abbreviations: IP = investigational product.

Part 1: Escalation Phase:

BMS-986218 Monotherapy Escalation (Part 1A), each participant will be administered intravenous doses of BMS-986218 as follows:

- The planned flat dose levels for BMS-986218 are 2, 4, 7, 20, 40, 70, 100, 150, and 200 mg Q4W (up to approximately 108 DLT-evaluable participants) or 10, 20, 35, 50, 75, and 100 mg Q2W (up to approximately 72 DLT-evaluable participants) per cycle, for up to 2 calendar years. The Q2W dosing schedule will start at a total dose level equivalent to a dose that has cleared safety in the Q4W dosing cohort (eg, 10 mg Q2W vs 20 mg Q4W), and continue evaluating higher doses up to the MTD equivalent of the Q4W dosing cohort. If supported by clinical and safety data, doses higher than 200 mg Q4W may be studied, and will be guided by Q4W equivalent doses that have cleared safety until the MTD equivalent of the Q4W dosing cohort is reached.
- Additionally, participants with advanced stage cutaneous melanoma, MSS CRC, NSCLC, or SCCHN will be treated with BMS-986218 on a Q2W schedule at a starting dose of 20 mg in the Part 1A PD cohort. Based on preliminary analysis of Treg count decrease in the tumor microenvironment, using single-cell ribonucleic acid (RNA) sequencing gene expression analysis, additional cohorts of participants at higher dose levels may be evaluated. For example, if the expected PD activity is not observed after 5 to 10 evaluable participants at the 20 mg dose level, then the next set of 5 to 10 evaluable participants may be enrolled at a higher dose level or Q4W schedule. Therefore, more than one dose level may be evaluated based on the pharmacodynamic results assessment. Any additional dose levels evaluated in the Q2W schedule of the Part 1A PD cohort will be a dose that has been determined to be safe and tolerable in either the Q2W escalation part or a dose equivalent to Q4W dose, which has been determined to be safe and tolerable in the Q4W dose escalation part. Approximately 20 evaluable participants per dose level (per dose schedule) may be treated as part of the PD cohort.
- Prior to declaring the MTD, and in consultation with Investigators, the Sponsor has the option to expand any dose level previously established to be tolerable in order to obtain additional experience or to investigate dose levels intermediate to those defined in the protocol. Planned dose levels may be modified, or intermediate dose levels added, based upon the BLRM analysis and clinical evaluation of all available safety and PK/pharmacodynamic data. Once the tolerability (during the DLT evaluation) of a dose level has been established, additional participants may be added at that dose level to better characterize the safety, PK, and pharmacodynamic profiles, for up to approximately 200 participants for study Part 1A.
- **Sentinel Participant:** During the dose-escalation phase, a staggered dosing (sentinel participant) approach will be used. The first participant to be dosed at Cycle 1 Day 1 of each dose level will be observed for 5 days, before additional participants (ie, Participant 2 onward in that cohort) receive study treatments in the same dose level. Initially, 3 participants will be enrolled at the start of each cohort, in accordance with the sentinel participant approach cited above. However, to allow for any unforeseen discontinuations (such as disease progression) before the 8-week DLT period (56 days) is completed, extra participants may be enrolled in each dose escalation cohort.

The Safety Evaluation of Combination Doses of BMS-986218 with Nivolumab (Part 1B): This will be initiated starting at 1 dose level below current safety cleared Q4W monotherapy cohort, defined from BLRM and an overall assessment of all available safety, PK/pharmacodynamic, and efficacy data of the BMS-986218 Monotherapy Escalation (Part 1A).

- The starting dose of BMS-986218 was 1 dose level lower than the Q4W 40 mg monotherapy dose level of BMS-986218, which had demonstrated an acceptable safety profile and was administered in combination with nivolumab at the flat dose of 480 mg Q4W. Dose escalation and determination of MTD for the Safety Evaluation of Combination Doses of BMS-986218 with Nivolumab (Part 1B) will be guided by BLRM-copula. Subsequent dose selection of the combination will be based on evaluating the recommendation from BLRM-copula and an overall assessment of all available safety and PK/pharmacodynamic data. Safety evaluation and tumor assessment will be performed Q8W (2 cycles). If toxicity is unacceptable at any combination dose level, additional combination dose level(s) may be evaluated using BMS-986218 and/or nivolumab (eg, dose of 240 mg Q4W). Selection of dose level for each study drug will be based on the nature and attribution of observed DLTs in previously evaluated dose levels. An intermediate dose level of BMS-986218 and/or an intermediate dose level of nivolumab Q4W may be evaluated in additional cohort(s). No intra-subject dose escalation or de-escalation of BMS-986218 or nivolumab is allowed at any dose level.
- Up to approximately 84 evaluable participants will be enrolled in Part 1B.
- **Sentinel Participant:** The sentinel participant rule will be followed. The first participant to be dosed at Cycle 1 Day 1 of each dose level will be observed for 5 days, before additional participants (ie, Participant 2 onward in that cohort) receive study treatments at the same dose level. Initially, 3 participants will be enrolled at the start of

each cohort, in accordance with the sentinel participant approach cited above; however, to allow for any unforeseen discontinuations (eg, disease progression) before the 8-week DLT period (56 days) is completed, extra participants may be enrolled in each dose cohort.

Dose Limiting Toxicities: For the purpose of guiding dose escalation, DLTs will be defined based on the incidence, intensity, and duration of AEs that are possibly related to study treatment. The DLT period will be 8 weeks (56 days) in both the BMS-986218 Monotherapy Dose Escalation (Part 1A) and the Safety Evaluation of Combination Doses of BMS-986218 with Nivolumab (Part 1B). Any toxicities that occur beyond the DLT period will be accounted for in making final dose level decisions.

Part 2: Expansion Phase

BMS-986218 Monotherapy Cohort Expansion in Cutaneous Melanoma (Part 2A)

- Part 2A will evaluate the preliminary efficacy of BMS-986218 monotherapy relative to ipilimumab monotherapy in a cohort of participants with advanced cutaneous melanoma who have received prior immunotherapy with an anti-PD-1 or anti-PD-L1 containing regimen and must have progressive or recurrent disease after prior anti-PD-1/PD-L1 directed therapy. Participants must not have received prior anti-CTLA-4 therapy in the advanced or metastatic setting. Three dose levels or schedules for BMS-986218 from the Part 1A Q4W monotherapy escalation will be evaluated that have had at least 6 DLT evaluable participants and meet safety criteria: one at 7 mg Q4W, one at 20 mg Q4W, and one at 70 mg Q4W. Evaluating a number of different doses will aid in selecting the regimen that will ultimately provide the optimal benefit-risk ratio to future study participants.

BMS-986218 Cohort Expansion - Monotherapy (Part 2B)

- In Part 2B, the preliminary efficacy of BMS-986218 will be investigated in tumor types where ipilimumab did not demonstrate a sufficient level of efficacy in previous studies and tumors in which a high level of Treg infiltration correlates with a poor prognosis. The tumor types to be evaluated will include NSCLC (adenocarcinoma or squamous cell subtypes only; at least 22 participants required per study arm); other tumor types may be explored in the future. Participants should have received and then progressed on or relapsed/recurrence after anti-PD-1/PD-L1 directed therapy in monotherapy or in combination with chemotherapy. Prior anti-CTLA-4 therapy is allowed for no more than 20% of participants. Three dose levels or schedules for BMS-986218 from the Part 1A Q4W monotherapy escalation will be evaluated that have had at least 6 DLT evaluable participants and meet safety criteria: one at 7 mg Q4W, one at 20 mg Q4W, and one at 70 mg Q4W. The rationale for evaluating multiple dose levels is to optimize the benefit-risk ratio for the participant. BMS-986218 will be administered for a maximum duration of 2 calendar years regardless of treatment delays.

BMS-986218 Cohort Expansion - Combination Therapy in NSCLC (Part 2C)

In the BMS-986218 Combination Therapy Cohort Expansion (Part 2C), the preliminary efficacy and safety of BMS-986218 in combination with nivolumab will be investigated in participants whose NSCLC has progressed or relapsed after anti-PD-1/PD-L1 therapy. Participants must not have received prior anti-CTLA-4 therapy in the advanced or metastatic setting. Any selected BMS-986218 Part 2C dose will not exceed the highest Part 1B administered dose that has cleared safety, with a minimum of 6 evaluable participants for Safety Evaluation. More than one dose may be evaluated in Part 2C. The dose(s) of BMS-986218 selected for Part 2C will be based on the totality of available safety, PK, and pharmacodynamic data from Part 1 and Part 2. The nivolumab dose found to be tolerable in Part 1B will be used in Part 2C. In Part 2C, participants will be treated Q4W for a maximum duration of 2 calendar years regardless of treatment delays.

BMS-986218 Cohort Expansion - Combination Therapy in MSS CRC (Part 2D)

In the BMS-986218 Combination Therapy Cohort Expansion (Part 2D), the preliminary efficacy and safety of BMS-986218 in combination with nivolumab will be investigated in participants with MSS CRC who have progressed or relapsed on at least 1 prior standard therapy. Participants must not have received prior anti-CTLA-4 therapy in the advanced or metastatic setting. The selected BMS-986218 Part 2D dose will not exceed the highest Part 1B administered dose that has cleared safety, with a minimum of 6 evaluable participants for Safety Evaluation. The

dose(s) of BMS-986218 selected for Part 2D will be based on the totality of available safety, PK, and pharmacodynamic data from Part 1 and Part 2. The nivolumab dose found to be tolerable in Part 1B will be used in Part 2D. In Part 2D, participants will be treated Q4W for a maximum duration of 2 calendar years regardless of treatment delays.

Study Assessments:

- **Safety Assessments:** Safety assessments will be based on reported AE reports and the measurement results of vital signs, electrocardiograms, physical examinations, and clinical laboratory tests. AEs will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA) and the incidence of observed AEs will be tabulated and reviewed for potential significance and clinical importance. AEs will be assessed continuously during the study and for 100 days after the last dose of BMS-986218 in the case of monotherapy, and the last dose of BMS-986218 and nivolumab for combination therapy. Local laboratories will perform the clinical laboratory tests and will provide reference ranges for these tests. Both AEs and laboratory tests will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03.
- **PK Assessments**: The PK of BMS-986218 will be derived from serum concentration vs time data. The PK parameters that will be assessed include: maximum observed plasma concentration (Cmax), time of maximum observed serum concentration, area under the serum concentration-time curve (AUC) from time zero to the time of the last quantifiable concentration, AUC in 1 dosing interval, observed serum trough concentration at the end of a dosing interval, total body clearance, average serum concentration over a dosing interval at steady state, accumulation index for AUC and Cmax, and terminal elimination half-life. Individual participant PK parameter values will be derived by noncompartmental methods by a validated PK analysis program. Actual times will be used for the final analyses. Sparse ipilimumab and nivolumab serum concentration-time data will be collected and may be used in an integrated population PK or exposure-response analysis along with data from other ipilimumab and nivolumab studies, which would be the subject of a separate report.
- **Immunogenicity Assessments:** Serum samples for BMS-986218, ipilimumab, and nivolumab anti-drug antibodies (ADAs) will be collected from all participants at specified timepoints.

[redacted]

- **Efficacy Assessments:**
  - Efficacy assessments for the anti-tumor activity of BMS-986218, alone and in combination with nivolumab, will be based on tumor measurements, using RECIST v1.1 or per PCWG 3 criteria for prostate, with computed tomography and/or magnetic resonance imaging, as appropriate, at baseline and Q8W (± 1 week) for the Q4W and Q2W dosing regimens during the treatment period, except the Randomized BMS-986218 Monotherapy Cohort Expansion in Cutaneous Melanoma (Part 2A), where tumor assessment in participants receiving BMS-986218 or ipilimumab will occur at 12 weeks from first dose (± 1 week), prior to initiating the next cycle of treatment. After that, subsequent tumor imaging assessments to be performed Q8W (± 1 week). Tumor imaging assessments are to be performed prior to initiating next cycle of treatment.
  - Efficacy assessments for the anti-tumor activity of ipilimumab are to be performed 12 weeks from first dose, regardless of dose delays, if any (± 1 week). Tumor imaging assessments are to be performed prior to initiating next cycle of treatment. Participants who remain free of subsequent therapy will undergo the second tumor imaging assessment at 24 weeks from first dose ± 1 week. After that, participants who remain free of subsequent therapy will undergo tumor imaging assessment Q8W (± 1 week) until subsequent tumor-directed therapy is initiated or until 48 weeks after discontinuation of study treatment/EOT visit, and then Q12W (± 2 weeks) for a total duration of 2 years.
  - Images will be submitted to an imaging core lab. Image acquisition guidelines and submission process will be outlined in the CA022001 Imaging Manual to be provided by the core laboratory.

Data Monitoring Committee: No.

BMS has developed a multi-layered process to ensure safety monitoring through close collaboration of study site Investigators, the BMS study team, and the BMS Worldwide Patient Safety (WWPS)-led Safety Management Team

(SMT). This collaborative process constitutes the safety monitoring plan for the study. To support safety oversight, BMS has established ongoing processes for collection, review, analysis, and submission of individual AE reports and their aggregate analyses. Because this is an open-label study, WWPS, the BMS Medical Monitor, and the Investigators will have access to all data necessary for safety evaluation.

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

2 SCHEDULE OF ACTIVITIES

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

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

Procedure	Screening Visit (Days -28 to -1)	Notes
Eligibility Assessments		
Informed Consent	X	A participant is considered enrolled only when a protocol-specific ICF is signed.
IRT Participant Assignment	X	After the participants meet all eligibility criteria, sites will use IRT for participant number assignment. Subsequent visits will be registered into the IRT system for drug supply (see Section 5.1.1).
Inclusion/Exclusion Criteria	X	See Section 6.1 and Section 6.2.
Medical History	X	Include any toxicities or allergy related to previous treatments and tumor characteristics (eg, mutation status, receptor status, viral status, if available). All medical history relevant to the disease under study, and COVID-19 vaccines more than 30 days prior to first study treatment.
Prior Cancer Therapies	X	
Concomitant Medications	X	Within 14 days prior to randomization/treatment assignment. Vaccine use within 30 days prior to first study treatment.
ECOG Performance Status	X	
Safety Assessments		
PE	X	If the screening PE is performed within 72 hours prior to dosing on Day 1, then a single examination may count as both the screening and predose evaluation on C1D1.
Physical Measurements	X	Includes height and weight.
Vital Signs	X	Includes body temperature, respiratory rate, and seated/supine blood pressure and heart rate. Blood pressure and heart rate should be measured after the participant has been resting quietly for at least 5 minutes.
Oxygen Saturation	X	Pulse oximetry collected at rest.
ECG	X	ECGs should be recorded after the participant has been supine for at least 5 minutes and prior to blood draws. Screening ECG is to be collected as a single reading (see Section 9.1.3).
Laboratory Tests	X	See Clinical Laboratory Assessments in Section 9.1.4 and Table 9.1.4-1. There will be a minus-72-hour window from C1D1 during screening for the collection of laboratory tests.
Urinalysis	X	Microscopic urine reflex only for urinalysis positive for blood/protein/leukocytes.

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

Procedure	Screening Visit (Days -28 to -1)	Notes
Serology	X	Includes hepatitis C Ab, hepatitis B surface antigen, and HIV-1 and HIV-2 Ab (see Section 9.1.4 and Table 9.1.4-1).
Pregnancy Test	X	For WOCBP only. Serum to be collected at screening and within 24 hours prior to dosing on Day 1 of each treatment cycle. Serum pregnancy test may be taken on the first day of treatment, provided results are available prior to starting study therapy. If pregnancy test is taken within 24 hours of dosing (C1D1), a further pregnancy test is not required.
FSH	X	Women only, as needed to document postmenopausal status.
Adverse Event Reporting		
Assessment of Signs/Symptoms/ Clinical Complaints	X	
Monitor for SAEs	X	All SAEs must be collected from the date of participant's written consent until 100 days after discontinuation of dosing. All AEs (SAEs or nonserious AEs) associated with SARS-CoV-2 infection collected from time of consent.
Tumor Assessments		
Body Imaging	X	Refer to Imaging Assessment details in Section 9.3.1. CT and MRI scans should be acquired with a 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.
Brain Imaging	X	MRI without and with contrast of the brain required at screening only if participant is symptomatic or has history of brain metastasis and has not had brain imaging within 30 days of anticipated first study drug administration. CT of the brain without and with contrast may be performed if MRI is contraindicated. Refer to Imaging Assessment details in Section 9.3.1. CT and MRI scans should be acquired with a 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.

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

Procedure	Screening Visit (Days -28 to -1)	Notes
Bone Scan	X	Required for participants with prostate cancer for evaluation of bone disease; otherwise, as clinically indicated. Refer to Imaging Assessment details in Section 9.3.1. Every attempt should be made to image each participant using an identical acquisition protocol on the same scanner for all imaging timepoints.
Clinical Treatment Supplies		
Dispense Study Treatment	X	Study treatments (BMS-986218, ipilimumab, and nivolumab) to be supplied by BMS and in assigned vials per IRT (see Section 5.1.1, Table 2-2, Table 2-3, and Table 2-4).
[redacted]		

Abbreviations: Ab = antibody; AE = adverse event; BMS = Bristol-Myers Squibb; C1D1 = Cycle 1 Day 1; CT = computed tomography; [redacted] ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FSH = follicle stimulating hormone; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; ICF = informed consent form; IRT = Interactive Response Technology; MRI = magnetic resonance imaging; [redacted] PE = physical examination; RNA = ribonucleic acid; SAE = serious adverse events; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WOCBP = women of childbearing potential.

Table 2-2: On-Treatment - Schedule of Activities for Q4W Dosing Schedules in BMS-986218 Monotherapy Escalation (Part 1A), Safety Evaluation of Combination Doses of BMS-986218 with Nivolumab (Part 1B), Randomized BMS-986218 Monotherapy Cohort Expansion in Cutaneous Melanoma (Part 2A), Randomized BMS-986218 Monotherapy Cohort Expansion (Part 2B), and Combination Cohort Expansions (Part 2C and Part 2D)

Procedure	Cycle 1 (28 Days in Length) (Visit Window ± 2 Days, except for C1D1)				Cycle 2 (28 Days in Length) (Visit Window ± 2 Days)				Cycles 3 and Beyond (Each Cycle 28 Days in Length) (Visit Window ± 2 Days)	EOT[a,b]	Notes
	DLT Period is Cycles 1 and 2										
	D1	D8	D15	D22	D1	D8	D15	D22	D1		
Safety Assessments											
ECOG Performance Status	X				X				X	X	
PE	X				X				X	X	
Symptom Directed PE		X	X	X		X	X	X			
Weight	X				X				X	X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	For BMS-986218, vital signs will be obtained within 30 minutes before the start of the infusion and then every 15 minutes (± 5 minutes) from the start of the infusion until 60 minutes after completion of the infusion for the first 3 doses of study treatment on C1D1, C2D1, and C3D1. For all cycles after cycle 3, vital signs and oxygen saturation are to be taken before the infusion and at the end of each infusion. For nivolumab, vital signs will be obtained within 30 minutes before the start of the infusion and then every 30 minutes (± 5 minutes) from the start

Table 2-2: On-Treatment - Schedule of Activities for Q4W Dosing Schedules in BMS-986218 Monotherapy Escalation (Part 1A), Safety Evaluation of Combination Doses of BMS-986218 with Nivolumab (Part 1B), Randomized BMS-986218 Monotherapy Cohort Expansion in Cutaneous Melanoma (Part 2A), Randomized BMS-986218 Monotherapy Cohort Expansion (Part 2B), and Combination Cohort Expansions (Part 2C and Part 2D)

Procedure	Cycle 1 (28 Days in Length) (Visit Window ± 2 Days, except for C1D1)				Cycle 2 (28 Days in Length) (Visit Window ± 2 Days)				Cycles 3 and Beyond (Each Cycle 28 Days in Length) (Visit Window ± 2 Days)	EOT[a,b]	Notes
	DLT Period is Cycles 1 and 2										
	D1	D8	D15	D22	D1	D8	D15	D22	D1		
											of the infusion until completion of the infusion. If any vital sign is abnormal (based upon clinician assessment) at the final check, the participant must be observed further for a period of time, as clinically indicated.
Oxygen Saturation	X				X				X		Oxygen saturation to also be performed in conjunction with vital signs monitoring on these days. For all cycles after Cycle 3, vital signs and oxygen saturation are to be taken before the infusion and at the end of each infusion.
ECG	X				X				X	X	ECGs should be recorded after the participant has been supine for at least 5 minutes and prior to blood draws. ECGs to be performed in triplicate in association with PK sampling, at predose and EOI, on Day 1 of both Cycle 1 and Cycle 3 for Part 1A only (see Section 9.1.3). Single safety ECGs to be performed for all other time points.

Table 2-2: On-Treatment - Schedule of Activities for Q4W Dosing Schedules in BMS-986218 Monotherapy Escalation (Part 1A), Safety Evaluation of Combination Doses of BMS-986218 with Nivolumab (Part 1B), Randomized BMS-986218 Monotherapy Cohort Expansion in Cutaneous Melanoma (Part 2A), Randomized BMS-986218 Monotherapy Cohort Expansion (Part 2B), and Combination Cohort Expansions (Part 2C and Part 2D)

Procedure	Cycle 1 (28 Days in Length) (Visit Window ± 2 Days, except for C1D1)				Cycle 2 (28 Days in Length) (Visit Window ± 2 Days)				Cycles 3 and Beyond (Each Cycle 28 Days in Length) (Visit Window ± 2 Days)	EOT[a,b]	Notes
	DLT Period is Cycles 1 and 2										
	D1	D8	D15	D22	D1	D8	D15	D22	D1		
											Beyond Cycle 3, ECGs must be performed every 3 cycles up to EOT.
Laboratory Tests	X	X	X	X	X	X	X	X	X	X	There will be a minus-72-hour window for collection of laboratory tests on Day 1 of each cycle and a window of ± 2 days for all other timepoints. Coagulation assessment at screening only. See Section 9.1.4 and Table 9.1.4-1.
[redacted]											
Urinalysis	X				X				As clinically indicated; microscopic urine reflex only for urinalysis positive for blood/protein/ leukocyte esterase	X	

Table 2-2: On-Treatment - Schedule of Activities for Q4W Dosing Schedules in BMS-986218 Monotherapy Escalation (Part 1A), Safety Evaluation of Combination Doses of BMS-986218 with Nivolumab (Part 1B), Randomized BMS-986218 Monotherapy Cohort Expansion in Cutaneous Melanoma (Part 2A), Randomized BMS-986218 Monotherapy Cohort Expansion (Part 2B), and Combination Cohort Expansions (Part 2C and Part 2D)

Procedure	Cycle 1 (28 Days in Length) (Visit Window ± 2 Days, except for C1D1)				Cycle 2 (28 Days in Length) (Visit Window ± 2 Days)				Cycles 3 and Beyond (Each Cycle 28 Days in Length) (Visit Window ± 2 Days)	EOT[a,b]	Notes
	DLT Period is Cycles 1 and 2										
	D1	D8	D15	D22	D1	D8	D15	D22	D1		
Pregnancy Test (WOCBP only)	X				X				X	X	Serum/urine to be collected within 24 hours prior to dosing. Pregnancy test may be completed on the first day of treatment, provided that the results are available before the start of study therapy. Serum or urine pregnancy test must be performed within 24 hours prior to administration of study treatment (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG).
Adverse Event Reporting and Concomitant Medication Assessments											
Monitor for Non-SAEs	Non-SAEs will be collected starting with the first dose of study medication and through 100 days following the last dose of study treatment.										Section 9.2 and Appendix 3. All AEs (SAEs or nonserious AEs) including those associated with SARS-CoV-2 infection must be collected continuously during the treatment period.
Monitor for SAEs	All SAEs must be collected from the date of the participant's written consent until 100 days following the last dose of study treatment.										Section 9.2 and Appendix 3.
Concomitant Medications	X	X	X	X	X	X	X	X	X		

Table 2-2: On-Treatment - Schedule of Activities for Q4W Dosing Schedules in BMS-986218 Monotherapy Escalation (Part 1A), Safety Evaluation of Combination Doses of BMS-986218 with Nivolumab (Part 1B), Randomized BMS-986218 Monotherapy Cohort Expansion in Cutaneous Melanoma (Part 2A), Randomized BMS-986218 Monotherapy Cohort Expansion (Part 2B), and Combination Cohort Expansions (Part 2C and Part 2D)

Procedure	Cycle 1 (28 Days in Length) (Visit Window ± 2 Days, except for C1D1)				Cycle 2 (28 Days in Length) (Visit Window ± 2 Days)				Cycles 3 and Beyond (Each Cycle 28 Days in Length) (Visit Window ± 2 Days)	EOT[a,b]	Notes
	DLT Period is Cycles 1 and 2										
	D1	D8	D15	D22	D1	D8	D15	D22	D1		
PK Assessments											
Serial Blood Sampling	See Table 9.5-2 and Table 9.5-5 of the PK and immunogenicity sampling schedule and Section 9.5.										
Immunogenicity (ADA) Assessments	See Table 9.5-2 and Table 9.5-5 of the PK and immunogenicity sampling schedule and Section 9.5.										
[redacted]											

Table 2-2: On-Treatment - Schedule of Activities for Q4W Dosing Schedules in BMS-986218 Monotherapy Escalation (Part 1A), Safety Evaluation of Combination Doses of BMS-986218 with Nivolumab (Part 1B), Randomized BMS-986218 Monotherapy Cohort Expansion in Cutaneous Melanoma (Part 2A), Randomized BMS-986218 Monotherapy Cohort Expansion (Part 2B), and Combination Cohort Expansions (Part 2C and Part 2D)

Procedure	Cycle 1 (28 Days in Length) (Visit Window ± 2 Days, except for C1D1)				Cycle 2 (28 Days in Length) (Visit Window ± 2 Days)				Cycles 3 and Beyond (Each Cycle 28 Days in Length) (Visit Window ± 2 Days)	EOT[a,b]	Notes
	DLT Period is Cycles 1 and 2										
	D1	D8	D15	D22	D1	D8	D15	D22	D1		
Imaging Assessments											
Body Imaging	Tumor imaging assessment to be performed Q8W from first dose (± 1 week), prior to initiating next cycle of treatment (for Part 1A, Part 1B, Part 2B, Part 2C, and Part 2D). Tumor imaging assessment to be performed at 12 weeks from the first dose, regardless of dose delays, if any (± 1 week), prior to initiating the next cycle of treatment, for participants in the Randomized BMS-986218 Monotherapy Cohort Expansion in Cutaneous Melanoma (Part 2A). After that, subsequent tumor imaging assessments to be performed Q8W (± 1 week), prior to initiating the next cycle of treatment. Participants who remain free of subsequent therapy will undergo tumor imaging assessment Q8W (± 1 week) until subsequent tumor-directed therapy is initiated or until 48 weeks after discontinuation of study treatment/EOT visit, and then Q12W (± 2 weeks) for a total duration of 2 years.										The same imaging modality is to be used for all assessments, per RECIST v1.1 (Appendix 5) or per PCWG 3 criteria for prostate (Appendix 12). Tumor assessment to be performed prior to initiating next cycle of treatment. CT and MRI scans 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.
Brain Imaging	Participants with history of brain metastasis will have MRI performed as clinically indicated and at the discretion of the Investigator.										MRI without and with contrast of the brain should be performed. CT of the brain without and with contrast may be obtained if MRI is contraindicated. CT and MRI scans 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.

Table 2-2: On-Treatment - Schedule of Activities for Q4W Dosing Schedules in BMS-986218 Monotherapy Escalation (Part 1A), Safety Evaluation of Combination Doses of BMS-986218 with Nivolumab (Part 1B), Randomized BMS-986218 Monotherapy Cohort Expansion in Cutaneous Melanoma (Part 2A), Randomized BMS-986218 Monotherapy Cohort Expansion (Part 2B), and Combination Cohort Expansions (Part 2C and Part 2D)

Procedure	Cycle 1 (28 Days in Length) (Visit Window ± 2 Days, except for C1D1)				Cycle 2 (28 Days in Length) (Visit Window ± 2 Days)				Cycles 3 and Beyond (Each Cycle 28 Days in Length) (Visit Window ± 2 Days)	EOT[a,b]	Notes
	DLT Period is Cycles 1 and 2										
	D1	D8	D15	D22	D1	D8	D15	D22	D1		
[redacted]											

Table 2-2: On-Treatment - Schedule of Activities for Q4W Dosing Schedules in BMS-986218 Monotherapy Escalation (Part 1A), Safety Evaluation of Combination Doses of BMS-986218 with Nivolumab (Part 1B), Randomized BMS-986218 Monotherapy Cohort Expansion in Cutaneous Melanoma (Part 2A), Randomized BMS-986218 Monotherapy Cohort Expansion (Part 2B), and Combination Cohort Expansions (Part 2C and Part 2D)

Procedure	Cycle 1 (28 Days in Length) (Visit Window ± 2 Days, except for C1D1)				Cycle 2 (28 Days in Length) (Visit Window ± 2 Days)				Cycles 3 and Beyond (Each Cycle 28 Days in Length) (Visit Window ± 2 Days)	EOT[a,b]	Notes
	DLT Period is Cycles 1 and 2										
	D1	D8	D15	D22	D1	D8	D15	D22	D1		
[redacted]											

Table 2-2: On-Treatment - Schedule of Activities for Q4W Dosing Schedules in BMS-986218 Monotherapy Escalation (Part 1A), Safety Evaluation of Combination Doses of BMS-986218 with Nivolumab (Part 1B), Randomized BMS-986218 Monotherapy Cohort Expansion in Cutaneous Melanoma (Part 2A), Randomized BMS-986218 Monotherapy Cohort Expansion (Part 2B), and Combination Cohort Expansions (Part 2C and Part 2D)

Procedure	Cycle 1 (28 Days in Length) (Visit Window ± 2 Days, except for C1D1)				Cycle 2 (28 Days in Length) (Visit Window ± 2 Days)				Cycles 3 and Beyond (Each Cycle 28 Days in Length) (Visit Window ± 2 Days)	EOT[a,b]	Notes
	DLT Period is Cycles 1 and 2										
	D1	D8	D15	D22	D1	D8	D15	D22	D1		
Clinical Treatment Supplies											
BMS-986218 Administration	X				X				X		Study treatments, BMS-986218 and nivolumab, to be supplied by BMS; vials assigned by IRT must be used.
Nivolumab Administration (Part 1B, 2C, and 2D only)	X				X				X		

Abbreviations: ADA = anti-drug antibody; AE = adverse event; BMS = Bristol-Myers Squibb; CXDY = Cycle X, Day Y, as an example; CT = computed tomography; D = day; DLT = dose-limiting toxicity; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOI = end of infusion; [redacted] EOT = end of treatment; [redacted] hCG = human chorionic gonadotropin; [redacted] IRT = Interactive Response Technology; MRI = magnetic resonance imaging; PCWG 3 = Prostate Cancer Working Group 3; PE = physical examination; PK = pharmacokinetic; Q8W = every 8 weeks; Q12W = every 12 weeks; [redacted] RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WOCBP = women of childbearing potential.

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

[b] For participants who complete all scheduled cycles of therapy, the EOT visit will be the same as the last scheduled and completed on-treatment visit (eg, Cycle 3 Day 21) and the start of the Safety Follow-up period. For participants who do not complete all scheduled cycles of therapy, the EOT visit will be the most recent on treatment visit (with all available safety and response data); it does not need to be repeated and will be considered as the start of the Safety Follow-up period.

Table 2-3: On-Treatment - Schedule of Activities for Q2W Dosing Schedules in BMS-986218 Monotherapy Escalation (Part 1A)

Procedure	Cycle 1 (28 Days in Length) (Visit Window ± 2 Days, except for C1D1)				Cycle 2 (28 Days in Length) (Visit Window ± 2 Days)				Cycles 3 and Beyond (Each Cycle 28 Days in Length) (Visit Window ± 2 Days)	EOT[a,b]	Notes
	DLT Period is Cycles 1 and 2										
	D1	D8	D15	D22	D1	D8	D15	D22	D1 & D15		
Safety Assessments											
ECOG Performance Status	X		X		X		X		X	X	
PE	X		X		X		X		X	X	
Symptom Directed PE		X		X		X		X			
Weight	X		X		X		X		X	X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	For BMS-986218, vital signs will be obtained within 30 minutes before the start of the infusion and then every 15 minutes (± 5 minutes) from the start of the infusion until 60 minutes after completion of the infusion for the first 3 doses of study treatment on C1D1, C1D15, and C2D1. For all doses after C2D1, vital signs and oxygen saturation are to be taken before the infusion and at the end of infusion. If any vital sign is abnormal (based upon clinician assessment) at the final check, the participant must be observed further for a period of time, as clinically indicated.

Table 2-3: On-Treatment - Schedule of Activities for Q2W Dosing Schedules in BMS-986218 Monotherapy Escalation (Part 1A)

Procedure	Cycle 1 (28 Days in Length) (Visit Window ± 2 Days, except for C1D1)				Cycle 2 (28 Days in Length) (Visit Window ± 2 Days)				Cycles 3 and Beyond (Each Cycle 28 Days in Length) (Visit Window ± 2 Days)	EOT[a,b]	Notes
	DLT Period is Cycles 1 and 2										
	D1	D8	D15	D22	D1	D8	D15	D22	D1 & D15		
Oxygen Saturation	X		X		X		X		X		Oxygen saturation to also be performed in conjunction with vital signs monitoring on these days. For all infusions after C2D1, vital signs and oxygen saturation are to be taken before the infusion and at the end of each infusion.
ECG	X		X		X		X		X	X	ECGs should be recorded after the participant has been supine for at least 5 minutes and prior to blood draws. ECGs to be performed in triplicate in association with PK sampling, at predose and EOI, on Day 1 of both Cycle 1 and Cycle 3 for Part 1A only (see Section 9.1.3). Single safety ECGs to be performed for all other time points. Beyond Cycle 3, ECGs must be performed every 3 cycles up to EOT.
Laboratory Tests	X	X	X	X	X	X	X	X	X	X	There will be a minus-72-hour window for collection of laboratory tests on Day 1 of each cycle and a window of ± 2 days for all other timepoints. Coagulation assessment at screening only. See Section 9.1.4 and Table 9.1.4-1.

Table 2-3: On-Treatment - Schedule of Activities for Q2W Dosing Schedules in BMS-986218 Monotherapy Escalation (Part 1A)

Procedure	Cycle 1 (28 Days in Length) (Visit Window ± 2 Days, except for C1D1)				Cycle 2 (28 Days in Length) (Visit Window ± 2 Days)				Cycles 3 and Beyond (Each Cycle 28 Days in Length) (Visit Window ± 2 Days)	EOT[a,b]	Notes
	DLT Period is Cycles 1 and 2										
	D1	D8	D15	D22	D1	D8	D15	D22	D1 & D15		
[redacted]											
Urinalysis	X		X		X		X		As clinically indicated; microscopic urine reflex only for urinalysis positive for blood/protein/ leukocyte esterase	X	
Pregnancy Test (WOCBP only)	X				X				X (Day 1 only)	X	Serum/urine for pregnancy test to be collected within 24 hours prior to dosing on Day 1 of each cycle. Pregnancy test may be completed on the first day of treatment, provided the results are available before the start of study therapy. Serum or urine pregnancy test must be performed within 24 hours prior to administration of study treatment on Day 1 of each cycle (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG).

Table 2-3: On-Treatment - Schedule of Activities for Q2W Dosing Schedules in BMS-986218 Monotherapy Escalation (Part 1A)

Procedure	Cycle 1 (28 Days in Length) (Visit Window ± 2 Days, except for C1D1)				Cycle 2 (28 Days in Length) (Visit Window ± 2 Days)				Cycles 3 and Beyond (Each Cycle 28 Days in Length) (Visit Window ± 2 Days)	EOT[a,b]	Notes
	DLT Period is Cycles 1 and 2										
	D1	D8	D15	D22	D1	D8	D15	D22	D1 & D15		
Adverse Event Reporting and Concomitant Medication Assessments											
Monitor for Non-SAEs	Non-SAEs will be collected starting with the first dose of study medication and through 100 days following the last dose of study treatment.										Section 9.2 and Appendix 3. All AEs (SAEs or nonserious AEs) including those associated with SARS-CoV-2 infection must be collected continuously during the treatment period.
Monitor for SAEs	All SAEs must be collected from the date of the participant's written consent until 100 days following the last dose of study treatment.										Section 9.2 and Appendix 3.
Concomitant Medications	X	X	X	X	X	X	X	X	X		
PK Assessments											
Serial Blood Sampling	See Table 9.5-3 of the PK and immunogenicity sampling schedule and Section 9.5.										
Immunogenicity (ADA) Assessments	See Table 9.5-3 of the PK and immunogenicity sampling schedule and Section 9.5.										
[redacted]											

Table 2-3: On-Treatment - Schedule of Activities for Q2W Dosing Schedules in BMS-986218 Monotherapy Escalation (Part 1A)

Procedure	Cycle 1 (28 Days in Length) (Visit Window ± 2 Days, except for C1D1)				Cycle 2 (28 Days in Length) (Visit Window ± 2 Days)				Cycles 3 and Beyond (Each Cycle 28 Days in Length) (Visit Window ± 2 Days)	EOT[a,b]	Notes
	DLT Period is Cycles 1 and 2										
	D1	D8	D15	D22	D1	D8	D15	D22	D1 & D15		
Imaging Assessments											
Body Imaging	Tumor imaging assessment to be performed Q8W from the first dose (± 1 week), prior to initiating next cycle of treatment in Part 1A. Participants who remain free of subsequent therapy will undergo tumor imaging assessment Q8W (± 1 week) until subsequent tumor-directed therapy is initiated or until 48 weeks after discontinuation of study treatment/EOT visit, and then Q12W (± 2 weeks) for a total duration of 2 years.										The same imaging modality is to be used for all assessments, per RECIST v1.1 (Appendix 5) or per PCWG 3 criteria for prostate (Appendix 12). Tumor assessment to be performed prior to initiating next cycle of treatment. CT and MRI scans 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.
Brain Imaging	Participants with history of brain metastasis will have MRI performed as clinically indicated and at the discretion of the Investigator.										MRI without and with contrast of the brain should be performed. CT of the brain without and with contrast may be obtained if MRI is contraindicated. CT and MRI scans 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.

Table 2-3: On-Treatment - Schedule of Activities for Q2W Dosing Schedules in BMS-986218 Monotherapy Escalation (Part 1A)

Procedure	Cycle 1 (28 Days in Length) (Visit Window ± 2 Days, except for C1D1)				Cycle 2 (28 Days in Length) (Visit Window ± 2 Days)				Cycles 3 and Beyond (Each Cycle 28 Days in Length) (Visit Window ± 2 Days)	EOT[a,b]	Notes
	DLT Period is Cycles 1 and 2										
	D1	D8	D15	D22	D1	D8	D15	D22	D1 & D15		
[redacted]											

Table 2-3: On-Treatment - Schedule of Activities for Q2W Dosing Schedules in BMS-986218 Monotherapy Escalation (Part 1A)

Procedure	Cycle 1 (28 Days in Length) (Visit Window ± 2 Days, except for C1D1)				Cycle 2 (28 Days in Length) (Visit Window ± 2 Days)				Cycles 3 and Beyond (Each Cycle 28 Days in Length) (Visit Window ± 2 Days)	EOT[a,b]	Notes
	DLT Period is Cycles 1 and 2										
	D1	D8	D15	D22	D1	D8	D15	D22	D1 & D15		
[redacted]											
Clinical Treatment Supplies											
BMS-986218 Administration	X		X		X		X		X		Study treatment, BMS-986218, to be supplied by BMS; vials assigned by IRT must be used.

Abbreviations: ADA = anti-drug antibody; AE = adverse event; BMS = Bristol-Myers Squibb; CXDY = Cycle X Day Y, as an example; CT = computed tomography; D = day; DLT = dose-limiting toxicity; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOI = end of infusion; hCG = human chorionic gonadotropin; [redacted] IRT = Interactive Response Technology; MRI = magnetic resonance imaging; PCWG 3 = Prostate Cancer Working Group 3; PE = physical examination; PK = pharmacokinetic; Q8W = every 8 weeks; Q12W = every 12 weeks;

RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WOCBP = women of childbearing potential.

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

[b] For participants who complete all scheduled cycles of therapy, the EOT visit will be the same as the last scheduled and completed on-treatment visit (eg, Cycle 3 Day 21) and the start of the Safety Follow-up Period. For participants who do not complete all scheduled cycles of therapy, the EOT visit will be the most recent on-treatment visit (with all available safety and response data); it does not need to be repeated and will be considered as the start of the Safety Follow-up Period.

Table 2-4: On-Treatment - Schedule of Activities for Q3W Dosing Schedule for Ipilimumab in the Randomized BMS-986218 Monotherapy Cohort Expansion in Cutaneous Melanoma (Part 2A)

Procedure	Cycle 1 (21 Days in Length) (Visit Window ± 2 Days, except for C1D1)			Cycle 2 (21 Days in Length) (Visit Window ± 2 Days)			Cycle 3 and Cycle 4 (21 Days in Length) (Visit Window ± 2 Days)			EOT[a,b]	Notes
	D1	D8	D15	D1	D8	D15	D1	D8	D15		
Safety Assessments											
ECOG Performance Status	X			X			X			X	
PE	X			X			X			X	
Symptom Directed PE		X	X		X	X					
Weight	X			X			X			X	
Vital Signs	X	X	X	X	X	X	X			X	For ipilimumab, vital signs will be obtained within 30 minutes before the start of the infusion and then every 30 minutes (± 5 minutes) from the start of the infusion until completion of the infusion. If any vital sign is abnormal (based upon clinician assessment) at the final check, the participant must be observed further for a period, as clinically indicated.
Oxygen Saturation	X			X			X				
ECG	X			X			X			X	ECGs should be recorded after the participant has been supine for at least 5 minutes and prior to blood draws. Single safety ECGs to be done prior to each infusion for all treatment cycles. ECGs must be performed on Day 1 of each cycle and at EOT.

Table 2-4: On-Treatment - Schedule of Activities for Q3W Dosing Schedule for Ipilimumab in the Randomized BMS-986218 Monotherapy Cohort Expansion in Cutaneous Melanoma (Part 2A)

Procedure	Cycle 1 (21 Days in Length) (Visit Window ± 2 Days, except for C1D1)			Cycle 2 (21 Days in Length) (Visit Window ± 2 Days)			Cycle 3 and Cycle 4 (21 Days in Length) (Visit Window ± 2 Days)			EOT[a,b]	Notes
	D1	D8	D15	D1	D8	D15	D1	D8	D15		
Laboratory Tests	X	X	X	X	X	X	X			X	There will be a minus-72-hour window for collection of laboratory tests on Day 1 of each cycle and a window of ± 2 days window for all other timepoints. Coagulation assessments will be performed at screening only. See Section 9.1.4 and Table 9.1.4-1.
[redacted]											
Urinalysis	X			X			As clinically indicated; microscopic urine reflex only for urinalysis positive for blood/protein/leukocyte esterase.			X	
Pregnancy Test (WOCBP only)	X			X			X			X	Serum/urine to be collected within 24 hours prior to dosing. Pregnancy test may be completed on the first day of treatment, provided the results are available before the start of study therapy. Serum or urine pregnancy test must be performed within 24 hours prior to administration of study treatment (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG).

Table 2-4: On-Treatment - Schedule of Activities for Q3W Dosing Schedule for Ipilimumab in the Randomized BMS-986218 Monotherapy Cohort Expansion in Cutaneous Melanoma (Part 2A)

Procedure	Cycle 1 (21 Days in Length) (Visit Window ± 2 Days, except for C1D1)			Cycle 2 (21 Days in Length) (Visit Window ± 2 Days)			Cycle 3 and Cycle 4 (21 Days in Length) (Visit Window ± 2 Days)			EOT[a,b]	Notes
	D1	D8	D15	D1	D8	D15	D1	D8	D15		
Adverse Event Reporting and Concomitant Medication Assessments											
Monitor for Non-SAEs	Non-SAEs will be collected starting with the first dose of study medication and through 100 days following last dose of study treatment.										Section 9.2 and Appendix 3. All AEs (SAEs or nonserious AEs) including those associated with SARS-CoV-2 infection must be collected continuously during the treatment period
Monitor for SAEs	All SAEs must be collected from the date of the participant's written consent until 100 days following the last dose of study treatment.										Section 9.2 and Appendix 3.
Concomitant Medications	X	X	X	X	X	X	X	X	X		
PK Assessments											
Serial Blood Sampling	See Table 9.5-4 of the PK and immunogenicity sampling schedule and Section 9.5.										
Immunogenicity (ADA) Assessments	See Table 9.5-4 of the PK and immunogenicity sampling schedule and Section 9.5.										
Imaging Assessments											
Body Imaging	Tumor imaging assessment to be performed at 12 weeks from the first dose, regardless of dose delays, if any (± 1 week). After that, subsequent tumor imaging assessments to be performed Q8W (± 1 week). Participants who remain free of subsequent therapy will undergo tumor imaging assessment Q8W (± 1 week) until subsequent tumor-directed therapy is initiated or until 48 weeks after discontinuation of study treatment/EOT visit, and then Q12W (± 2 weeks) for a total duration of 2 years.										The same imaging modality is to be used for all assessments, per RECIST v1.1 (Appendix 5). CT and MRI scans 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.

Table 2-4: On-Treatment - Schedule of Activities for Q3W Dosing Schedule for Ipilimumab in the Randomized BMS-986218 Monotherapy Cohort Expansion in Cutaneous Melanoma (Part 2A)

Procedure	Cycle 1 (21 Days in Length) (Visit Window ± 2 Days, except for C1D1)			Cycle 2 (21 Days in Length) (Visit Window ± 2 Days)			Cycle 3 and Cycle 4 (21 Days in Length) (Visit Window ± 2 Days)			EOT[a,b]	Notes
	D1	D8	D15	D1	D8	D15	D1	D8	D15		
Brain Imaging	Participants with history of brain metastasis will have MRI performed as clinically indicated and at the discretion of the Investigator.										MRI without and with contrast of the brain should be performed. CT of the brain without and with contrast may be obtained if MRI is contraindicated. CT and MRI scans 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.
[redacted]											

Table 2-4: On-Treatment - Schedule of Activities for Q3W Dosing Schedule for Ipilimumab in the Randomized BMS-986218 Monotherapy Cohort Expansion in Cutaneous Melanoma (Part 2A)

Procedure	Cycle 1 (21 Days in Length) (Visit Window ± 2 Days, except for C1D1)			Cycle 2 (21 Days in Length) (Visit Window ± 2 Days)			Cycle 3 and Cycle 4 (21 Days in Length) (Visit Window ± 2 Days)			EOT[a,b]	Notes
	D1	D8	D15	D1	D8	D15	D1	D8	D15		
[redacted]											

Table 2-4: On-Treatment - Schedule of Activities for Q3W Dosing Schedule for Ipilimumab in the Randomized BMS-986218 Monotherapy Cohort Expansion in Cutaneous Melanoma (Part 2A)

Procedure	Cycle 1 (21 Days in Length) (Visit Window ± 2 Days, except for C1D1)			Cycle 2 (21 Days in Length) (Visit Window ± 2 Days)			Cycle 3 and Cycle 4 (21 Days in Length) (Visit Window ± 2 Days)			EOT[a,b]	Notes
	D1	D8	D15	D1	D8	D15	D1	D8	D15		
Clinical Treatment Supplies											
Ipilimumab Administration	X			X			C3 and C4 only				Ipilimumab to be administered for up to a maximum of 4 doses. Ipilimumab study treatment to be supplied by BMS; vials assigned by IRT must be used.

Abbreviations: ADA = anti-drug antibody; AE = adverse event; BICR = blinded independent central review; C = cycle; CXDY = Cycle X Day Y, as an example; D = day; DLT = dose-limiting toxicity; ECG = electrocardiogram; [redacted] EOT = end of treatment; [redacted] hCG = human chorionic gonadotropin; [redacted] IRT = Interactive Response Technology; MRI = magnetic resonance imaging; PCWG 3 = Prostate Cancer Working Group 3; PE = physical examination; PK = pharmacokinetic; [redacted] Q8W = every 8 weeks; Q12W = every 12 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

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

[b] For participants who complete all scheduled cycles of therapy, the EOT visit will be the same as the last scheduled and completed on-treatment visit (eg, Cycle 4 Day 21) and the start of the Safety Follow-up Period. For participants who do not complete all scheduled cycles of therapy, the EOT visit will be the most recent on-treatment visit (with all available safety and response data); it does not need to be repeated and will be considered the start of the Safety Follow-up Period.

Table 2-5: Follow-up Procedural Outline for All Study Parts (CA022001)

Procedure	Safety Follow-up			Response Follow-up	Survival Follow-up[b]	Notes
	Follow-up 1 30 Days[a] (± 7 Days)	Follow-up 2 60 Days (± 7 Days)	Follow-up 3 100 Days (± 7 Days)			
Safety Assessments						
PE	X	X	X			
Vital Signs	X	X	X			Includes body temperature, seated/supine blood pressure, and heart rate.
Laboratory Tests	X	X	X			Laboratory tests also as clinically indicated; See laboratory assessments in Section 9.1.4 and Table 9.1.4-1.
Urinalysis	As clinically indicated (see Section 9.1.4).					
Pregnancy Test	X	X	X			For WOCBP, serum/urine pregnancy test is to be performed (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG) (see Section 9.2.5). For additional country-local requirements, refer to Appendix 8.
Adverse Event Reporting and Concomitant Medication Assessments						
Monitor for Non-SAEs	X	X	X			Non-serious AEs will be collected starting with the first dose of study medication and through 100 days after discontinuation of dosing (Section 9.2 and Appendix 3). Participants will be followed for all SAEs, and all AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection until resolution, the condition stabilizes, the event is otherwise explained, the event is deemed irreversible, the participant is lost to follow-up (as defined in Section 8.3), or for suspected cases, until SARS-CoV-2 infection is ruled-out.

Table 2-5: Follow-up Procedural Outline for All Study Parts (CA022001)

Procedure	Safety Follow-up			Response Follow-up	Survival Follow-up[b]	Notes
	Follow-up 1 30 Days[a] (± 7 Days)	Follow-up 2 60 Days (± 7 Days)	Follow-up 3 100 Days (± 7 Days)			
Monitor for SAEs	X	X	X			All SAEs must be collected from the date of the participant's written consent until 100 days after discontinuation of dosing. Participants will be followed for all SAEs, non-serious AEs of special interest (as defined in Section 9.2.3), and all AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection until resolution, the condition stabilizes, the event is otherwise explained, the event is deemed irreversible, the participant is lost to follow-up (as defined in Section 8.3), or for suspected cases, until SARS-CoV-2 infection is ruled-out.
Concomitant Medication Assessments	X	X	X			
Sample Collection						
PK Assessments	See Table 9.5-2, Table 9.5-3, Table 9.5-4, and Table 9.5-5 of the PK and immunogenicity sampling schedule and Section 9.5.					
Immunogenicity (ADA) Assessments	See Table 9.5-2, Table 9.5-3, Table 9.5-4, and Table 9.5-5 of the PK and immunogenicity sampling schedule and Section 9.5.					
Efficacy Assessments						

Table 2-5: Follow-up Procedural Outline for All Study Parts (CA022001)

Procedure	Safety Follow-up			Response Follow-up	Survival Follow-up[b]	Notes
	Follow-up 1 30 Days[a] (± 7 Days)	Follow-up 2 60 Days (± 7 Days)	Follow-up 3 100 Days (± 7 Days)			
Tumor/Response Assessments				X		At the time of the EOT visit or at the time of study treatment discontinuation, all participants will continue to have radiologic and clinical tumor assessments every Q8W (± 1 week) until subsequent tumor-directed therapy is initiated or until 48 weeks after discontinuation of study treatment/EOT visit, and then Q12W (± 2 weeks) for a total duration of 2 years. Radiologic assessments for participants who have ongoing clinical benefit and remain free of subsequent therapy may continue to be collected after participants complete the Survival Follow-up Period of the study. Scans will be submitted to an imaging core laboratory for review by BICR at a later date, or at any time during the study at the Sponsor's discretion. CT and MRI scans 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.
Brain Imaging				X		As clinically indicated. CT and MRI scans 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.
Bone Scan				X		Required for participants with prostate cancer for evaluation of bone disease; otherwise, as clinically indicated. Every attempt should be made to image each participant using an identical acquisition protocol on the same scanner for all imaging timepoints.

Table 2-5: Follow-up Procedural Outline for All Study Parts (CA022001)

Procedure	Safety Follow-up			Response Follow-up	Survival Follow-up[b]	Notes
	Follow-up 1 30 Days[a] (± 7 Days)	Follow-up 2 60 Days (± 7 Days)	Follow-up 3 100 Days (± 7 Days)			
Subsequent Treatments (Anti-cancer)	X	X	X		X	
Assessment of Participant Survival Status					X	Participant status will be assessed by any documented clinic visit or telephone contact Q12W.
[redacted]						

Abbreviations: ADA = anti-drug antibody; AE = adverse event; BICR = blinded independent central review; CR = complete response; EOT = end of treatment; [redacted] EOT = end of treatment; [redacted] hCG = human chorionic gonadotropin; [redacted] PE = physical examination; PR = partial response; PK = pharmacokinetics; [redacted] Q8W = every 8 weeks; Q12W = every 12 weeks; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SD = stable disease; WOCBP = women of child bearing potential.

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

[b] Survival Follow-up will be measured Q12W (± 2 weeks) for up to 4 years from the date of the first dose of study treatment.

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 sample may be obtained up to 5 minutes earlier than the nominal timepoint, ensuring that the pharmacokinetics (PK) samples can be collected on time.

3 INTRODUCTION

This is a Phase 1/2a, first-in-human (FIH) study of BMS-986218, a non-fucosylated (NF) variant of the anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) monoclonal antibody (mAb), alone and in combination with nivolumab (anti-programmed cell death 1 [PD-1]), in humans with advanced solid tumors.

3.1 Study Rationale

Anti-CTLA-4 (ipilimumab) and anti-PD-1 (nivolumab) are approved immunotherapies that define the field of checkpoint blockade. Ipilimumab is the first immunotherapy to show a survival advantage in late-stage metastatic melanoma and has also demonstrated a significant 25% reduction in risk of recurrence or death in the adjuvant treatment in melanoma. Blockade of CTLA-4 by ipilimumab has demonstrated anti-tumor activity in other malignancies, including lung, prostate cancer, and renal cell carcinoma (RCC). However, no significant activity was observed in bladder, colorectal, esophageal, pancreatic, gastric, hepatocellular, or breast cancer. Ipilimumab is also currently in clinical development in combination with nivolumab. The combination was associated with a greater benefit in melanoma compared to each single agent. Benefit with the combination has also been observed in non-small cell lung cancer (NSCLC) and RCC and is currently being evaluated in other tumor types. The activation of a pre-existing but attenuated immune response to cancer by checkpoint blockade is associated with an adverse event (AE) profile that is inherent to immune activation. Ipilimumab treatment-related AEs can involve multiple organ systems (digestive, skin, and endocrine) that require cessation of drug and treatment with steroids, which attenuate the AEs but do not maintain anti-tumor responses. The combination regimen is associated with an increased incidence of AEs compared to nivolumab monotherapy, but a similar overall AE profile. Developing a new anti-CTLA-4 antibody (Ab) with a more manageable AE profile and an increased depth and breadth of response would provide a significant improvement to anti-CTLA-4 therapy.

BMS-986218 (CTLA-4.4g1fa-nf) is a human mAb against CTLA-4. The sequence is derived from the original hybridoma 10D1. The amino acid sequence is the same as that of ipilimumab but differs solely in its glycosylation pattern. The Ab is expressed in a fucosyltransferase-8 knockout Chinese hamster ovary cell line. Compared to ipilimumab, the glycans attached to the heavy chain Ab do not contain fucose. As a consequence, the NF Ab harbors a higher affinity for Fcγ receptors and improves antibody-dependent cellular cytotoxicity (ADCC) in addition to the CTLA-4 blocking activity of ipilimumab. T-regulatory cells (Tregs) are highly infiltrating in tumors, where they play an important role in impairing anti-tumor immune response by dampening effector cytolytic T-cell function. Tregs in tumors express higher levels of CTLA-4, and some studies have shown that part of the mechanism of action of ipilimumab is related to Treg depletion triggered by ADCC mediation once ipilimumab binds to CTLA-4-positive Tregs; however, this aspect is

controversial and ipilimumab may not be a strong ADCC-mediating Ab. Pre-clinical studies with anti-CTLA-4-NF show enhanced ADCC compared to ipilimumab, correlating with more profound Treg depletion in the tumor (but not the periphery). Therefore, it is expected that anti-CTLA-4-NF will result in a more efficacious therapy by combining CTLA-4 blocking with the depletion of Tregs expressing CTLA-4.

Based on this differentiated mechanism of action, this study will evaluate the safety and preliminary efficacy of BMS-986218 alone and in combination with nivolumab in tumors where ipilimumab did not demonstrate sufficient clinical activity as referenced in Section 5.1.2.4.

3.2 Background

Cancer immunotherapy rests on the premise that tumors can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. An effective immune response in this setting is thought to rely on immune surveillance of tumor antigens expressed on cancer cells that ultimately results in an adaptive immune response and cancer cell death. Meanwhile, tumor progression may depend upon acquisition of traits that allow cancer cells to evade immunosurveillance and escape effective innate and adaptive immune responses.[1,2]

Current immunotherapy efforts attempt to break the apparent tolerance of the immune system to tumor cells and antigens by either introducing cancer antigens by therapeutic vaccination or by modulating regulatory checkpoints of the immune system, such as CTLA-4, PD-1, or PD-L1 inhibition. T-cell stimulation is a complex process involving the integration of numerous positive as well as negative co-stimulatory signals in addition to antigen recognition by the T-cell receptor.[3] Collectively, these signals govern the balance between T-cell activation and tolerance.

3.2.1 BMS-986218

BMS-986218 is a fully human immunoglobulin G1 (hIgG1) mAb against CTLA-4, an inhibitory receptor expressed on activated effector T cells and Tregs. BMS-986218 shares the same amino acid sequence and ligand blocking properties as ipilimumab but is produced in cells deficient for alpha-(1,6)-fucosyltransferase (Fut8), the enzyme that mediates fucosylation of the Ab carbohydrate side chain at N-linked glycopeptides. Therefore, BMS-986218 is an NF version of ipilimumab, which has increased affinity for the activating Fcγ receptor, cluster differentiation (CD) 16. Increasing the affinity of the Ab for CD16 increases the Ab-dependent cellular cytotoxicity of target expressing cells elicited by the Ab. This increase in effector function has been shown to mediate specific depletion of immune suppressive Tregs at the tumor site of mouse tumor models.[4,5] Therefore, BMS-986218 may increase the anti-tumor immune response through 2 distinct mechanisms of action: the activation of effector CD4 and CD8 T cells by blocking the inhibitory function of CTLA-4, and the depletion of tumor infiltrating Tregs.

This study will evaluate the safety, tolerability, and preliminary efficacy of intravenous (IV) doses of BMS-986218, administered as monotherapy and in combination with nivolumab in participants with advanced solid tumors, and is expected to determine the maximum tolerated dose/recommended Phase 2 dose (MTD/RP2D) of BMS-986218 to be used in future studies as monotherapy or in combination with nivolumab.

As of the date of this protocol, the overall safety experience with BMS-986218 as either a monotherapy or in combination is under active investigation and currently emerging. BMS-986218 monotherapy in Part 1A has been administered Q4W at doses of 2 mg, 4 mg, 7 mg, 20 mg, 40 mg, 70 mg, 100 mg, and 150 mg. In addition, BMS-986218 has also been administered as monotherapy in Part 1A Q2W at 20 mg, 35 mg, and 50 mg. BMS-986218 has also been administered in combination with nivolumab at dose of 20 mg BMS-986218 + 480 mg nivolumab. The MTD of BMS-986218 as a monotherapy or in combination with nivolumab has not been reached, and dose escalation is currently ongoing. Overall, the safety profile of BMS-986218 as a single agent and in combination with nivolumab is clinically manageable.

Additional details on the safety and PK profile of BMS-986218 are summarized in the BMS-986218 IB.[6]

It is anticipated that anti-CTLA-4-NF Ab (BMS-986218), administered as a single agent or in combination with anti-PD-1 Ab (nivolumab), will demonstrate adequate safety and tolerability, as well as a favorable benefit-risk profile, to support further clinical testing. No prospective hypotheses are being formally evaluated.

The scientific rationale for the study design is discussed in greater detail in Section 5.4. Additional details are summarized in the BMS-986218 Investigator Brochure (IB).[6]

3.2.1.1 BMS-986218 Nonclinical Pharmacology

BMS-986218 binds to a human CTLA-4-expressing cell line equivalently to ipilimumab, with a concentration required for 50% efficacy (EC50) of 1.4 nM. The Ab, however, binds CD16 with significantly higher affinity (24- to 30-fold higher, depending on the CD16 polymorphism). Due to this increase in CD16 binding, BMS-986218 mediates increased natural killer (NK) cell-mediated ADCC of CTLA-4 expressing cells such as activated CD4 or Treg target cells compared to ipilimumab. The Ab also induces interleukin (IL)-2 secretion by human peripheral blood mononuclear cells (PBMCs) in response to Staphylococcal enterotoxin B (SEB) stimulation to a greater extent than ipilimumab.

Murine syngeneic tumor models have validated the anti-tumor efficacy mediated by CTLA-4 blockade.[7] In these models, the activity of a mouse surrogate Ab to murine CTLA-4 (9D9) has been shown to be dependent on the ability of the Ab to bind to activating Fcγ receptors.[4,5] In order to mimic the interactions between human Abs and human FcγRs, 9D9 was produced as either a human IgG1 (hIgG1) or an NF hIgG1 (hIgG1-NF). Anti-tumor efficacy was then tested in mice that have had mouse Fcγ receptors knocked out, and transgenically express human Fcγ receptors instead. The 9D9-hIgG1-NF Ab produced significantly greater anti-tumor efficacy when compared to the hIgG1. Maximal tumor growth inhibition (TGI) achieved with the hIgG1-NF Ab was 99% compared to 61% for the hIgG1. Immune monitoring of tumor-infiltrating lymphocytes from the same experiment indicated that Treg depletion from the tumor site was increased by the hIgG1-NF compared with the hIgG1.

Increased activity of BMS-986218 is not restricted to mouse models; in a cynomolgus vaccine study, BMS-986218 enhanced the immune response to an Ad5 viral vaccine to a greater extent

than ipilimumab. This is evident both through increased CD8 tetramer responses, as well as increased Ki-67 expression on CD8 T cells. Consistent with what was seen in mouse models, there was no evidence of depletion of peripheral Treg cells after administration of BMS-986218.

The in vitro and in vivo data indicate that BMS-986218 can enhance ADCC activity of ipilimumab and improve anti-tumor immune responses, supporting the development of this Ab for the treatment of cancer. Additional details are summarized in the BMS-986218 IB.[6]

3.2.1.2 BMS-986218 Nonclinical Pharmacokinetics

The PK and pharmacodynamic response of BMS-986218 was evaluated in cynomolgus monkeys and compared with the PK/pharmacodynamics of ipilimumab. Additional PK/pharmacodynamic studies were conducted using anti-mouse CTLA-4 Abs with either hIgG1 (9D9-hIgG1) or NF hIgG1 (9D9-hIgG1-NF) as surrogates for ipilimumab and BMS-986218, respectively. In cynomolgus monkeys, following a single intravenous (IV) dose of 10 mg/kg of BMS-986218, total plasma clearance (CLTp) was low (4 mL/day/kg) and the terminal serum half-life (T-HALF) was 14 days. Similar PK results in monkeys were obtained with ipilimumab (T-HALF = 14 days and CLTp = 3.6 mL/day/kg). After a single 3- or 10-mg/kg intraperitoneal dose of the surrogate mAbs 9D9-hIgG1-NF and 9D9-hIgG1 to C57BL/6 mice, the T-HALF was approximately 3 to 4 days and the exposure (based on area under the concentration-time curve [AUC] vs time curve extrapolated to infinity) following dose normalization was similar for the surrogate antibodies (68 and 61 μg•day/mL for 9D9-hIgG1-NF and 9D9hIgG1, respectively), suggesting that non-fucosylation does not alter the PK of the Ab in human Fc receptor (FcR) knock-in mice. The steady-state volume of distribution (Vss) of BMS-986218 in monkeys indicated that BMS-986218 resides in the extracellular space. Additional details are summarized in the BMS-986218 IB.[6]

Prediction of Human Pharmacokinetic and Dose Projection for BMS-986218

The human PK of BMS-986218 is predicted to be the same as that of ipilimumab. This is based on their similar PK profiles in cynomolgus monkeys and nearly identical Ab structures. Compared to ipilimumab, the lack of the posttranslational fucosylation of BMS-986218 in the hIgG1 Fc region is expected to have little impact on the Ab PK.[8] Thus, the human clearance (CL), Vss, and T-HALF of BMS-986218 are projected to be 4.5 mL/d/kg, 91 mL/kg, and 15 days, respectively.[9]

The human efficacious dose of BMS-986218 for maximum tumor efficacy is projected to be 3 mg/kg. At exposures predicted for this dose, the mouse surrogate, 9D9-huIgG1-NF, was able to achieve ~90% TGI% in human FcR-transgenic mice bearing MC38 syngeneic tumor. In the same mouse tumor model, 9D9-huIgG1-NF appeared to be 10-fold more potent than 9D9-huIgG1, likely due to its enhanced Fc effector function (to deplete tumor Treg cells). If similar Fc-mediated potency improvement is observed in patients, BMS-986218 may achieve better anti-tumor efficacy than ipilimumab at the projected human efficacious dose.

3.2.1.3 BMS-986218 Nonclinical Toxicology

The cynomolgus monkey was selected as the toxicology species because, like ipilimumab, BMS-986218 binds specifically to macaque CTLA-4, but not to homologous CTLA-4 in other traditional toxicology species (mouse, rat, rabbit), and has pharmacologic activity only in

monkeys. In surface plasmon resonance (SPR) experiments, the binding affinity and on-and-off rates of ipilimumab to cyno-CTLA-4 were generally comparable (and/or up to within 4-fold of each other).[10] The enhanced Fc binding and immunostimulatory activity of BMS-986218 resulted in a greater incidence and severity of autoimmune/gastrointestinal (GI) toxicity in monkeys than was observed previously for ipilimumab.[11] The differences in toxicity profile may be explained, in large part, by the enhanced potency and the higher doses tested for BMS-986218 vs ipilimumab. In a 1-month toxicity study in monkeys (n = 5/sex/group) at weekly doses of 3, 15, or 75 mg/kg IV,[12] profound enhancement of T-cell activation occurred at all doses following neoantigen immunization (keyhole limpet hemocyanin [KLH], necessary and enforcing factor [Nef], and glycosaminoglycan [Gag] peptides), consistent with the pharmacology of BMS-986218. BMS-986218 was clinically tolerated by monkeys at the low dose of 3 mg/kg/week (mean AUC from time zero to 168 hours [AUC(0-168h)] = 11,300 µg•h/mL) with generally mild loose feces in some animals and minimal body weight decrease. At higher doses of ≥ 15 mg/kg/week (mean AUC[0-168h] = 32,300 µg•h/mL), BMS-986218 treatment resulted in early euthanasia of 1 and 6 monkeys at 15 and 75 mg/kg/week, respectively, from Days 22 through 53 due to profound clinical toxicity (decreased feeding behavior, liquid feces, blood in feces, thin body condition, body weight loss, and/or dehydration). The predominant BMS-986218-related microscopic finding was generally dose-related lymphohistiocytic inflammation within a variety of tissues at all doses, but with fewer tissues affected and generally minimal findings at the low dose. The GI tract (stomach, cecum, and colon) and the kidney were the most severely and consistently affected, whereas additional organs were affected at higher doses. BMS-986218 was immunogenic in 57% (17/30) of monkeys. Most BMS-986218-related changes were partially or fully reversible, with the exceptions of 1 animal at 75 mg/kg/week included above that was euthanatized on Day 53 due to unresolved GI toxicity from the dosing period, lymphohistiocytic inflammation that generally persisted to the end of the 6-week recovery period, and unchanged or progressive increases in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) at ≥ 15 mg/kg. Based on the tolerability and generally mild severity of lymphohistiocytic tissue inflammation, the highest non-severely toxic dose (HNSTD) in this study was considered to be 3 mg/kg/week (mean AUC 0-168h = 11,300 µg•h/mL).

Although ipilimumab was not studied in monkeys at doses as high as 75 mg/kg, ipilimumab was tolerated without adverse effects at overlapping doses: up to 30 mg/kg administered every 3 days for 3 doses,[13,14,15] at 10 mg/kg administered weekly for 1 month (mean AUC 0-168h = 31,600 µg•h/mL),[16] at 1 mg/kg administered weekly for 10 weeks,[17] at up to 10 mg/kg administered approximately monthly for up to 6 months, and at 30 mg/kg administered every 3 weeks to pregnant female monkeys (ie, no maternal effects).[17,18,19] Of over 100 monkeys treated with ipilimumab, only 1 drug-related humane sacrifice occurred due to colitis following 2 monthly doses of 10 mg/kg in a pharmacology study; and another monkey at 10 mg/kg/month in combination with another immunomodulatory Ab and simian immunodeficiency virus DNA vaccines developed dermatitis/rash 4 weeks following a 3-month dosing period. Thus, BMS-986218 appears to have a more potent toxicologic profile than ipilimumab affecting greater numbers of monkeys at overlapping exposures.

The BMS-986218 HNSTD corresponds to exposure (AUC) multiples of approximately 283-fold and 2.8× the projected exposures at the proposed starting FIH dose (2 mg IV, AUC[4-week] 160 µg•h/mL) and highest projected dose for the FIH study (200 mg IV, AUC[4-week] 16,008 µg•h/mL), respectively. The HNSTD corresponds to maximum observed plasma concentration (Cmax) multiples of approximately 177-fold and 1.8× the projected Cmax at the starting FIH dose (2 mg IV, 0.75 µg/mL) and highest proposed doses for the FIH study (200 mg IV, 75 µg/mL), respectively. As compared to the ipilimumab efficacious dose of 3 mg/kg (Q3W) that is approved for use, the starting dose of BMS-986218 is approximately 0.03 mg/kg or 100-fold lower, and the highest projected dose of BMS-986218 is approximately equivalent (3 mg/kg).

In qualitative exploratory in vitro cell activation and cytokine release assays using human PBMC,[20,21] in vitro incubation of human PBMCs with dry-coated BMS-986218, as well as an isotype-matched control mAb (anti-KLH IgG1-NF), led to significant NK cell activation (as measured by increased CD25 and CD69 expression) at concentrations ≥ 1 µg/well. Additionally, increased release of IL-1β, IL-6, IL-8, interferon gamma (IFN-γ), and tumor necrosis factor alpha (TNF-α) relative to phosphate buffered saline (PBS) control occurred in a majority of donors by 66 hours of incubation with either dry-coated BMS-986218 or anti-KLH IgG1-NF. Importantly, the superagonist positive control mAb TGN 5.11A1 induced activation of both T cells and B cells; however, neither BMS-986218 nor isotype control caused activation of either of those cell populations following 18 to 66 hours of incubation. Further, incubation with BMS-986218 and anti-KLH IgG1 NF did not lead to release of IL-2, IL-5, or IL-10, which was released following incubation with the superagonist positive control mAb TGN 5.11A1. Given the similar levels of release of specific cytokines and NK cell activation with BMS-986218 and anti-KLH IgG1-NF, these findings were not considered to be target mediated. Rather, these results suggest Fc receptor engagement of the NF Fc tail of both BMS-986218 and the isotype-matched control Ab. The profile of cytokines released, IL-1β, IL-6, IL-8, and TNF-α, are consistent with FcγR engagement, primarily on NK cells and monocytes.

Despite the activation and cytokine release observed with BMS-986218 and the isotype control under these superphysiologic conditions, clinical trial data from similar NF IgG1 constructs indicate that these antibodies do not have significant non-target related cytokine release in humans. BMS-986012, an NF hIgG1 that binds to fucosyl-GM1, has been administered in human clinical trials without incidence of cytokine-storm like reactions up to 1000 mg/dose, with mean maximal serum concentrations up to approximately 376 µg/mL.[22] Furthermore, in physiologically relevant whole blood assay, clinically relevant concentrations of BMS-986218 in solution induced a modest NK cell activation in a few donors at concentrations ≥ 75 µg/mL, and induced modest cytokine release potential similar to that of ipilimumab.[14,15,23,24] These findings are also in agreement with clinical data indicating that ipilimumab does not elicit adverse cytokine release in humans.[25]

Overall, BMS-986218 has demonstrated acceptable pharmacologic, nonclinical PK, pharmacodynamic, and manageable toxicologic properties that support the transition of BMS-986218 into early clinical development. Additional details are summarized in the BMS-986218 IB.[6]

3.2.2 Nivolumab

Nivolumab is a fully human, IgG4 (kappa) isotype mAb that binds to PD-1 with nanomolar affinity (dissociation constant, 3.06 nM) and a high degree of specificity. Nivolumab blocks binding of PD-1 to its ligands PD-L1 and programmed death ligand 2 (PD-L2). Nonclinical in vitro testing of nivolumab demonstrated that binding to PD-1 results in enhanced T-cell proliferation and release of IFN-γ in vitro in mixed lymphocyte reaction and cytomegalovirus assays.

The nonclinical safety of nivolumab was evaluated in a comprehensive toxicology program in mice and monkeys and was submitted as part of Biologics License Application 125527.[26] Details of the in vitro and in vivo nonclinical pharmacology studies conducted to support the development of nivolumab can be found in Section 4.1 of the nivolumab IB.[27]

While nivolumab was well tolerated in cynomolgus monkeys, there is a potential for enhanced toxicity when combined with other immunostimulatory agents. However, nonclinical studies with nivolumab did not predict clinically relevant adverse effects (eg, no evidence of immune-mediated adverse effects was observed in nonclinical toxicology studies with nivolumab). Therefore, combination nonclinical toxicology studies with BMS-986218 and nivolumab have not been conducted and are not required by the International Conference on Harmonisation S9 Note for Guidance on Nonclinical Evaluation for Anticancer Pharmaceuticals.[28] The safety of the combination will be carefully monitored in the planned clinical trial.

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).

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, gastric cancer, squamous cell carcinoma of the head and neck (SCCHN), urothelial cancer, hepatocellular carcinoma (HCC), and colorectal cancer (CRC). In confirmatory trials, nivolumab as monotherapy demonstrated a statistically significant improvement in overall survival (OS) as compared with the current standard of care in patients with advanced or metastatic NSCLC, unresectable or metastatic melanoma, advanced RCC, or recurrent or metastatic SCCHN. Details of the clinical activity in these various malignancies are provided in the USPI and SmPC.

For nivolumab monotherapy, the safety profile is similar across tumor types. The only exception is pulmonary inflammation AEs, which may be numerically greater in participants with NSCLC. In NSCLC patients, it can be difficult to distinguish between nivolumab-related and nivolumab-unrelated causes of pulmonary symptoms and radiographic changes. There is no relationship between the incidence, severity, or causality of AEs and the nivolumab dose level. Additional details on the safety profile of nivolumab, including results from other clinical studies, are summarized in the nivolumab IB.[27]

3.2.3 Ipilimumab

Ipilimumab (BMS-734016, MDX010, and MDX-CTLA-4) is a fully human monoclonal IgG1κ specific for human cytotoxic T-lymphocyte antigen 4 (CTLA-4, CD152). CTLA-4 is expressed on

a subset of activated T cells on which it acts as a negative regulator of T-cell activity. Ipilimumab is a mAb that binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation, including the activation and proliferation of tumor infiltrating T-effector cells. Inhibition of CTLA-4 signaling can also reduce Treg function, which may contribute to a general increase in T-cell responsiveness, including the anti-tumor response. Ipilimumab has been administered to more than 19,500 subjects (total number of participants enrolled in ipilimumab studies) in several cancer types in completed and ongoing studies, as well as a compassionate use program. Ipilimumab has been approved for use in over 47 countries including the US (Mar-2011), the European Union (Jul-2011), and Australia (Jul-2011).

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

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

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

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

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

Dose-dependent toxicity and the relative efficacy of ipilimumab 3 mg/kg vs 10 mg/kg were established in a Phase 3 study in advanced melanoma (CA184169).

Ipilimumab monotherapy prolongs survival in subjects with pretreated and previously untreated advanced melanoma and has demonstrated anti-tumor activity in other malignancies, including lung cancer, prostate cancer, and RCC.[29]

Additional details on the safety profile and clinical benefit of ipilimumab alone and in combination with nivolumab, including results from clinical studies in melanoma, prostate, lung, kidney, bladder, or breast tumors are summarized in the ipilimumab and nivolumab IBs.[27,29]

3.3 Benefit-Risk Assessment

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

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

Current clinical experience with BMS-986218 is summarized in Section 3.2.1. Clinical benefit has not been established in patients with advanced cancer.

In the absence of completed clinical studies with BMS-986218, the evaluation of risk is largely based on information from nonclinical studies with BMS-986218 in monkeys (Section 3.2.1) and potential effects based on the proposed mechanism of action and clinical evidence from ipilimumab therapy.

The nonclinical GLP toxicology assessment of BMS-986218 has demonstrated a dose-related toxicity profile of immune-mediated adverse events (imAEs) and cytokine release potential compatible with the expected mechanism of action (see Section 3.2.1.3).

In combination therapy of BMS-986218 and nivolumab, as observed in the combination of ipilimumab and nivolumab, it is possible that a higher incidence of imAEs may occur with the combination of the 2 antibodies. The safety profile of nivolumab monotherapy and the combination of ipilimumab and nivolumab are defined based on experience with more than 17,700 subjects as either monotherapy or in combination therapy. The frequency and types of immune-mediated adverse reactions are similar across multiple types of tumors and are described in the Reference Safety Information in the current nivolumab IB.[27] Unanticipated side effect events may also occur.

The proposed clinical studies of BMS-986218 have been designed to minimize the overall risk to participants; measures will include the following:

- Continuous safety assessments will be utilized by the Investigators and Sponsor to determine whether additional safety measures or termination of the study is required at any time. In addition, AEs and serious adverse events (SAEs) will be reviewed on an ongoing basis by the Bristol-Myers Squibb (BMS) Medical Monitor (or designee) and WorldWide Patient Safety (WWPS) representatives to monitor for any safety signals or trends. As BMS-986218 is an experimental agent, it is possible that unforeseen, unknown, or unanticipated reactions may occur. However, based on the nonclinical safety profile of BMS-986218, and the 212-fold exposure margin (based on AUC from the nonclinical HNSTD of 3 mg/kg/week in monkeys) built into the planned starting dose of 2 mg (flat dose; 0.03 mg/kg administered to a 70-kg participant), the potential safety risks are expected to be minimized.

- Study treatment administration will occur at infusion centers with medical monitoring and the capability to manage infusion reactions or anaphylaxis. The protocol provides a treatment algorithm for infusion reactions. In addition to conventional safety measures for infusion of biologic agents, all participants will undergo observation and assessment for signs of infusion reaction for 60 minutes post infusion following the first 3 doses of BMS-986218 for each participant. Furthermore, to assess for potential effects of lymphocyte activation, a sentinel participant will be monitored for 5 days at each dose level.
- Management algorithms for ipilimumab/nivolumab-induced AEs involving the GI, renal, pulmonary, hepatic, endocrinopathy, skin, neurologic, and cardiac systems are included in the protocol (see Section 7.6.2).
- Participants who develop imAEs may require prolonged treatment with high-dose corticosteroids and other immunosuppressive agents. This could increase the risk of opportunistic infections. The imAE management algorithms in the protocol recommend antibiotic prophylaxis against opportunistic infections in such situations.
- Complete blood counts and chemistry (including liver enzyme) tests will be performed prior to administration of study therapy and on a weekly basis during the first 8 weeks of treatment in monotherapy and the first 8 weeks of the combination between BMS-986218 and nivolumab. In addition, complete physical examinations (PEs) will be conducted on Day 1 of each new cycle, along with weekly symptom-directed targeted PEs during the first 8 weeks of treatment. Due to the potential risk of exaggerated inflammatory response, participants with autoimmune disorders or chronic viral infections, or those who are at risk for flare of auto-immunity or immune-related diseases will be excluded.

For the proposed clinical studies of BMS-986218, the overall risk for participating in these trials will also be minimized.

- [redacted]
- The amount of blood sampling poses limited risk to the participant and includes discomfort, pain, and bleeding. The amount of total blood is reduced to the minimal quantity required to address the need of safety monitoring, standard of care, PK/anti-drug antibodies (ADAs), [redacted] needs and is below the recommended daily limits for each treatment day.

Whether BMS-986218 both as a single agent and in combination with nivolumab 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 as defined in Section 6.2. If a participant has a confirmed SARS-CoV-2 infection while on study treatment, dose delay or interruption of study treatment is required as described in Section 7.6. [redacted]

The study has been designed with study visits that allow for close monitoring of participants' safety throughout the clinical trial (Section 2), and participants are encouraged to contact the investigator if an intercurrent illness develops between study visits. Testing for COVID-19 to inform decisions about clinical care during the study should follow local standard practice.

Non-live COVID-19 vaccination is considered a simple concomitant medication within the study. However, the efficacy and safety of non-live vaccines (including non-live COVID-19 vaccines) in participants receiving BMS-986218 is unknown.

In conclusion, the potential direct benefit to participants in this study is that both single-agent and combined therapies with these investigational agents may result in a greater proportion of participants with stabilization of disease, objective response, progression-free survival, OS, or increased duration of response (DOR) than those observed with standard therapy or other investigational immunotherapy. It is also possible that both single-agent and combined therapies may reverse T-cell exhaustion and achieve responses in 1) tumor types known to be poorly responsive to nivolumab or ipilimumab, 2) tumors in relapse after anti-PD-1 or anti-PD-L1 therapy, and/or 3) tumors where high Treg infiltration correlates with a worse prognosis.

The potential for direct benefit described above warrants evaluating BMS-986218 both as a single agent and in combination with nivolumab in this Phase 1 clinical study with risk mitigation described above.

4 OBJECTIVES AND ENDPOINTS

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

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Primary	
• To characterize the safety, tolerability, and DLTs and to determine the MTD/RP2D of BMS-986218 administered as monotherapy and in combination with nivolumab in participants with advanced solid tumors • To evaluate the efficacy and safety of BMS-986218 monotherapy relative to ipilimumab in participants with advanced cutaneous melanoma previously treated with anti-PD-1/PD-L1 immunotherapy (Part 2A only) • To evaluate the efficacy and safety of BMS-986218 alone and in combination with nivolumab in NSCLC (Part 2B and Part 2C)	• Incidence of AEs, SAEs, AEs meeting protocol-defined DLT criteria, AEs leading to discontinuation, and death • ORR, mDOR, and PFSR at 24, 36, and 48 weeks by RECIST v1.1

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
• To evaluate the efficacy and safety of BMS-986218 alone and in combination with nivolumab in MSS CRC (Part 2D)	
Secondary • To evaluate the preliminary efficacy of BMS-986218 alone and in combination with nivolumab in advanced solid tumors (Part 1A and Part 1B)	• ORR, mDOR, and PFSR at 24, 36, and 48 weeks by RECIST v1.1 or PCWG 3
• To characterize the PK and immunogenicity of BMS-986218 when administered alone and in combination with nivolumab	• Summary measures of PK parameters and incidence of ADA to BMS-986218
[redacted]	

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
[redacted]	

Abbreviations: [redacted] DLT = dose-limiting toxicity; DOR = duration of response; [redacted] mDOR = median duration of response; MSS CRC = microsatellite stable colorectal cancer; NSCLC = non-small cell lung cancer; ORR = objective response rate; [redacted] PCWG 3 = Prostate Cancer Working Group; [redacted] PFSR = progression-free survival rate; [redacted]

5 STUDY DESIGN

5.1 Overall Design

- This is a Phase 1/2a, open-label study of BMS-986218, administered as a single agent and in combination with nivolumab, in participants with advanced solid tumors. The study is comprised of 2 parts, dose escalation and dose expansion.
- Part 1: The Dose Escalation Phase, where the dose of BMS-986218, given alone or in combination with nivolumab, is escalated to determine the MTD/RP2D.
  - The BMS-986218 Monotherapy Dose Escalation (Part 1A) will escalate the dose of BMS-986218 to determine the MTD/RP2D. The study will evaluate the safety and tolerability of BMS-986218 once every 4 weeks (Q4W), given alone, based on DLTs, using a Bayesian Logistic Regression Model (BLRM) employing the escalation with overdose control principle (EWOC). In addition, to further evaluate the safety and tolerability of BMS-986218, an alternative once-every-2-weeks (Q2W) dosing schedule will be explored to characterize the safety and PK of BMS-986218. The Q2W dosing schedule will start at a total dose level equivalent to a dose that has cleared safety in the Q4W dosing cohort (eg, 10 mg Q2W vs 20 mg Q4W). Subsequent Q2W doses will be guided by Q4W equivalent doses that have cleared safety and will continue evaluating higher Q2W doses up to the MTD equivalent of the Q4W dosing cohort. Based on the preliminary PK from the Q4W dosing cohorts, at the steady state, the Q2W dosing schedule is projected to provide approximately the same AUCtau (tau = 4 weeks) as the Q4W dosing schedule, and approximately 70% Cmax as the Q4W dosing schedule. Intra-participant movement between treatment regimens/dosing schedules is not permitted. Additionally, participants with advanced stage cutaneous melanoma, colorectal cancer microsatellite stable (MSS CRC), NSCLC, or SCCHN will be treated with BMS-986218 on a Q2W or Q4W schedule in the Part 1A pharmacodynamic (PD) cohort. The Safety Evaluation of Combination Doses of BMS-986218 with Nivolumab (Part 1B) will evaluate the safety and tolerability of doses of BMS-986218 in combination with nivolumab. The combination of BMS-986218 with nivolumab will be evaluated using a BLRM employing the EWOC principle. Starting at least 1 dose level lower than the current monotherapy dose level of BMS-986218 demonstrating an acceptable safety profile, BMS-986218 will be studied in combination with a 480 mg Q4W flat dose of nivolumab. Determination of the MTD for the Safety Evaluation of Combination Doses of BMS-986218 with Nivolumab (Part 1B) will be guided by BLRM copula.
- Part 2: The Expansion Phase, where the cohort of participants is expanded to gather additional safety, tolerability, preliminary efficacy, PK, and pharmacodynamic information in specific patient populations, regarding BMS-986218 alone and in combination with nivolumab.
  - The Randomized BMS-986218 Monotherapy Cohort Expansion in Cutaneous Melanoma (Part 2A) will evaluate the preliminary efficacy of BMS-986218 monotherapy relative to ipilimumab monotherapy in a cohort of cutaneous melanoma participants who have received prior immunotherapy with an anti-PD-1 or anti-PD-L1 containing regimen and must have progressive or recurrent disease after prior PD-1/PD-L1 directed therapy. Three dose levels or schedules for BMS-986218 from the Part 1A Q4W monotherapy escalation will be evaluated that have had at least 6 DLT evaluable participants and meet safety criteria: one at 7 mg Q4W, one at 20 mg Q4W, and one at 70 mg Q4W. Evaluating

multiple different doses will aid in selecting the regimen that will ultimately provide the optimal benefit-risk ratio to future study participants. Participants must not have received prior anti-CTLA-4 therapy in the advanced or metastatic setting.

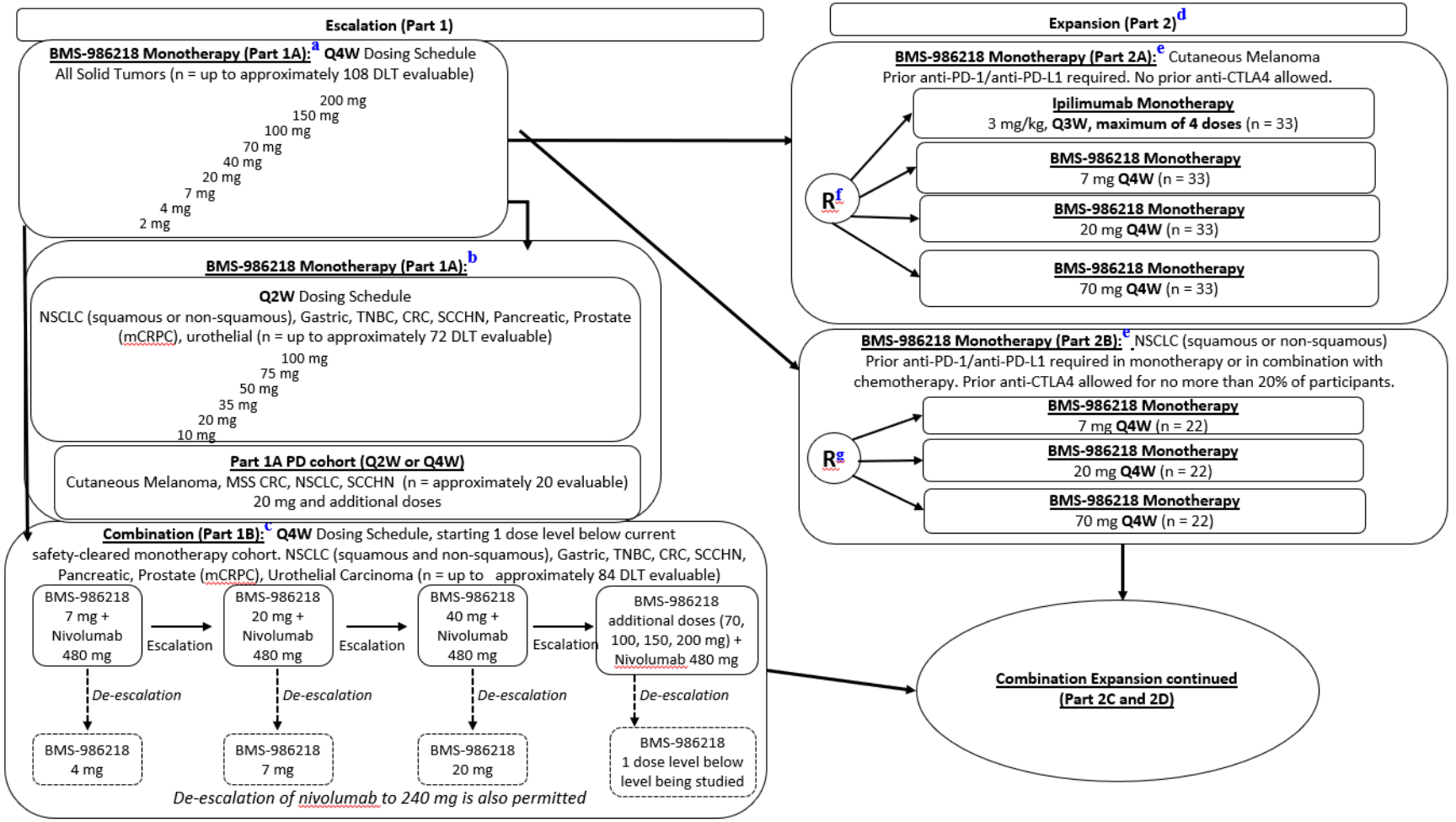
  - The Randomized BMS-986218 Monotherapy Cohort Expansion (Part 2B) will evaluate the preliminary efficacy of BMS-986218 in NSCLC in participants who have received, and then progressed on, relapsed, or have been intolerant to standard systemic therapies with proven survival benefit. Additionally, participants must have progressed or have had recurrent disease after prior immunotherapy with anti-PD-1/anti-PD-L1 either as monotherapy or in combination with other agents. Prior anti-CTLA4 therapy either as monotherapy or in combination is not required, but is allowed; however, no more than 20% of participants are allowed prior anti-CTLA4 therapy. Participants who have been intolerant to prior immunotherapy are excluded. Three dose levels or schedules for BMS-986218 from the Part 1A Q4W monotherapy escalation will be evaluated that have had at least 6 DLT evaluable participants and meet safety criteria: one at 7 mg Q4W, one at 20 mg Q4W, and one at 70 mg Q4W. The rationale for evaluating multiple dose levels is to optimize the benefit-risk ratio for the participant.

- In the BMS-986218 Combination Therapy Cohort Expansion (Part 2C) in NSCLC, the preliminary efficacy and safety of BMS-986218 in combination with nivolumab will be assessed in participants with NSCLC who have progressed or relapsed after anti-PD-1/PD-L1 therapy. Participants must not have received prior anti-CTLA-4 therapy in the advanced or metastatic setting. One or more doses to be evaluated in Part 2C will be selected from the range of doses assessed as tolerable in Part 1B, and which do not exceed the MTD or highest dose administered that has cleared safety. These dose(s) will be selected based on the totality of available safety, tolerability, efficacy, PK and PD data. The evaluation of efficacy in Part 2C will initially occur at one or more dose levels starting with up to 20 participants at each dose level. Additional participants up to 40 at a dose level may be evaluated following initial signal assessment. In Part 2C, participants will be treated Q4W for up to 2 calendar years regardless of treatment delays.
- In the BMS-986218 Combination Therapy Cohort Expansion in MSS CRC (Part 2D), the preliminary efficacy and safety of BMS-986218 in combination with nivolumab will be assessed in participants with MSS CRC who have progressed or relapsed on at least 1 prior standard therapy. Participants must not have received prior anti-CTLA-4 therapy in the advanced or metastatic setting. The dose to be evaluated in Part 2D will be selected from the range of doses assessed as tolerable in Part 1B, and which do not exceed the MTD or highest dose administered that has cleared safety. The dose will be selected based on the totality of available safety, tolerability, efficacy, PK, and PD data. Regardless of whether or not RAS mutation status is known, all participants will be tested during screening for extended RAS (NRAS and KRAS) and BRAF mutation status. Results from this testing at screening is not required prior to receiving treatment on study. The RAS status evaluation will be conducted with the goal of enrolling approximately 20 participants each with either mutation or wild-type with respect to extended RAS status. The Sponsor may elect to prioritize enrollment of participants based on mutation status. In Part 2D, participants will be treated Q4W for up to 2 calendar years regardless of treatment delays.

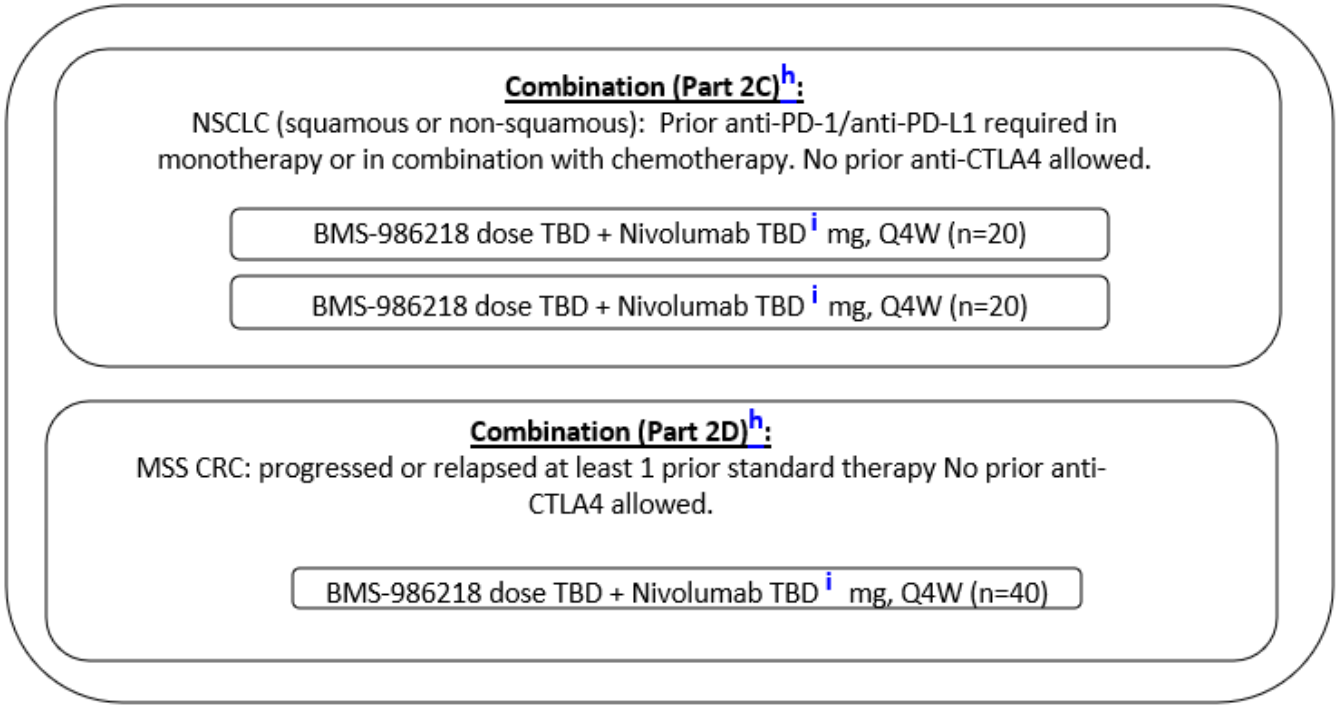
The duration of the study will be approximately 5 years.

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

Figure 5.1-1: Study Design Schematic



Combination Expansion continued (Part 2C and 2D)



[a] If Part 1 is open upon the decision to initiate Part 2, treatment in the 2 parts will occur in parallel. If supported by clinical and safety data, doses higher than 200 mg may be studied until MTD is reached, and further details will be provided in a subsequent protocol amendment at such time.

[b] If Part 1 is open upon the decision to initiate Part 2, treatment in the 2 parts will occur in parallel. If supported by clinical and safety data, doses higher than 100 mg may be studied until MTD equivalent is reached in participants, and further details will be provided in a subsequent protocol amendment at such time.

[c] If Part 1B is open upon the decision to initiate Part 2C and Part 2D, treatment in the 2 parts will occur in parallel. If supported by clinical and safety data, doses higher than 200 mg BMS-986218 may be studied until MTD is reached, and further details will be provided in a subsequent protocol amendment at such time.

[d] Tumor-specific eligibility criteria are detailed in Section 6.

[e] Additional participants may be treated or randomized to further evaluate emerging data or subgroups of interest if needed but not to exceed 40 participants per dose level in Part 2A and Part 2B.

[f] Participants will be treated or randomized, which will include ipilimumab monotherapy and BMS-986218 at different dose levels.

[g] Participants will be treated or randomized.

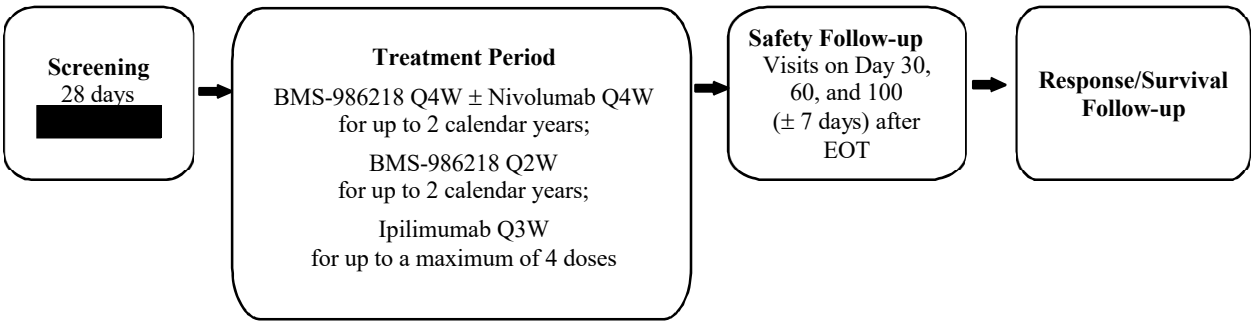
[h] Dose(s) of BMS-986218 selected for Part 2C and Part 2D will be based on the totality of preliminary safety, tolerability, efficacy, PK and PD data. Refer to Section 5.1.2.4 for additional details.

[i] The nivolumab dose found to be tolerable in Part1B will be used in Part 2 combination expansions (Part 2C and Part 2D)

Abbreviations: CTLA = cytotoxic T-lymphocyte-associated protein 4; DLT = dose-limiting toxicity; mCRPC = metastatic castration-resistant prostate cancer; MSS CRC = microsatellite stable colorectal cancer; MTD = maximum tolerated dose; NSCLC = non-small cell lung cancer; PD = pharmacodynamic; PD-L1 = programmed death-ligand 1; Q2W = every 2 weeks; Q3W = every 3 weeks; Q4W = every 4 weeks; R = randomized; SCCHN = squamous cell carcinoma of the head and neck; TNBC = triple-negative breast cancer.

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

Figure 5.1-2: Study Period and Participant Flow for BMS-986218, Ipilimumab, and Nivolumab



Abbreviations: EOT = end of treatment; Q2W = every 2 weeks; Q3W = every 3 weeks; Q4W = every 4 weeks.

5.1.1 Screening Period

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 (ICF). The screening assessments are shown in Table 2-1. If a participant exceeds the 28-day screening period due to a study-related procedure (eg, [redacted] waiting for a study-related laboratory value), the participant must be re-consented, but does not require a new participant identification number. In this situation, the fewest number of procedures from the initial screening should be repeated to qualify the participant, while maintaining participant safety and eligibility. Within a given disease type, participants meeting all eligibility criteria will be enrolled in the study using an Interactive Response Technology (IRT) according to the part and treatment arm availability.

5.1.2 Treatment Period

The dosing regimens of BMS-986218 are Q4W and Q2W. All participants will be treated with BMS-986218 Q4W ± nivolumab Q4W for up to 2 calendar years, BMS-986218 Q2W for up to 2 calendar years, and/or ipilimumab Q3W for up to a maximum of 4 doses. Each cycle of the treatment period will be 4 weeks in length, with the exception of the treatment arms with Q3W dosing of ipilimumab in the Randomized BMS-986218 Monotherapy Cohort Expansion in Cutaneous Melanoma (Part 2A), for which each cycle of ipilimumab will be 3 weeks in length. Continuous safety evaluation and tumor assessment for participants receiving BMS-986218 or nivolumab will guide the decision to treat a participant with additional cycles of study therapy if the participant has confirmed clinical benefit (up to a maximum of 2 calendar years for BMS-986218 Q4W ± nivolumab Q4W; or up to a maximum of 2 calendar years for BMS-986218 Q2W). Tumor assessments will occur every 8 weeks (Q8W) for participants receiving BMS-986218 and nivolumab for all study parts, except the Randomized BMS-986218 Monotherapy Cohort Expansion in Cutaneous Melanoma (Part 2A), where tumor assessment in participants receiving BMS-986218 or ipilimumab will occur at 12 weeks from first dose (± 1 week), prior to initiating the next cycle of treatment. After that, subsequent tumor imaging assessments to be performed Q8W (± 1 week), prior to initiating the next cycle of treatment.

Participants who remain free of subsequent therapy will undergo tumor imaging assessment Q8W (± 1 week) until subsequent tumor-directed therapy is initiated or until 48 weeks after discontinuation of study treatment/EOT visit, and then Q12W (± 2 weeks) for a total duration of 2 years.

Weekly study visits will be performed for the first 8 weeks following the first dose of study treatment for the BMS-986218 Monotherapy Escalation (Part 1A), Safety Evaluation of Combination Doses of BMS-986218 with Nivolumab (Part 1B), the Randomized BMS-986218 Monotherapy Cohort Expansion in Cutaneous Melanoma (Part 2A), the Randomized BMS-986218 Monotherapy Cohort Expansion (Part 2B), the BMS-986218 Combination Therapy Cohort Expansion in NSCLC (Part 2C) and the BMS-986218 Combination Therapy Cohort Expansion in microsatellite stable colorectal cancer (MSS CRC) (Part 2D) followed by study visits Q4W thereafter. During Cycle 1 and Cycle 3 of the treatment period, additional study visits to collect samples for intensive PK, ADA, and cytokine assessments are required. See Section 9.5 for further details.

In the BMS-986218 Monotherapy Escalation (Part 1A), the Randomized BMS-986218 Monotherapy Cohort Expansion in Cutaneous Melanoma (Part 2A), and the Randomized BMS-986218 Monotherapy Cohort Expansion (Part 2B), BMS-986218 will be administered Q4W. An alternative BMS-986218 dosing schedule of Q2W (with dosing on Day 1 and Day 15 of each 28-day cycle) will also be explored for monotherapy escalation using data obtained from the Q4W schedule. BMS-986218 will be infused over 30 minutes, except in the low-dose cohorts where infusion times may be shorter. BMS-986218 will require a 60-minute observation period following the completion of the infusion for the first 3 doses for each participant. Ipilimumab will be administered Q3W and will be infused over 30 minutes.

In the Safety Evaluation of Combination Doses of BMS-986218 with nivolumab (Part 1B), the BMS-986218 Combination Therapy Cohort Expansion in NSCLC (Part 2C), and BMS-986218 Combination Therapy Cohort Expansion in MSS CRC (Part 2D), each combination treatment cycle will be comprised of 1 dose of BMS-986218 in combination with 1 dose of nivolumab administered Q4W. When both BMS-986218 and nivolumab are given in combination, nivolumab will be given first, over 30 minutes, followed by BMS-986218 over 30 minutes, beginning at least 30 minutes after completion of the infusion of nivolumab. BMS-986218 infusions will require a 60-minute observation period following the completion of the infusion for the first 3 doses for each participant. For participants receiving combination doses of BMS-986218 with nivolumab, a 30-minute infusion of nivolumab will be followed by a 30-minute observation period, followed by an infusion of BMS-986218 and a 60-minute observation period following the first 3 infusions for each participant. Ipilimumab infusions will require a 30-minute observation period following the completion of the infusion for the first 3 doses for each participant. Additional infusion details for nivolumab and ipilimumab are given in the Pharmacy Manual.

5.1.2.1 The BMS-986218 Monotherapy Escalation (Part 1A)

Up to approximately 108 DLT-evaluable participants will be treated during the BMS-986218 Monotherapy Escalation (Part 1A) of the study for the Q4W schedule. Each participant will be

administered IV doses of BMS-986218 in planned flat dose levels of 2, 4, 7, 20, 40, 70, 100, 150, and 200 mg Q4W per cycle, for up to 2 calendar years. If supported by clinical and safety data, doses higher than 200 mg may be studied until MTD is reached, and further details will be provided in a subsequent protocol amendment at such time.

An alternative dosing schedule of BMS-986218 Q2W will also be explored to further characterize the safety, PK, and pharmacodynamics of BMS-986218. Up to approximately 72 DLT-evaluable participants will be treated with 10, 20, 35, 50, 75, and 100 mg Q2W during the BMS-986218 Monotherapy Escalation (Part 1A) of the study for the Q2W schedule. The Q2W dosing schedule will start at a total dose level equivalent to a dose that has cleared safety in the Q4W dosing cohort (eg, 10 mg Q2W vs 20 mg Q4W), and continue evaluating higher doses up to the MTD equivalent of the Q4W dosing cohort. If supported by clinical and safety data, doses higher than 100 mg Q2W may be studied, and will be guided by Q4W equivalent doses that have cleared safety until MTD equivalent of the Q4W dosing cohort is reached. Based on the preliminary PK from the Q4W dosing cohorts, at the steady state, the Q2W dosing schedule is projected to provide approximately the same AUCtau (tau = 4 weeks) as Q4W dosing schedule, and approximately 70% Cmax as Q4W dosing schedule.

Additionally, participants with advanced stage cutaneous melanoma, microsatellite stable colorectal cancer (MSS CRC), NSCLC, or SCCHN will be treated with BMS-986218 on a Q2W schedule at a starting dose of 20 mg in the Part 1A pharmacodynamic (PD) cohort. Based on preliminary analysis of Treg count decrease in the tumor microenvironment, using single-cell ribonucleic acid (RNA) sequencing gene expression analysis, additional cohorts of participants at higher dose levels may be evaluated. For example, if the expected PD activity is not observed after 5 to 10 evaluable participants at the 20 mg dose level, then the next set of 5 to 10 evaluable participants may be treated at a higher dose level or Q4W schedule. Therefore, more than one dose level may be evaluated based on the PD results assessment.

Any additional dose levels evaluated in the Q2W schedule of the Part 1A PD cohort will be a dose that has been determined to be safe and tolerable in either the Q2W escalation part or a dose equivalent to the Q4W dose, which has been determined to be safe and tolerable in the Q4W dose escalation part. Approximately 20 evaluable participants per dose level (per dose schedule) may be treated as part of the PD cohort. Each participant will be administered IV doses of BMS-986218 Q2W or Q4W per cycle, for up to 2 calendar years.

Prior to declaring the MTD, and in consultation with Investigators, the Sponsor has the option to expand any dose level previously established to be tolerable in order to obtain additional experience or to investigate dose levels intermediate to those defined in the protocol. Planned dose levels may be modified, or intermediate dose levels added, based upon the BLRM analysis and clinical evaluation of all available safety and PK/pharmacodynamic data. Once the tolerability (during the DLT evaluation) of a dose level has been established, additional participants may be added at that dose level to better characterize the safety, PK, and pharmacodynamic profiles (not to exceed a total of 200 evaluable participants across dose levels and schedules). Additional information on DLTs can be found in Section 7.6.1.

Sentinel Participant:

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

Initially, 3 participants will be enrolled at the start of each cohort, in accordance with the sentinel participant approach cited above. However, to allow for any unforeseen discontinuations (such as disease progression) before the 8-week DLT period (56 days) is completed, extra participants may be enrolled in each dose escalation cohort.

5.1.2.2 The Safety Evaluation of Combination Doses of BMS-986218 with Nivolumab (Part 1B)

The Safety Evaluation of Combination Doses of BMS-986218 with Nivolumab (Part 1B) will be initiated starting at 1 dose level below current safety cleared Q4W monotherapy cohort, defined from BLRM and an overall assessment of all available safety, PK/pharmacodynamic, and efficacy data of the BMS-986218 Monotherapy Escalation (Part 1A).

In the Safety Evaluation of Combination Doses of BMS-986218 with Nivolumab (Part 1B), the starting dose of BMS-986218 was 1 dose level lower than the Q4W 40 mg monotherapy dose level of BMS-986218, which had demonstrated an acceptable safety profile and was administered in combination with nivolumab at the flat dose of 480 mg Q4W. Dose escalation and determination of MTD for the Safety Evaluation of Combination Doses of BMS-986218 with Nivolumab (Part 1B) will be guided by BLRM-copula. Subsequent dose selection of the combination will be based on evaluating the recommendation from BLRM-copula and an overall assessment of all available safety and PK/pharmacodynamic data. Safety evaluation and tumor assessment will be performed Q8W (2 cycles). If toxicity is unacceptable at any combination dose level, additional combination dose level(s) may be evaluated using BMS-986218 and/or nivolumab (eg, dose of 240 mg Q4W). Selection of dose level for each study drug will be based on the nature and attribution of observed DLTs in previously evaluated dose levels. An intermediate dose level of BMS-986218 and/or an intermediate dose level of nivolumab Q4W may be evaluated in additional cohort(s). No intra-subject dose escalation or de-escalation of BMS-986218 or nivolumab is allowed at any dose level.

At no time will the dose of BMS-986218 in the Safety Evaluation of Combination Doses of BMS-986218 with Nivolumab (Part 1B) exceed the highest tolerated dose in the BMS-986218 Monotherapy Escalation (Part 1A). Dose escalation in each cohort, within the constraints cited above, will be enrolled in parallel. Up to approximately 84 DLT-evaluable participants will be enrolled in Part 1B. Additional information on DLTs can be found in Section 7.6.1.

Sentinel Participant:

The sentinel participant rule will be followed. The first participant to be dosed at Cycle 1 Day 1 of each dose level will be observed for 5 days, before additional participants (ie, Participant 2 onward in that cohort) receive study treatments at the same dose level. Initially, 3 participants will be enrolled at the start of each cohort, in accordance with the sentinel participant approach cited

above; however, to allow for any unforeseen discontinuations (eg, disease progression) before the 8-week DLT period (56 days) is completed, extra participants may be enrolled in each dose cohort.

5.1.2.3 Dose Escalation Decisions for the BMS-986218 Monotherapy Escalation (Part 1A) and the Safety Evaluation of Combination Doses of BMS-986218 with Nivolumab (Part 1B)

The dose-escalation phase of the study will evaluate the safety and tolerability of BMS-986218, given alone or in combination with nivolumab, based on DLTs, using a BLRM (for the BMS-986218 Monotherapy Escalation [Part 1A]) and a BLRM-copula (for the Safety Evaluation of Combination Doses of BMS-986218 with Nivolumab [Part 1B]).

During the monotherapy and combination therapy dose-escalation phase, a set of approximately 3 participants will be treated at each specified dose level. Cohort tolerability assessment with subsequent participant enrollment and dose recommendation will occur when at least 2 evaluable participants within a cohort have completed an 8-week DLT period. Any toxicities that occur beyond the DLT period will be accounted for in making dose level decisions and/or dose level modifications. Additional information on DLTs can be found in Section 7.6.1.

If the potential DLT occurring in the third evaluable participant regarding the specific dose level does not influence the dose recommendation by BLRM or the BLRM-copula, the next dose level may proceed without waiting for the third participant to complete the corresponding DLT observation period, after discussion and agreement between the Sponsor and Investigators. Continuous re-assessment of dose recommendation, by BLRM in the BMS-986218 Monotherapy Escalation (Part 1A) and BLRM-copula in the Safety Evaluation of Combination Doses of BMS-986218 with Nivolumab (Part 1B), will be performed for each dose level. Planned dose levels for dose escalation are provided in Table 5.5.2-1.

Planned dose levels may be modified, or intermediate dose levels added, based upon the BLRM-copula analysis for combination and clinical evaluation of all available safety and PK/pharmacodynamic data. Once the tolerability (during the DLT evaluation) of a dose level has been established, additional participants may be added at that dose level to better characterize the safety, PK, and pharmacodynamic profiles.

The monotherapy doses of BMS-986218, selected for the Randomized BMS-986218 Monotherapy Cohort Expansion in Cutaneous Melanoma (Part 2A), the BMS-986218 Cohort Expansion - Monotherapy (Part 2B), and the combination therapy doses of BMS 986218, selected for BMS-986218 Cohort Expansion - Combination Therapy in NSCLC (Part 2C) and BMS-986218 Cohort Expansion - Combination Therapy in MSS CRC (Part 2D) will be based on evaluating the recommendation from BLRM and an overall assessment of all available safety, PK/pharmacodynamic, and efficacy data.

5.1.2.4 The Randomized BMS-986218 Monotherapy Cohort Expansion in Cutaneous Melanoma (Part 2A), the BMS-986218 Cohort Expansion - Monotherapy (Part 2B), and the BMS-986218 Cohort Expansion - Combination Therapy (Part 2C and Part 2D)

The purpose of the BMS-986218 cohort expansions is to gather preliminary efficacy information in specific patient populations regarding BMS-986218 alone and in combination with nivolumab. [redacted]

Continuous evaluation of toxicity events in the BMS-986218 cohort expansions will be performed throughout enrollment for all expansion cohorts. If, at any time, the aggregate rate of treatment-related toxicities meeting DLT criteria exceeds 33% across all participants treated in cohort expansions, the findings will be discussed, and further enrollment will be interrupted. Depending on the nature and grade of the toxicity, and after assessing the benefit-risk ratio, a new dose for all cohorts may be initiated at a previously tested lower dose level or at a dose level intermediate to previously tested lower dose levels.

The Randomized BMS-986218 Monotherapy Cohort Expansion in Cutaneous Melanoma (Part 2A) will evaluate the preliminary efficacy of BMS-986218 monotherapy relative to ipilimumab monotherapy in a cohort of participants with advanced cutaneous melanoma who have received prior immunotherapy with an anti-PD-1 or anti-PD-L1 containing regimen and must have progressive or recurrent disease after prior anti-PD-1/PD-L1 directed therapy. Participants must not have received prior anti-CTLA-4 therapy. Three dose levels or schedules for BMS-986218 from the Part 1A Q4W monotherapy escalation will be evaluated that have had at least 6 DLT evaluable participants and meet safety criteria: one at 7 mg Q4W, one at 20 mg Q4W, and one at 70 mg Q4W, and ipilimumab 3 mg/kg (Q3W, 3-week treatment cycle for up to a maximum of 4 doses [which are to be completed within 16 weeks of the first dose in case of any delays]).

In the BMS-986218 Monotherapy Cohort Expansion (Part 2B), the preliminary efficacy of BMS-986218 will be investigated in tumor types where ipilimumab did not demonstrate a sufficient level of efficacy in previous studies and tumors in which a high level of Treg infiltration correlates with a poor prognosis. The tumor types to be evaluated will include NSCLC (adenocarcinoma or squamous cell subtypes only; at least 22 participants required per study arm); other tumor types may be explored in the future. Participants will be randomized evenly across study arms. Three dose levels or schedules for BMS-986218 from the Part 1A Q4W monotherapy escalation will be evaluated that have had at least 6 DLT evaluable participants and meet safety criteria: one at 7 mg Q4W, one at 20 mg Q4W, and one at 70 mg Q4W. BMS-986218 will be administered for a maximum duration of 2 calendar years when dosed Q4W. Participants should have received and then progressed on or relapsed/recurrence after anti-PD-1/PD-L1 directed therapy in monotherapy or in combination with chemotherapy. Prior anti-CTLA-4 therapy is allowed for no more than 20% of participants.

In the BMS-986218 Combination Therapy Cohort Expansion in NSCLC (Part 2C) , the preliminary efficacy and safety of BMS-986218 in combination with nivolumab will be investigated in participants whose NSCLC has progressed or relapsed after anti-PD-1/PD-L1

therapy. Participants must not have received prior anti-CTLA-4 therapy in the advanced or metastatic setting. Any selected BMS-986218 Part 2C dose will not exceed the highest Part 1B administered dose that has cleared safety, with a minimum of 6 evaluable participants for Safety Evaluation. More than one dose may be evaluated in Part 2C. The dose(s) of BMS-986218 selected for Part 2C will be based on the totality of preliminary safety, PK, and PD data from Part 1 and Part 2. The nivolumab dose found to be tolerable in Part 1B will be used in Part 2C. In Part 2C, participants will be treated Q4W for up to 2 calendar years regardless of treatment delays.

In the BMS-986218 Combination Therapy Cohort Expansion in MSS CRC (Part 2D) the preliminary efficacy and safety of BMS-986218 in combination with nivolumab will be investigated in participants with MSS CRC who have progressed or relapsed on at least 1 prior standard therapy. Participants must not have received prior anti-CTLA-4 therapy in the advanced or metastatic setting. Any selected BMS-986218 Part 2D dose will not exceed the highest Part 1B administered dose that has cleared safety, with a minimum of 6 evaluable participants for Safety Evaluation. The dose of BMS-986218 selected for Part 2D will be based on the totality of preliminary safety, PK, and PD data from Part 1 and Part 2. The nivolumab dose found to be tolerable in Part 1B will be used in Part 2D. In Part 2D, participants will be treated Q4W for up to 2 calendar years regardless of treatment delays.

In all study parts, participants with unconfirmed progressive disease, stable disease (SD), partial response (PR), or complete response (CR) at the end of a given cycle will continue to the next treatment cycle. Participants will be allowed to continue study treatment until the first occurrence of any of the following:

- Completion of the maximum duration of study therapy (up to 2 calendar years for BMS-986218 Q4W ± nivolumab Q4W; up to 2 calendar years for BMS-986218 Q2W; up to a maximum of 4 doses for ipilimumab Q3W).
- Confirmed progressive disease defined by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (Appendix 5) or per Prostate Cancer Working Group (PCWG 3) criteria for prostate (Appendix 12) unless participants meet criteria for treatment beyond progression (Section 8.1.1).
- Clinical deterioration suggesting that no further benefit from treatment is likely.
- Intolerability to therapy.
- Participant meets criteria for discontinuation of study treatment as shown in Section 8.1.

5.1.2.5 Treatment Beyond Progression

Tumor progression and response endpoints will be assessed using RECIST v1.1 criteria for solid tumors (Appendix 5) or per PCWG 3 criteria for prostate (Appendix 12). Treatment beyond progression may be allowed in selected participants with initial RECIST v1.1/PCWG 3-defined progressive disease following discussion and agreement with the BMS Medical Monitor (or designee), if the benefit-risk assessment favors continued administration of study treatment (eg, participants are continuing to experience clinical benefit as assessed by the Investigator, tolerating treatment, and meeting other criteria, see Section 8.1.1).

5.1.3 Follow-up

5.1.3.1 Safety Follow-up Period

Upon completion of study therapy (up to a maximum of 2 calendar years for BMS-986218 Q4W ± nivolumab Q4W; up to a maximum of 2 calendar years for BMS-986218 Q2W; up to a maximum of 4 doses for ipilimumab Q3W), or once the decision is made to discontinue the participant from treatment (ie, at end of treatment [EOT]), all participants will enter the Safety Follow-up Period.

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

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

5.1.3.2 Response Follow-up Period

At the time of the EOT visit or at the time of study treatment discontinuation, all participants will continue to have radiologic and clinical tumor assessments Q8W (± 1 week) until subsequent tumor-directed therapy is initiated. Participants who remain free of subsequent therapy will continue to receive tumor assessment scans Q8W for the first 48 weeks after discontinuation of study treatment/EOT visit and then Q12W (± 2 weeks) for a total duration of 2 years. Subsequently, they will continue to receive tumor assessment scans as per standard of care guidelines, or at a minimum of every 6 months up to 2 years following the last dose of study treatment, or until new tumor-directed therapy initiation/withdrawal of study consent. Radiologic assessments for participants who have ongoing clinical benefit may continue to be collected after participants complete the survival follow up period of the study. Scans will be submitted to an imaging core laboratory for review by blinded independent central review (BICR) at a later date or at any time during the study at the Sponsor's discretion.

5.1.3.3 Survival Follow-up Period

In parallel with the Safety Follow-up Period, all participants will start the Survival Follow-up Period. Participants will be followed-up by telephone Q12W (± 2 weeks) from EOT for up to 4 years following the first dose of study treatment or until death, loss to follow-up, withdrawal of consent, or conclusion of the study, whichever comes first. [redacted] Participants with stable disease (SD), partial response (PR), or complete response (CR) will have both the Response Follow-up period and Survival Follow-up

Period occur simultaneously during the 2-year follow-up period. The duration of this follow-up is up to 4 years following the first dose of study treatment, although a longer follow-up period could be considered in selected cases if an efficacy signal is apparent. Tumor assessment scans, for participants who have ongoing clinical benefit beyond the 4-year period following the first dose of study treatment, may continue to be collected as part of standard-of-care treatment. Subsequent therapies will also be recorded in this Survival Follow-up Period.

5.1.4 Data Monitoring Committee and Other External Committees

Based upon the stage of the study and appropriate safety monitoring procedures described below, BMS has determined that a Data Monitoring Committee is not necessary for this study.

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

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

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

5.2 Number of Participants

The approximate total number of evaluable participants will be up to 684 as shown below:

- Part 1 - Dose Escalation Phase: Up to approximately 284 evaluable participants may be treated in the escalation phase including:
    - Part 1A - up to approximately 200 evaluable participants for the BMS-986218 Monotherapy Escalation
        - Part 1A Q4W monotherapy - up to approximately 108 DLT-evaluable participants will be treated.
        - Part 1A Q2W monotherapy - up to approximately 72 DLT-evaluable participants will be treated.

        - Part 1A PD cohort - approximately 20 evaluable participants will be treated in the Part 1 PD cohorts.
            - In addition, in order to evaluate more than one dose level or schedule, up to 40 additional evaluable participants may be treated in the Part 1A PD cohorts (from participants initially planned for other Part 1 cohorts), provided the total number of participants in Part 1 is not exceeded.
    - Part 1B - up to approximately 84 DLT-evaluable participants for the Safety Evaluation of Combination Doses of BMS-986218 with Nivolumab.

- Part 2 - Dose Expansion Phase: The remaining 400 response-evaluable participants represent the potential number of participants in BMS-986218 cohort expansions who may be either randomized (Part 2A and Part 2B) or treated (Part 2C and Part 2D) including:
    - Part 2A - for the Randomized BMS-986218 Monotherapy Cohort Expansion in Cutaneous Melanoma, approximately 132 evaluable participants will be randomized, with 33 evaluable participants per arm required.
    - Part 2B - for the BMS-986218 Monotherapy Cohort Expansion in NSCLC, approximately 66 evaluable participants will be randomized, with 22 evaluable participants per arm required.
    - In Part 2A and Part 2B, additional participants may be treated or randomized to further evaluate emerging data or subgroups of interest if needed but not to exceed a total of 40 evaluable participants per arm. If additional participants are treated or randomized in Part 2A and Part 2B, then up to 160 response-evaluable participants (= 40 participants × 4 arms) and 120 response-evaluable participants (= 40 participants × 3 arms) can be randomized in Part 2A and Part 2B, respectively.
    - Part 2C - for the BMS-986218 Combination Therapy Cohort Expansion in NSCLC, approximately 40 response-evaluable participants will be treated. If more than one dose level is evaluated, additional participants (up to 40 response-evaluable participants per dose level) may be enrolled, up to 80 response-evaluable participants (= 40 participants × 2 arms).
    - Part 2D - for the BMS 986218 Combination Therapy Cohort Expansion in MSS CRC, approximately 40 response-evaluable participants will be treated, with the goal of treating approximately 20 participants each with either mutation or wild-type with respect to extended RAS status.

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

5.3 End of Study Definition

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

5.4 Scientific Rationale for Study Design

BMS-986218 is being investigated in humans with advanced solid tumors; either as monotherapy or in combination with nivolumab. The study design includes the following:

- 28-day screening period
- Up to 2 calendar year treatment period for BMS-986218 Q4W ± nivolumab Q4W, up to 2 calendar year treatment period for BMS-986218 Q2W, and up to a maximum of 4 doses for ipilimumab Q3W
- Dose escalation phase
- Cohort expansion phase
- Safety Follow-up Period
- Response/Survival Follow-up Period

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

5.4.1 Rationale for the BMS-986218 Monotherapy Escalation (Part 1A) and the Safety Evaluation of Combination Doses of BMS-986218 with Nivolumab (Part 1B) Design

The safety of BMS-986218 in the BMS-986218 Monotherapy Dose Escalation (Part 1A) will be evaluated at different dose levels. Based on the totality of data, select dose levels that have cleared safety for at least 6 DLT evaluable participants in Part 1A will be further evaluated in combination with nivolumab. The safety of CTLA-4 blockade with ipilimumab has been extensively characterized in more than 22,571 subjects with different cancer types (refer to the ipilimumab IB for further details[29]). Modifying the ipilimumab structure to retain affinity for CTLA-4 with enhanced ADCC may result to a different dose/effect relationship and AE profile. The flat dose of 2 mg (0.03 mg/kg) of BMS-986218 in the monotherapy dose escalation is lower than the dose safely tested in animals and will allow an accurate evaluation of the tolerability of BMS-986218.

When ipilimumab and nivolumab are used in combination, there is an increased incidence of AEs, but the AE profile is similar to those observed with each single agent. The relative contribution of ipilimumab and nivolumab to the balance between tolerability and efficacy is not fully characterized. Because the dose level of ipilimumab relative to nivolumab that could offer the best balance between safety and efficacy is unknown, the combination of BMS-986218 with nivolumab will be evaluated using a BLRM employing the EWOC principle. This design will help to identify the dose regimen of the combination of BMS-986218 and nivolumab with the optimal benefit-risk profile.

The BLRM with an overdose control principle escalation was selected as an appropriate design for this study. It offers more accuracy and efficiency in determining the true MTD compared to rule-based methods (such as 3 + 3 design) by incorporating external information from pre-clinical studies as well as historical clinical trials. The EWOC principle limits the risk of exposing participants in the next cohort to an intolerable or toxic dose. Hence, it ensures that safety is not compromised during dose escalation. Simulation results demonstrate that BLRM allows fast

escalation when the expected toxicity is very low, and limits participants treated at sub-therapeutic doses, which is attributed to the adaptive Bayesian learning from previous doses. In addition, BLRM has greater applicability to the combination therapy setting compared to other model-based methods. After completing the BMS-986218 Monotherapy Escalation (Part 1A), the drug associated dose toxicity profiles will be characterized and incorporated as prior knowledge into the drug expansion phase of the study, the Safety Evaluation of Combination Doses of BMS-986218 with Nivolumab (Part 1B), or used in future studies.

5.4.2 Rationale for BMS-986218 Monotherapy in Participants Previously Treated with Anti-PD-1/PD-L1 Immunotherapy

Cancer immunotherapies that target the immunosuppressive checkpoint receptors CTLA-4 or PD-1 and its ligand, PD-L1, have changed the landscape of anti-cancer immunotherapy. In particular, checkpoint inhibitors targeting PD-1 and PD-L1 have demonstrated unprecedented clinical efficacy in more than 15 cancer types, including melanoma, NSCLC, RCC, urothelial carcinoma, SCCHN, and Hodgkin's lymphoma.[30] Nevertheless, primary resistance to anti-PD-1 therapies is common, affecting up to 60% of patients in some cancer types. Furthermore, it is now becoming apparent that encouraging initial responses observed among some patients can be undone by their development of acquired resistance to anti-PD-1 therapies, leading to disease relapse.[31] In the current understanding of mechanisms contributing to the development of resistance to anti-PD-1 therapy, overexpression of other immune checkpoints (TIM-3, LAG-3, and CTLA-4) and influx of Tregs (which co-express these molecules) have been demonstrated to promote either primary or acquired resistance to anti-PD-1 therapy.[32,33]

A transcriptional signature associated with resistance to PD-1 immunotherapy, termed as Innate PD-1 RESistance (IPRES) was reported. Notably, over 30% of patients whose melanomas expressed the IPRES signature responded to CTLA-4 blockade (ipilimumab), suggesting that the IPRES signature does not indicate resistance to every immunotherapy.[34]

In light of these data, targeting CTLA-4 and depleting Tregs should present a valuable mechanism to overcome anti-PD-1 resistance.

5.4.3 Rationale for the Use of Ipilimumab as a Comparator

Ipilimumab was chosen as the comparator to BMS-986218 in the Randomized BMS-986218 Monotherapy Cohort Expansion in Cutaneous Melanoma (Part 2A) because both agents share a similar Ab structure and affinity for CTLA-4. Modification of the Fc portion is intended to enhance the ADCC activity of BMS-986218 compared to ipilimumab. A head-to-head comparison in melanoma participants, in which ipilimumab has demonstrated a positive benefit-risk profile, will allow a more complete comparison of the Treg depletion potential, an evaluation of the potential response benefit of the defucosylation in BMS-986218, as well as a better or comparable safety profile.

The dose and schedule of 3 mg/kg ipilimumab Q3W are based on the approved recommended dose in advanced cutaneous melanoma. Continuous treatment of both regimens will be evaluated to determine the benefit-risk profile of a recurrent immune stimulation by targeting CTLA-4 and

Tregs. There is currently no clinical trial evaluating the efficacy and safety of continuous administration of ipilimumab in participants who have received prior immunotherapy with an anti-PD-1 or anti-PD-L1 containing regimen and have progressive or recurrent disease after prior PD-1/PD-L1 directed therapy. The decision to test the activity in participants previously treated with anti-PD-1/PD-L1 therapy is based on the potential to re-stimulate the immune response by using a different mechanism of action.

5.4.4 Rationale for the Combination of BMS-986218 and Nivolumab

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

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

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

In pre-clinical models, combined pathway blockade increased proliferation of effector CD8+ and CD4+ T cells and decreased intratumoral Tregs compared to single pathway blockade.

The combination of ipilimumab and nivolumab is approved in the US for the treatment of advanced melanoma. Information regarding safety and efficacy can be found in the nivolumab IB.[27] The combination of nivolumab and ipilimumab is currently under evaluation in various doses, schedules of administration, and other tumor types. Results showed promising activity with higher, but tolerable toxicity than ipilimumab or nivolumab alone. Different doses and schedules of administration were evaluated with different outcomes in terms of safety, tolerability, and efficacy depending on tumor type.

Based on the described synergy between ipilimumab and nivolumab, the current study will evaluate the combination of BMS-986218 with nivolumab to generate more information about the safety, tolerability, and efficacy of the combination with the rationale that the addition of Treg depletion and ADCC-triggered inflammation could increase the synergy between both agents.

5.4.5 Rationale for Two Years Fixed Duration of Treatment with Checkpoint Blockade

The optimal duration of immunotherapy is an important question and continues to be investigated. Accumulating data suggest that 2 years of PD-1 checkpoint inhibitor treatment may be sufficient for long-term benefit. CA209003, a dose-escalation cohort expansion trial evaluating the safety and clinical activity of nivolumab in participants with previously treated advanced solid tumors

(including 129 participants with NSCLC), specified a maximum treatment duration of 2 years. Among 16 participants with non-small cell lung cancer (NSCLC) who discontinued nivolumab after completing 2 years of treatment, 12 participants were alive after > 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.[35] 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% and 18% for squamous and non-squamous NSCLC, respectively).[36]

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

In contrast, a shorter duration of nivolumab of only 1 year was associated with increased risk of progression in previously treated participants with NSCLC, suggesting that treatment beyond 1 year is likely needed. In CA209153, participants with previously treated advanced NSCLC who completed 1 year of nivolumab therapy were randomized to either continue or stop treatment, with the option of retreatment upon progression. Among 163 participants still on treatment at 1 year and without progression, those who were randomized to continue nivolumab had significant improvement in PFS compared to those who were randomized to stop treatment, with median PFS (post-randomization) not reached vs 10.3 months, respectively; HR = 0.42 (95% CI: 0.25, 0.71). With a median follow-up of 14.9 months post-randomization, there also was a trend for participants on continued treatment to live longer (OS HR = 0.63 [95% CI: 0.33, 1.20]). Of note, the PFS curves in both groups plateau approximately 1 year after randomization (ie, 2 years after treatment initiation), suggesting that there may be minimal benefit in extending treatment beyond a total of 2 years.[37]

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

5.4.6 Rationale for Treatment Beyond Progression

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

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

These phenomena were observed in the BMS Phase 2 study (CA209003) of nivolumab in patients with solid tumors. Two hypotheses potentially explain these phenomena. First, enhanced

inflammation within tumors could lead to an increase in tumor size, which would appear as enlarged index lesions and as newly visible small non-index lesions. Over time, both the malignant and inflammatory portions of the mass may then decrease, leading to overt signs of clinical improvement. Alternatively, in some individuals, the kinetics of tumor growth may initially outpace anti-tumor immune activity. With sufficient time, the anti-tumor activity will dominate and become clinically apparent. Therefore, it is important to avoid premature discontinuation of the study treatment that might induce a non-conventional response pattern in some patients.

5.4.7 Rationale for Tumor Selection

Specific tumors were selected to evaluate the potential therapeutic effect of BMS-986218 based on the following rationale:

- Previously demonstrated efficacy of ipilimumab in cutaneous melanoma.
- Tumor types where ipilimumab has shown some sign of activity but with no significant improvement in survival, such as NSCLC, RCC, triple-negative breast cancer (TNBC), and gastric adenocarcinoma; see the ipilimumab IB[29] for additional details.
- Participants with tumors who have received prior immunotherapy with an anti-PD-1 or anti-PD-L1 containing regimen and must have progressive or recurrent disease after prior PD-1/PD-L1 directed therapy (eg, cutaneous melanoma, NSCLC, RCC) will be evaluated to determine if targeting CTLA-4 and/or depleting Tregs might be an interesting strategy to re-stimulate the immune system, based on their potential contribution to the resistance to anti-PD-1 therapy.[32,33]
- Tumors for which high Treg infiltration has been correlated with worse prognosis and for which current immunotherapies have not demonstrated efficacy, such as TNBC[38,39] or advanced stage pancreatic ductal adenocarcinoma (PDAC).[40,41]
- Tumors such as NSCLC, SCCHN, MSS CRC, and cutaneous melanoma for which high Treg or T-cell infiltration has been observed by flow cytometry (undisclosed in house data), compared to other tumor types and the depletion of such Treg cells, could be evaluated [redacted]

5.4.8 Rationale for Open-label Design

This study will use an open-label design to ensure that immune-related toxicities in participants receiving immunotherapy are promptly identified and managed.

For all study parts, Investigator-reported best overall response will be used to determine response-related endpoints. Scans will be submitted to an imaging core laboratory for review by BICR at a later date or at any time during the study at the Sponsor's discretion.

[redacted]

[redacted]

5.5 Justification for Planned Dose Selection

5.5.1 BMS-986218

5.5.1.1 BMS-986218 Rationale for Starting Dose in Humans

Introduction

Four methods were used to assess the starting dose of BMS-986218: 1) nonclinical toxicology data, 2) pharmacology using anti-tumor efficacy data for a mouse surrogate (9D9-hIgG1-NF), 3) clinical safety data from an ipilimumab exposure-response (ER) of safety analysis, and 4) in vitro cytokine release data. The method with the lowest starting dose determined selection of the starting dose in the FIH study. The toxicology-based approach for the starting dose selection utilized the HNSTD identified from a 1-month repeat-dose toxicity study in cynomolgus monkeys. The pharmacology-based method leveraged anti-tumor efficacy data from a mouse surrogate (9D9-hIgG1-NF) to project the human efficacious dose and the starting dose. The third approach was based on the clinical safety data of ipilimumab, because BMS-986218 is the NF form of ipilimumab, and toxicity for this class of molecules is often associated with exaggerated pharmacology. Furthermore, data from an in vitro cytokine release assay were considered as part of the FIH starting dose selection by targeting the in vitro no-effect level as the Cmax value of the starting dose. As a result, the lowest dose (ie, 0.03 mg/kg [2-mg flat dose]) among these approaches was recommended as the FIH starting dose of BMS-986218. The details of each of these approaches are discussed below. Collectively, the proposed FIH starting dose represents the intent of ensuring adequate participant safety while limiting the number of cancer participants receiving sub-therapeutic doses.

Starting Dose Calculated From the HNSTD in Monkeys[12]

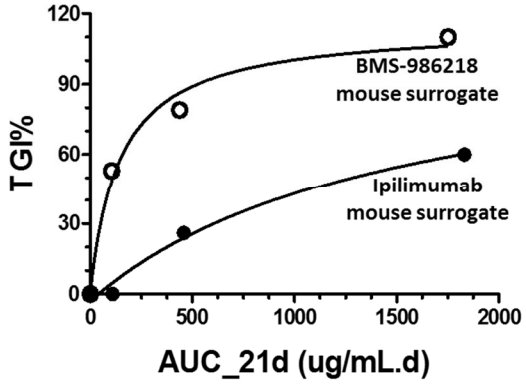
BMS-986218 contains an NF hIgG1fa Fc. Its constant of dissociation (Kd) for the human V158 and F158 isotypes was 9.5 and 190 nM, respectively, whereas the Kd value for monkey CD16a was 7.5 nM.[42] These results suggest that the cynomolgus monkey is a relevant toxicology species for BMS-986218. In a GLP 1-month repeat-dose toxicity study, BMS-986218 exhibited dose-related GI toxicity at all dose levels (3, 15, and 75 mg/kg/week) and resulted in early euthanasia in some animals at 15 and 75 mg/kg/week. BMS-986218 also exhibited dose-related, minimal to moderate, lymphohistiocytic inflammation within a variety of organs and tissues. As a

result, the 3-mg/kg/week dose was considered as the HNSTD, and the no observed adverse effect level was not established in the study. Based on the predicted steady-state exposure at the HNSTD (AUC[0-168h] 11,300 µg•h/mL obtained after the last dose of 3 mg/kg/week) and the predicted human clearance (4.5 mL/d/kg), the FIH starting dose range of BMS-986218, after applying a safety factor of 6-fold, was calculated to be 0.33 (exposure based) to 0.5 mg/kg (dose based).

Starting Dose Selection Based on Pharmacologic Activity in Human CTLA-4 Knock-in Mice Bearing MC38 Syngeneic Tumor[43]

The anti-mouse CTLA-4 Ab (9D9), with a binding affinity similar to its human counterpart, reformatted with either regular or NF hIgG1 (9D9-hIgG1 and 9D9-hIgG1-NF) was used as the mouse surrogates of ipilimumab and BMS-986218, respectively. These molecules were studied for anti-tumor efficacy in human FcR knock-in mice bearing MC38 syngeneic tumors. The relationship between systemic exposure (AUC from 0 to 21 days [AUC (0-21d)]) and anti-tumor efficacy (the percentage of tumor growth inhibition [%TGI]) was explored to project a human efficacious dose and subsequently the FIH starting dose (Figure 5.5.1.1-1). Based on the exposure-efficacy analysis, 9D9-hIgG1-NF appeared to be 10-fold more potent than 9D9-hIgG1 (eg, a 10-fold lower dose is needed to achieve the same efficacy).

Figure 5.5.1.1-1: Exposure and Efficacy Relationship of 9D9-hIgG1 and 9D9-hIgG1NF in Human CTLA4 KnockIn MC38 Mouse Tumor Model



	9D9-hIgG1 (ipilimumab mouse surrogate)	9D9-hIgG1 (BMS-986218 Mouse surrogate)
Emax (TGI%)	116	114
$EAUC_{50}$ (µg*day/mL)	1512	147

AUC_21d = area under the curve from time zero to 21 days; EAUC50 = area-under-the-concentration-time curve producing 50% of the maximum effect; Emax = maximum effect.

At the exposure (AUC[0-21d]) of 588 µg•d/mL, 9D9-hIgG1-NF is expected to reach 90% TGI. Targeting the same exposure in humans and assuming that the human PK of BMS-986218 is the same as that of ipilimumab (CL of 4.5 mL/d/kg), the human efficacious dose was projected to be 2.6 mg/kg. Subsequently, targeting the mouse exposure corresponding to 20% TGI, the FIH starting dose was predicted to be 0.2 mg/kg.

Starting Dose Selection Based on Ipilimumab Clinical Exposure and Response of Safety Analysis in Melanoma Patients[44]

An ER of safety analysis conducted with ipilimumab data from previously treated advanced melanoma participants showed that, the probability of Grade 3+ imAEs occurred at approximately 3% in participants receiving 0.3 mg/kg.[44] The probability of Grade 3+ imAEs increased to 11% and 23% at ipilimumab doses of 3 and 10 mg/kg, respectively. Targeting similar Grade 3+ imAE rates as ipilimumab at 0.3 mg/kg and considering a 10-fold improvement in anti-tumor efficacy of BMS-986218 over ipilimumab (based on anti-tumor efficacy studies using mouse surrogates), the FIH starting dose was selected to be 0.03 mg/kg (2-mg flat dose).

Starting Dose Calculated from the In Vitro Cytokine Release Assay[20]

The in vitro cytokine release of BMS-986218 was tested in both soluble and dry-coated assay formats. In the soluble assay, minor NK-cell activation was observed at concentrations ≥ 75 µg/mL; therefore, the no-effect level was 7.5 µg/mL. In the dry-coated assay, the no-effect level was estimated to be 1 µg/mL (based on the assay format of 0.3 µg BMS-986218 dry-coated in the well containing 0.3 mL buffer). At a higher concentration, NK cells were activated (ie, increase of %CD69+ and CD25+ NK cells), with an increase in the following cytokines: IL1β, IL6, IL8, IFN-γ, and TNF-α. BMS-986218 did not cause T-cell activation and corresponding IL2 release, which is a hallmark of TGN1412 superagonistic activity.[45] The NK cell activation and subsequent cytokine release by the enhanced Fc effector function of immobilized BMS-986218 indicate a potential increased risk of infusion reactions and cytokine release reactions that are common for antibodies with enhanced Fc effector function but manageable clinically.[46] To mitigate any NK cell activation-related safety risks at the starting dose, a human starting dose targeting the Cmax equal to the no-effect level of 1 µg/mL (assuming a plasma volume of 40 mL/kg) was calculated to be 0.04 mg/kg. At the starting dose, the Cmax is also 7.5-fold lower than the no-effect level from the soluble assay (7.5 µg/mL) to ensure the safety at the first dose.

Additional Considerations

Beyond the in vivo anti-tumor efficacy data using mouse surrogates, various in vitro activity evaluations also support the potency improvement of BMS-986218 over ipilimumab. Compared to ipilimumab, BMS-986218 had an equivalent binding affinity to human CTLA-4 but approximately 30-fold higher affinity to human CD16a. For example, the SPR Kd of ipilimumab for the human CD16a V158 and F158 isotypes was 310 and 4600 nM, respectively, whereas the corresponding Kd for BMS-986218 was 9.5 and 190 nM, respectively. The increased affinity of BMS-986218 to human CD16a is also in line with the results from an in vitro ADCC assay (concentration-dependent ADCC response with BMS-986218, but no significant ADCC with ipilimumab in 3 donors)[47] and a SEB-stimulated immune activation analysis (maximum response/EC50 of BMS-986218 vs ipilimumab: average 15-fold in 8 donors).[48] Therefore, when compared with ipilimumab, a 10-fold potency improvement applied to the FIH starting dose of BMS-986218 is well justified.

Conclusion

In summary, the totality of the nonclinical toxicology and pharmacology data of BMS-986218 as well as the clinical safety data of ipilimumab were considered in the selection of the FIH starting dose. The starting dose of 0.03 mg/kg (2-mg flat dose), derived from ipilimumab clinical safety data at 0.3 mg/kg with a 10-fold activity correction (based on anti-tumor efficacy data generated with mouse surrogates), is lowest among the 4 approaches used. This dose is about 6- to 10-fold below the starting dose calculated from toxicology- and pharmacology-based methods and is also supported by the no-effect level from the in vitro cytokine release assay. Therefore, 0.03 mg/kg converted to a flat dose of 2 mg using a body weight of 70 kg, is recommended as the FIH starting dose for BMS-986218.

5.5.2 Rationale for Dose Selection and Dosing Schedule

The dosing schedule for each part of Study CA022001 is summarized in Table 5.5.2-1, and the rationale for dose selection is presented in the following sections.

Table 5.5.2-1: Dosing Schedule by Study Part

Study Part	Tumor Types	Dose	Dose Schedule
Part 1A	all solid tumors	2, 4, 7, 20, 40, 70, 100, 150 and 200 mg	Q4W
	select solid tumors	10, 20, 35, 50, 75 and 100 mg	Q2W
Part 1B	select solid tumors	BMS-986218 starting at 20 mg	Q4W
		nivolumab 480 mg	Q4W
Part 2A	cutaneous melanoma[a]	ipilimumab 3 mg/kg	Q3W
		BMS-986218 at 7 mg	Q4W
		BMS-986218 at 20 mg	Q4W
		BMS-986218 at 70 mg	Q4W
Part 2B	NSCLC[b]	BMS-986218 at 7 mg	Q4W
		BMS-986218 at 20 mg	Q4W
		BMS-986218 at 70 mg	Q4W
Part 2C	NSCLC	BMS-986218 at doses not to exceed MTD[c]	Q4W
		Nivolumab[d]	Q4W
Part 2D	MSS CRC	BMS-986218 at doses not to exceed MTD[c]	Q4W
		Nivolumab[d]	Q4W

[a] Participants must have received prior immunotherapy with an anti-PD-1 or anti-PD-L1 containing regimen and must have progressive or recurrent disease after prior PD-1/PD-L1 directed therapy. Participants must not have received prior anti-CTLA-4 therapy.

[b] Participants must have received prior immunotherapy with an anti-PD-1 or anti-PD-L1 containing regimen. Prior anti-CTLA-4 is allowed, but for no more than 20% of participants.

[c] The dose(s) of BMS-986218 selected for Part 2C and Part 2D will be based on the preliminary safety, tolerability, efficacy, PK, and pharmacodynamic data. Refer to Section 5.1.2.4.

[d] Nivolumab combination dose to be defined from Part 1B; 1 or 2 combination dose regimens will be tested.

5.5.2.1 BMS-986218

A flat dose (mg) of BMS-986218 will be used in this study instead of a body size-based (ie, body weight or body surface area) dose. Therapeutic mAb doses have been routinely calculated on a body size basis. This practice assumes that dosing by body size significantly reduces variability in therapeutic mAb exposure.[49] However, recent analyses of marketed and experimental mAbs have demonstrated that body size-based dosing did not always offer advantages over flat dosing in reducing exposure variability. Many mAbs are target-specific with a relatively large therapeutic window that increases the tolerability of exposure variability. Additionally, patient-specific, disease-specific, and physiologic characteristics often contribute to exposure variability, resulting

in a generally smaller contribution of body size. Therefore, the dosing paradigm for mAbs should be assessed in the context of all of these unique characteristics.

With either dosing strategy, bias with respect to exposure is expected to occur in the extremes of the body weight distribution. In general, body size-based dosing could result in higher mAb concentrations in the heaviest participants (eg, 90th percentile), whereas flat dosing could lead to higher mAb concentrations in the lightest participants (eg, 10th percentile). Body weight distribution data from a clinical trial database of over 2500 adults with solid or hematologic cancers suggested a log-normal distribution of body weight with median, 10th percentile, and 90th percentile of 78 kg, 56 kg, and 112 kg, respectively.[50] To minimize the potential risk of higher exposures in the lowest body weight participants, the flat doses of BMS-986218 will be based on a body weight of 70 kg.

In addition to the above rationale, flat dosing offers practical advantages over body size-based dosing, including a convenient approach with respect to pharmacy preparation and clinical administration, and is also more likely to reduce the potential for dosing errors related to body size-based calculations.[49] Because the magnitude of the impact of body size on the human PK of BMS-986218 is not yet determined, the PK and safety data from the Phase 1/2a study will be evaluated to validate the flat dosing approach. If appropriate, based on the totality of the data, the Sponsor will consider a revision of the flat dosing strategy.

BMS-986218 will be administered Q4W. This dosing frequency is supported by the projected human T-HALF for BMS-986218 of 15 days. In addition, it complements the Q4W dosing regimen planned in the Safety Evaluation of Combination Doses of BMS-986218 with Nivolumab (Part 1B) and the BMS-986218 Cohort Expansion - Combination Therapy (Part 2C and Part 2D), thereby simplifying study logistics for both participants and Investigators.

In addition to Q4W dosing, an alternative schedule of administration of Q2W will be explored to characterize the safety and PK of BMS-986218 in participants with selected tumor types that may be more likely to have higher Treg levels at baseline. Q2W dosing may be the more relevant dosing frequency to achieve the pharmacodynamic goals of the program, given that Tregs are depleted within the first few days of BMS-986218 dosing and recover rapidly during the second week, as observed in preclinical models. Based on the PK data obtained from the Q4W dosing schedule, Q2W dosing will start at the AUC equivalent of a dose level that has cleared safety in the Q4W dosing cohort and continue evaluating higher doses up to the MTD.

Additionally, alternative BMS-986218 schedules of administration may also be explored. The dose level for such schedules will be based on the PK data obtained from the Q4W dosing schedule and will not exceed the MTD.

5.5.2.2 Nivolumab

In CA209004, a Phase 1b, open-label study of nivolumab in combination with ipilimumab in previously treated and untreated subjects with unresectable Stage III or Stage IV malignant melanoma, the following dose levels were evaluated during dose escalation: nivolumab 0.3 mg/kg + ipilimumab 3 mg/kg, nivolumab 1 mg/kg + ipilimumab 3 mg/kg, nivolumab 3 mg/kg +

ipilimumab 1 mg/kg, and nivolumab 3 mg/kg + ipilimumab 3 mg/kg. In CA209004, the nivolumab 3 mg/kg + ipilimumab 3 mg/kg cohort exceeded the MTD per protocol. Both nivolumab 1 mg/kg + ipilimumab 3 mg/kg and nivolumab 3 mg/kg + ipilimumab 1 mg/kg had similar clinical activity and acceptable safety. ER of efficacy analyses for nivolumab monotherapy across doses of 1 to 10 mg/kg revealed similar clinical activity (flat ER relationship), whereas ER of efficacy analyses for ipilimumab monotherapy across doses of 0.3, 3, and 10 mg/kg demonstrated increasing activity with an increase in dose and exposure. These data suggest that, in combination, a 3-mg/kg dose of ipilimumab may be more clinically impactful than a 3-mg/kg dose of nivolumab. However, for ipilimumab monotherapy, ER analyses of AEs leading to discontinuation or death and Grade 3+ imAEs demonstrated a higher risk of these events with increases in dose and exposure. A dose of 3 mg/kg of ipilimumab Q3W for 4 doses plus 1 mg/kg of nivolumab Q3W for 4 doses, followed by 3 mg/kg nivolumab Q2W until progression, was selected for further development following CA209004 and was eventually approved for the treatment of advanced melanoma.

A similar dose finding approach will be undertaken in the current protocol. During combination therapy dose escalation (Part 1B), BMS-986218 starting at 1 dose level below the current safety-cleared dose from the BMS-986218 Monotherapy Escalation (Part 1A) Q4W cohort will be studied in combination with nivolumab in order to identify a clinically tolerable combination dosing regimen that can be further evaluated in dose expansion. The nivolumab dose will be 480 mg Q4W, with de-escalation to 240 mg Q4W permitted in Part 1B, if agreed upon by the Sponsor and Investigators. There will be no intra-participant dose reductions of nivolumab allowed. In addition, if agreed upon by the Sponsor and the study Investigators, intermediate doses of BMS-986218 and/or nivolumab may be studied.

A nivolumab flat dose of 240 mg Q2W was approved in the US as monotherapy for unresectable or metastatic melanoma, metastatic NSCLC, and advanced RCC, and as maintenance therapy for unresectable or metastatic melanoma after induction therapy with nivolumab 1 mg/kg plus ipilimumab 3 mg/kg Q3W for 4 doses. Flat dosing of nivolumab was supported using PK and exposures characterized by integrated population pharmacokinetic (PPK) analyses of data from several Phase 1, 2, and 3 clinical trials of nivolumab monotherapy at doses ranging from 0.1 to 10 mg/kg. Nivolumab CL and Vss were found to increase with increasing body weight; however, these increases were less than proportional, indicating that mg/kg dosing represents an over-adjustment for the effect of body weight on nivolumab PK. Using the same PPK model, nivolumab exposures for flat (mg) dosing regimens (ie, 240 mg Q2W, 360 mg Q3W, and 480 mg Q4W) were simulated and evaluated against exposure data for nivolumab 3 mg/kg Q2W and 10 mg/kg Q2W doses. At these flat doses, simulated median (90% prediction interval [PI]) average steady state concentrations (Cavgss) were predicted to be similar (< 10% difference) to the median (90% PI) Cavgss for nivolumab 3 mg/kg Q2W in participants weighing 80 kg, which is the approximate median body weight of participants included in the PPK analyses described above. The predicted median (90% PI) steady-state peak concentrations were also predicted to be lower than those for nivolumab 10 mg/kg Q2W, which has been shown to be well tolerated. Given the PK, safety, and efficacy data for nivolumab monotherapy (mg/kg dosing) and the simulated flat

dosing exposure data described above, a nivolumab flat dose of 480 mg Q4W will be examined in combination with BMS-986218 in this study.

5.5.2.3 Rationale for Ipilimumab and Nivolumab 30-minute Infusions

Ipilimumab is currently approved for IV administration over 90 minutes. Recently, Momtaz et al. retrospectively reviewed computerized pharmacy records at their institution of all patients with metastatic solid tumor malignancies who received at least 1 dose of ipilimumab 3 or 10 mg/kg over 90 minutes between 01-Apr-2008 and 30-Jun-2013.[51] They found a low incidence of infusion-related reactions (IRRs): 2.2% and 4.3% for ipilimumab 3- and 10-mg/kg doses, respectively (P = 0.22, Fisher's exact test).[51] This finding led the Investigators to prospectively evaluate ipilimumab 3 mg/kg administered intravenously over 30 minutes. In the first 120 patients evaluated, the incidence of IRR was 5.8%, and the few reactions that were observed occurred at the second dose of ipilimumab.[51] Two of the 7 IRRs did not occur during the infusion. In addition, 6 of the 7 IRRs were Grade 2, and in no case were IRRs dose limiting. The Investigators concluded that the incidence of IRRs in patients receiving ipilimumab 3 mg/kg intravenously over 30 minutes was acceptably low although slightly higher than for the standard 90-minute infusion.[51] IRRs were managed according to institutional guidelines that included premedication with diphenhydramine and/or corticosteroids. It was concluded that ipilimumab 3 mg/kg can be safely infused over 30 minutes with an acceptable and manageable low incidence of IRRs.[51] In addition, after an IRR, patients can safely receive additional doses of ipilimumab with premedication.[51]

Nivolumab is currently approved for IV administration over 60 minutes. The impact of infusion time on nivolumab safety was assessed in a substudy conducted as part of an ongoing community-based trial (ie, CheckMate 153 [CA209153]) in participants with previously treated advanced or metastatic NSCLC.[52] In the substudy, 322 participants received nivolumab 3 mg/kg IV Q2W as a 30-minute infusion, and 355 participants received the same nivolumab regimen as a 60-minute infusion.

Overall, the safety profiles between the 30- and 60-minute infusion groups were similar. Any-grade treatment-related AEs were reported in 53% and 51% of participants given 30- or 60-minute infusions, respectively. Grade 3 to 4 treatment-related AEs were reported in 12% of participants in each infusion group. Among select AEs of any cause, Grade 3 to 4 events were comparable between infusion groups in the pulmonary (3% and 2%), hepatic (2% and 3%), and GI (2% and 2%) categories. Hypersensitivity/infusion reactions of any cause were reported in 8 (2%) and 5 (1%) participants administered 30- and 60-minute infusions, respectively. The incidence of Grade 3 to 4 hypersensitivity/infusion reactions was < 1% in each infusion group. Hypersensitivity/infusion reactions were managed either through dosing interruptions (8 participants given 30-minute infusions and 3 participants given 60-minute infusions), discontinuations (1 participant given a 30-minute infusion and 2 participants given 60-minute infusions), or administration of systemic corticosteroids (3 participants given 30-minute infusions and 1 participant given a 60-minute infusion). In addition, population PK modelling demonstrated similar predicted Cmax after the first nivolumab dose and at steady state in both infusion groups,

suggesting that a 30-minute infusion does not pose an increased safety risk due to an increase in nivolumab Cmax.

In conclusion, ipilimumab and nivolumab can be safely administered as 30-minute infusions, with a low incidence of infusion-related AEs. Given these findings, 30-minute infusions are being implemented across the ipilimumab and nivolumab development programs, including the FIH study CA022001.

6 STUDY POPULATION

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

6.1 Inclusion Criteria

1) Signed Written Informed Consent

a) The participant must sign the ICF prior to the performance of any study-related procedures that are not considered part of standard of care.

b) [redacted]

2) Type of Participants and Target Disease Characteristics

a) Participants must be at least 18 years old and have histologic or cytologic confirmation of a solid tumor that is advanced (metastatic, recurrent and/or unresectable) with measurable disease per RECIST v1.1 (Appendix 5) or per PCWG 3 criteria for prostate (Appendix 12) and have at least one soft-tissue lesion [redacted].

b) Eastern Cooperative Oncology Group Performance Status of 0 or 1 (Appendix 6).

c) The BMS-986218 Monotherapy Escalation (Part 1A):

i) ***Not applicable per Revised Protocol 03.*** All solid tumor histologies will be permitted during dose escalation, except for participants with primary central nervous system (CNS) tumors or tumors with CNS metastases as the only site of active disease.

ii) ***Not applicable per Revised Protocol 03.*** Participants must have received, and then progressed, relapsed, or been intolerant to all standard treatment regimens with proven survival benefit in the advanced or metastatic setting according to tumor type, if such a therapy exists.

iii) All solid tumor histologies will be permitted during dose escalation in the Q4W dosing schedule, except for participants with primary CNS tumors or tumors with CNS metastases as the only site of active disease.

iv) In the Q2W dose escalation schedule, select solid tumor histologies will be permitted during dose escalation, except for participants with CNS metastases as the only site of active disease. The included histologies will be NSCLC (squamous or adenocarcinoma), gastric adenocarcinoma (including gastroesophageal [GE] junction), TNBC, colorectal cancer (CRC; adenocarcinoma), pancreatic adenocarcinoma, metastatic castrate resistant prostate adenocarcinoma, urothelial carcinoma, or SCCHN (oral cavity, pharyngeal, oropharyngeal, hypopharynx, or laryngeal tumors only). Any

other cancers of the head and neck, including salivary gland and neuroendocrine tumors, are excluded from enrollment. Histologically confirmed recurrent or metastatic carcinoma of the nasopharynx, squamous cell carcinoma (SCC) of the skin of head and neck, and non-squamous histologies are not allowed. Additional tumor histologies may also be included by the Sponsor.

(1) ***Not applicable per Protocol Amendment 01 US:*** An additional group of participants with advanced stage cutaneous melanoma will also be enrolled. Other types of melanoma (eg ocular, mucosal) are not permitted.

v) Participants, other than those with cutaneous melanoma, must have received, and then progressed, relapsed, or become intolerant to, at least 2 standard treatment regimens with proven survival benefit in the advanced or metastatic setting according to tumor type, if such a therapy exists. If the participant refuses or is not eligible for these regimens, the reason must be documented in the medical record. For hormone-sensitive cancers, all previously received and available hormonal therapies will be considered as 1 systemic therapy regimen for the purposes of eligibility. For prostate cancer, only metastatic castrate resistant prostate cancer is allowed.

vi) ***Not applicable per Protocol Amendment 01 US:*** Participants in the Part 1A Q2W schedule with advanced stage cutaneous melanoma must have received, and then progressed, relapsed or intolerant to at least one standard treatment of proven survival benefit in the advanced or metastatic setting. Additionally, participants with cutaneous melanoma must have also been offered mutation-directed therapy (including but not limited to targeted therapy if BRAF V600 activating mutation) that has proven survival benefit if indicated. If a participant refuses such mutation directed therapy, it must be documented in the medical record. Only cutaneous melanoma is allowed. All other melanoma (eg, ocular, mucosal) are not allowed.

vii) Participants in the Part 1A PD cohort must have advanced stage cutaneous melanoma, NSCLC (squamous or adenocarcinoma), MSS CRC, or SCCHN (oral cavity, pharyngeal, oropharyngeal, hypopharynx, or laryngeal tumors only).

Participants with advanced stage cutaneous melanoma must have received, and then progressed, relapsed, or become intolerant to at least one standard treatment of proven survival benefit in the advanced or metastatic setting. Additionally, participants with cutaneous melanoma must have also been offered mutation-directed therapy (including but not limited to targeted therapy if BRAF V600 activating mutation) that has proven survival benefit if indicated. If a participant refuses such mutation-directed therapy, it must be documented in the medical record. Only cutaneous melanoma is allowed. Mucosal and uveal/ocular melanomas are not permitted; melanoma with unknown primary site may be enrolled if the investigator determines mucosal and uveal/ocular primary sites are unlikely.

Participants with NSCLC (squamous or adenocarcinoma), MSS CRC, or SCCHN (oral cavity, pharyngeal, oropharyngeal, hypopharynx, or laryngeal tumors only) must have received, and then progressed, relapsed, or become intolerant to at least 2 standard treatment regimens with proven survival benefit in the advanced or metastatic setting according to tumor type, if such therapies exist. If the participant

refuses or is not eligible for these regimens, the reason must be documented in the medical record.

d) ***Not applicable per Revised Protocol 03.*** The Safety Evaluation of Combination Doses of BMS-986218 with Nivolumab (Part 1B):

   i) ***Not applicable per Revised Protocol 03.*** All solid tumor histologies will be permitted during dose escalation, except for participants with primary CNS tumors or tumors with CNS metastases as the only site of active disease.

   ii) ***Not applicable per Revised Protocol 03.*** Participants must have received, and then progressed, relapsed, or been intolerant to, all standard treatment regimens with proven survival benefit in the advanced or metastatic setting according to tumor type, if such a therapy exists.

e) ***Not applicable per Revised Protocol 03.*** The Randomized BMS-986218 Monotherapy Cohort Expansion in Melanoma (Part 2A):

   i) ***Not applicable per Revised Protocol 03.*** Participants with advanced stage cutaneous melanoma who have received all standard therapies with proven survival benefit including prior immunotherapy with an anti-PD-1 or anti-PD-L1 containing regimen and must have progressive or recurrent disease after prior PD-1/PD-L1 directed therapy. Participants must not have received prior anti-CTLA-4 therapy in the advanced or metastatic setting.

f) ***Not applicable per Revised Protocol 03.*** The BMS-986218 Cohort Expansion - Monotherapy (Part 2B):

   i) ***Not applicable per Revised Protocol 03.*** Participants must have received, and then progressed, relapsed, or been intolerant to, all standard systemic therapies with proven survival benefit according to their tumor types in the advanced or metastatic setting, if such a therapy exists. The following permitted tumor histologies will be evaluated in individual cohorts:

      (1). RCC

      (2). Urothelial Carcinoma

      (3). Advanced stage PDAC

g) ***Not applicable per Revised Protocol 03.*** The BMS-986218 Cohort Expansion - Combination Therapy (Part 2C):

   i) ***Not applicable per Revised Protocol 03.*** Participants must have received, and then progressed, relapsed, or been intolerant to, all standard systemic therapies according to their tumor types in the advanced or metastatic setting, if such a therapy exists. Participants must be immunotherapy naïve with the exception of tumor types for which immunotherapies have proved survival benefits. The following permitted tumor histologies will be evaluated in individual cohorts:

      (1) NSCLC: all participants with non-squamous histology must have known epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) status. Participants with an activating EGFR mutation must have received an EGFR tyrosine kinase inhibitor. Participants with an ALK translocation must have received an ALK inhibitor.

      (2) Gastric adenocarcinoma

(3) Urothelial carcinoma

(4) CRC

(5) Participants with advanced stage TNBC

ii) ***Not applicable per Revised Protocol 03.*** Participants with advanced stage cutaneous melanoma who have received prior immunotherapy with an anti-PD-1 or anti-PD-L1 containing regimen and must have progressive or recurrent disease after prior PD-1/PD-L1 directed therapy. Participants must not have received prior anti-CTLA-4 therapy in the advanced or metastatic setting.

iii) ***Not applicable per Revised Protocol 03.*** Other tumor types could be considered at the time of expansion based on scientific rationale and will be evaluated after the protocol has been amended to allow the enrollment in this new tumor specific individual cohort.

h) The Safety Evaluation of Combination Doses of BMS-986218 with Nivolumab (Part 1B):

i) Select solid tumor histologies will be permitted during dose escalation, except for participants with CNS metastases as the only site of active disease. The included histologies will be NSCLC (squamous or adenocarcinoma), gastric adenocarcinoma (including GE junction), TNBC, CRC (adenocarcinoma), pancreatic adenocarcinoma, metastatic castrate resistant prostate adenocarcinoma, urothelial carcinoma, or SCCHN (oral cavity, pharyngeal, oropharyngeal, hypopharynx, or laryngeal tumors only). Any other cancers of the head and neck, including salivary gland and neuroendocrine tumors, are excluded from enrollment. Histologically confirmed recurrent or metastatic carcinoma of the nasopharynx, SCC or other cancers of the skin of head and neck, and non-squamous histologies are not allowed. Additional tumor histologies may also be included by the Sponsor.

ii) Participants must have received, and then progressed, relapsed, or been intolerant to at least 2 systemic therapy regimens with proven survival benefit in the advanced or metastatic setting according to tumor type, where available. If the participant refuses or is not eligible for these regimens, the reason must be documented in the medical record. However, if anti-PD-1 therapy is approved in a given indication, participants are eligible to receive this treatment as part of the combination regimen in this study prior to having completed 2 prior systemic therapy regimens after discussion and agreement with the Medical Monitor (or designee). For hormone-sensitive cancers, all previously received and available hormonal therapies will be considered as 1 systemic therapy regimen for the purposes of eligibility. For prostate cancer, only metastatic castrate resistant prostate cancer is allowed.

i) The Randomized BMS-986218 Monotherapy Cohort Expansion in Cutaneous Melanoma (Part 2A):

i) Participants with advanced stage cutaneous melanoma who have received standard therapies with proven survival benefit including prior immunotherapy with an anti-PD-1 or anti-PD-L1 containing regimen and must have progressive or recurrent disease after prior PD-1/PD-L1 directed therapy. Participants must not have received prior anti-CTLA-4 therapy in the advanced or metastatic setting. Additionally, participants with cutaneous melanoma must have also been offered mutation-directed therapy, if indicated, that has proven survival benefit; if a participant refuses such therapy, it must be documented in the medical record. No more than 1 intervening therapy is allowed but not required between prior anti-PD-1/anti-PD-L1 containing

regimen and BMS-986218. No more than 70% of the randomized participants should have had progression of disease within a period of 6 months of start of therapy with anti-PD-1/PD-L1 agent. Only cutaneous melanoma is allowed. Mucosal and uveal/ocular melanomas are not allowed; melanoma with unknown primary site may be enrolled if the investigator determines mucosal and uveal/ocular primary sites are unlikely.

j) The BMS-986218 Cohort Expansion - Monotherapy (Part 2B):

   i) Participants must have received, and then progressed, relapsed, or been intolerant to at least 2 standard systemic therapies with proven survival benefit according to their tumor types in the advanced or metastatic setting, if available. If the participant refuses or is not eligible for these regimens, the reason must be documented in the medical record. Additionally, participants must have progressed or have recurrent disease after prior immunotherapy with anti-PD-1/anti-PD-L1 either by itself or in combination with other systemic therapy agents. No more than 1 intervening therapy is allowed but not required between prior anti-PD-1/anti-PD-L1 containing regimen and BMS-986218. Participants who have been intolerant to prior immunotherapy are excluded. Prior anti-CTLA4 therapy is allowed for no more than 20% of participants, and details of treatment (including dates, doses, and response) must be available.

      (1) Lung/NSCLC (adenocarcinoma or squamous cell carcinoma); additionally, for NSCLC, all participants with adenocarcinoma must have known EGFR, ALK, and ROS-1 status. Participants with an activating EGFR mutation, ALK translocation, or ROS-1 mutation must have received appropriate inhibitor therapy.

      (2) Other tumor histologies may also be included by the Sponsor.

k) The BMS-986218 NSCLC Cohort Expansion - Combination (Part 2C):

   i) Participants must have received, and then progressed, relapsed, or been intolerant to at least 2 standard systemic therapies (including anti-PD-1/anti-PD-L1 therapies) with proven survival benefit according to their tumor types in the advanced or metastatic setting, if available. If the participant refuses or is not eligible for these regimens, the reason must be documented in the medical record. Participants must have progressed or have recurrent disease after prior immunotherapy with anti-PD-1/anti-PD-L1 either by itself or in combination with other systemic therapy agents. No more than 1 intervening therapy is allowed but not required between prior anti-PD-1/anti-PD-L1 containing regimen and BMS-986218. Participants who have been intolerant to prior immunotherapy are excluded. Participants must not have received prior anti-CTLA-4 therapy in the advanced or metastatic setting.

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

      (1) Lung/NSCLC (adenocarcinoma or squamous cell carcinoma); all participants with adenocarcinoma must have known EGFR, ALK, Kirsten rat sarcoma viral oncogene homolog (KRAS), and ROS-1 status (when testing is available as per country/region standard of care practices), participants with an activating EGFR mutation, ALK translocation, or ROS-1 mutation must have received appropriate inhibitor therapy (as available per country/region standard of care). Note: If KRAS results are not known, then a sample (tissue of microscopic slides, tissue block, [redacted]

[redacted]) should be sent for testing locally. Circulating tumor DNA may be used if sequencing or polymerase chain reaction (PCR) results are not feasible, with prior Sponsor approval

l) The BMS-986218 MSS CRC Cohort Expansion - Combination (Part 2D):

i) Participants must have received and then progressed on or after, or have been intolerant or refractory to, at least 1 standard systemic therapy for metastatic and/or unresectable disease (or have progressed within 6 months of adjuvant therapy). If the participant refuses or is not eligible for these regimens, the reason must be documented in the medical record and participant can be enrolled.

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

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

ii) Participants must have known microsatellite instability (MSI) or mismatch repair status. Extended RAS (KRAS and NRAS), and BRAF status if known, should be documented.

(1) If known to be RAS wild-type, available treatments with demonstrated benefit (eg, anti-EGFR therapy) must have been received as prior treatments if consistent with approved local standard of care.

The Sponsor may elect to prioritize enrollment of participants based on mutation status to ensure approximately 50 % of patients treated are RAS mutant.

3) Physical and Laboratory Test Findings

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

i) Neutrophils $\geq 1{,}500/\mu L$.

ii) Platelets $\geq 80 \times 10^3/\mu L$ (transfusion to achieve this level is not permitted within 2 weeks of first study treatment administration).

iii) Hemoglobin ≥ 8 g/dL (transfusion to achieve this level is not permitted within 2 weeks of first study treatment administration).

b) Adequate hepatic function.

i) ALT and AST $\leq 3 \times$ upper limit of normal (ULN).

ii) Total bilirubin $\leq 1.5 \times$ ULN (except participants with Gilbert's Syndrome who must have normal direct bilirubin).

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

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

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

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

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

f) All toxicities attributed to systemic prior anti-cancer therapy other than alopecia must have resolved to Grade 1 (National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] version 4.03 [v4.03]) or baseline before administration of study drug.

4) Age and Reproductive Status

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

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

c) WOCBP must agree to follow instructions for method(s) of contraception (Appendix 4) for the duration of combination therapy treatment with study treatment BMS-986218 plus 5 months after the end of study treatment. WOCBP receiving monotherapy treatment with BMS-986218 or ipilimumab must agree to follow instructions for method(s) of contraception for the duration of monotherapy treatment with BMS-986218, or ipilimumab plus 3 months after the end of study treatment. Local laws and regulations may require use of alternative and/or additional contraception methods. See Appendix 4.

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

e) ***Not applicable per Protocol Amendment 06:*** Male participants who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception (Appendix 4) during combination treatment with study treatment BMS-986218 and nivolumab, plus 5 half-lives of nivolumab (~ 125 days), plus 90 days (duration of sperm turnover), for a total of 215 days post-treatment completion. Males who are sexually active with WOCBP must agree to follow instructions for methods of contraception during monotherapy treatment with BMS-986218 or ipilimumab plus 5 half-lives (~ 75 days) of BMS-986218 or ipilimumab plus 90 days (duration of sperm turnover) for a total of 165 days post-treatment completion. In addition, male participants must be willing to refrain from sperm donation during this time.

f) ***Not applicable per Protocol Amendment 06*:** Azoospermic males are exempt from contraceptive requirements. WOCBP who are continuously not heterosexually active are also exempt from contraceptive requirements, but still must undergo pregnancy testing as described in this section.

g) No additional contraceptive measures are required to be used in males.

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

6.2 Exclusion Criteria

1) Target Disease Exclusions

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

2) Prohibited Treatments

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

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

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

d) Prior participation in an anti-CTLA-4-NF clinical study or therapy.

e) Participants who have received prior curative radiation therapy must have been completed at least 4 weeks prior to study drug administration. Prior focal palliative radiotherapy must have been completed at least 2 weeks before study drug administration.

f) Continued luteinizing hormone-releasing hormone (LHRH)/gonadotropin-releasing hormone (GnRH) agonist therapy in men with castration-resistant prostate cancer after progression on an initial androgen deprivation regimen is allowed.

g) Any botanical preparation (eg, herbal supplements or traditional Chinese medicines) intended to treat the disease under study or provide supportive care within 4 weeks prior to treatment. If less than 4 weeks have elapsed from the last botanical supplement and the initiation of study treatment, the participant can be treated at the Investigator's discretion and after discussion and agreement with the Sponsor/Medical Monitor (or designee).

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

3) Medical History and Concurrent Diseases

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

b) Participants with other active malignancy requiring concurrent intervention.

c) Prior organ allograft.

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

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

e) Participants with the following:

i) Active, known, or suspected autoimmune disease.

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

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

a. Vitiligo.

b. Type 1 diabetes mellitus.

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

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

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

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

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

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

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

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

(2) Uncontrolled angina within the past 3 months.

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

(4) History of other clinically significant heart disease (eg, cardiomyopathy, congestive heart failure with New York Heart Association functional classification III to IV [Appendix 7], pericarditis, or significant pericardial effusion).

(5) History of myocarditis, regardless of etiology.

(6) Cardiovascular disease-related requirement for daily supplemental oxygen therapy.

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

v) History of chronic hepatitis as evidenced by the following:

(1) Positive test for hepatitis B surface antigen.

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

a. Participants with positive hepatitis C Ab and negative quantitative hepatitis C by PCR are eligible. History of resolved hepatitis A virus infection is not an exclusion criterion.

b. Additional testing or substitute testing per institutional guidelines to rule out infection is permitted.

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

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

- they have received antiretroviral therapy (ART) for at least 4 weeks prior to treatment assignment as clinical indicated while enrolled on study
- they continue on ART as clinically indicated while enrolled on study
- 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 by local requirements (Appendix 8). HIV-positive participants must be excluded in countries where mandated locally.

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

ix) ***Not applicable per Revised Protocol 03.*** Receipt of non-oncology vaccines containing live virus for prevention of infectious diseases within 4 weeks prior to first dose of study treatment.

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

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

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

xii) Participants who have received a live/attenuated vaccine within 30 days of first treatment.

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

f) Women who are pregnant or breastfeeding.

g) 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 medical monitor, there are no sequelae that would place the participant at a higher risk of receiving study treatment.

h) Previous SARS-CoV-2 vaccine within 14 days of C1D1. Note: 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.

i) Leptomeningeal metastases

4) Allergies and Adverse Drug Reaction

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

b) History of severe hypersensitivity reaction to any mAb.

5) Other Exclusion Criteria

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

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

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

6.3 Lifestyle Restrictions

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

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized/entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants; to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements (Appendix 9), as applicable; and to respond to queries from regulatory authorities. Minimal information includes date of consent, demography, screen failure details, eligibility criteria, and any SAEs.

6.4.1 Retesting During Screening

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

Retesting of laboratory parameters and/or other assessments during the extended screening period will be allowed.

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

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

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

- At least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared or positive RT-PCR or viral antigen test result, and
- At least 24 hours have passed since last fever without the use of fever-reducing medications, and
- Acute symptoms (eg, cough, shortness of breath) have resolved and
- In the opinion of the investigator, there are no SARS-CoV-2 infection sequelae that may place the participant at a higher risk of receiving investigational treatment.
- In the instance of a SARS-CoV-2 infection during screening, the screening period may be extended beyond the protocol-specified timeframe with Medical Monitor approval.
- Any screening tests already performed which could potentially be affected by the SARS-CoV-2 infection or its complications on an individual basis and agreed upon with the Medical Monitor (eg, safety labs, oxygen saturation, chest computed tomography [CT] scan) should be repeated.

7 TREATMENT

7.1 Treatments Administered

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

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

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

In this protocol, IPs are the following:

- BMS-986218
- Nivolumab
- Ipilimumab

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

Table 7.1-1: Investigational Product Description

Product Description / Class and Dosage Form	Potency	IP/ Non-IMP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per Label)
BMS-986218 for injection	200 mg/vial (20 mg/mL)	IP	Open Label	Vial	Store at 2°C to 8°C, protected from light
Nivolumab (BMS-936558) solution for injection	100 mg/vial (10 mg/mL)	IP	Open Label	Vial	2°C to 8°C. Protect from light and freezing
Nivolumab (BMS-936558) solution for injection	40 mg/vial (10 mg/mL)	IP	Open Label	Vial	2°C to 8°C. Protect from light and freezing
Ipilimumab (BMS-734016) solution for injection	200 mg/vial (5 mg/mL)	IP	Open Label	Vial	2°C to 8°C. Protect from light and freezing

7.1.1 BMS-986218

There will be no intra-participant dose escalations or reductions of BMS-986218 allowed. Participants may be dosed within the window per Table 2-2, Table 2-3, and Table 2-4.

Participants should be carefully monitored for infusion reactions during BMS-986218 administration. If an acute infusion reaction is noted, participants should be managed according to Section 7.6.5.

Doses of BMS-986218 may be interrupted, delayed, or discontinued, depending on how well the participant tolerates the treatment. Dosing visits are not skipped, only delayed.

BMS-986218 injection is to be administered as an IV infusion through a 0.2-micron pore size, low-protein binding in-line filter at the protocol-specified doses and infusion times. It is not to be

administered as an IV push or bolus injection. Prior to infusion, the BMS-986218 injection is diluted with 0.9% sodium chloride injection (normal saline) to required concentrations.

Detailed instructions for preparation, handling, dilution, and infusion of BMS-986218 injection may be provided in the Pharmacy Manual or in the IB.[6] Care must be taken to assure sterility of the prepared solution, as the product does not contain any antimicrobial preservative or bacteriostatic agent.

7.1.2 Nivolumab

No intra-participant dose escalations or reductions of nivolumab are allowed. Participants may be dosed within the window per Table 2-2.

Participants should be carefully monitored for infusion reactions during nivolumab administration. If an acute infusion reaction is noted, participants should be managed according to Section 7.6.5.

Doses of nivolumab may be interrupted, delayed, or discontinued, depending on how well the participant tolerates the treatment. Dosing visits are not skipped, only delayed.

Nivolumab infusion must be promptly followed by a flush of diluent to clear the line. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

7.1.3 Ipilimumab

There will be no intra-participant dose escalations or reductions of ipilimumab allowed. Participants may be dosed within the window per Table 2-4.

Participants should be carefully monitored for infusion reactions during ipilimumab administration. If an acute infusion reaction is noted, participants should be managed according to Section 7.6.5.

Doses of ipilimumab may be interrupted, delayed, or discontinued, depending on how well the participant tolerates the treatment. Dosing visits are not skipped, only delayed.

Ipilimumab is to be administered as a 30-minute IV infusion and may be infused using a volumetric pump with a 0.2- to 1.2-micron low-protein binding in-line filter at the protocol-specified dose. At the end of the infusion, flush the line with a sufficient quantity of diluent.

Detailed instructions for preparation, handling, dilution, and infusion of ipilimumab injection may be provided in the Pharmacy Manual or IB. Care must be taken to assure sterility of the prepared solution, as the product does not contain any antimicrobial preservative or bacteriostatic agent.

7.2 Handling and Dispensing

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

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

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

Please refer to the current version of the IB and/or pharmacy manual for complete storage, handling, dispensing, and infusion preparation information for BMS-986218, nivolumab, and ipilimumab.

7.3 Schedule of Dose for Each Investigational Product

The dosing schedule for each IP is detailed below in Table 7.3-1 all study parts.

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

Table 7.3-1: Selection and Timing of Dose for All Study Parts

Study Treatment	Flat Dose Levels	Frequency of Administration	Route of Administration	Infusion Time (Minutes)
BMS-986218	2, 4, 7, 20, 40, 70, 100, 150 or 200 mg	Q4W	IV	Doses administered over approximately 30 minutes.
BMS-986218	10, 20, 35, 50, 75 or 100 mg	Q2W	IV	Doses administered over approximately 30 minutes.
Ipilimumab	3 mg/kg[a]	Q3W (up to a maximum of 4 doses)	IV	Approximately 30 minutes
Nivolumab	480 mg	Q4W[b]	IV	Approximately 30 minutes

[a] Dosing calculations should be based on the body weight assessed at Cycle 1 Day 1 prior to the first dose of ipilimumab. If the participant's weight on the day of dosing differs by > 10% from the weight used to calculate the prior dose, the dose must be recalculated.

[b] For participants in the Safety Evaluation of Combination Doses of BMS-986218 with Nivolumab (Part 1B) and the BMS-986218 Cohort Expansion - Combination Therapy (Part 2C and Part 2D), a 30-minute infusion of nivolumab will be followed by a 30-minute observation period, followed by a 30-minute infusion of BMS-986218 and a 60-minute observation period following the first 3 infusions for each participant.

7.4 Method of Treatment Assignment

During the screening visit, the investigative site will call into the enrollment option of the IRT designated by BMS for assignment of a 5-digit participant number that will be unique across all sites. Enrolled participants, including those not dosed, will be assigned sequential participant numbers [redacted]. The patient identification number

(PID) will ultimately be comprised of the site number and participant number. For example, the first participant screened (ie, enrolled) at site number 1, will have a PID of [redacted]. Once it is determined that the participant meets the eligibility criteria following the screening visit, the investigative site will call the IRT to centrally assign the participant into the open dose panel. If Part 1 is open upon the decision to initiate Part 2, treatment in the 2 parts will occur in parallel.

In the Randomized BMS-986218 Monotherapy Cohort Expansion in Cutaneous Melanoma (Part 2A), all participants will be centrally randomized evenly across study arms, which will include: BMS-986218 monotherapy at 7 mg, 20 mg, 70 mg Q4W or ipilimumab 3 mg/kg Q3W (maximum of 4 doses).

In the Randomized BMS-986218 Monotherapy Cohort Expansion (Part 2B), participants will be randomized evenly across study arms, which will include: BMS-986218 at 7 mg, 20 mg, and 70 mg Q4W.

In Part 2A and Part 2B, if it is decided based on a preliminary assessment of anti-tumor activity that not all arms would need to continue enrollment, randomization would continue only in the arm(s) that remain open. In addition, more subjects may be enrolled in selected arm(s) as specified in Section 5.2 to better assess an initial signal.

In Part 2C Combination Expansion, multiple doses may be open concurrently. In that case, treatment assignments will alternate between the dose levels, with consecutively treated participants assigned to different parts through IRT whenever possible. If there are no openings available in the dose level to which the participant would be assigned by this algorithm, then the subject will be assigned to the next open dose.

In Part 2D Combination Expansion, participants will be assigned to one dose.

In Part 2, BMS-986218 Q4W will be administered for a maximum duration of 2 calendar years, and ipilimumab Q3W will be administered for a maximum of 4 doses.

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

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

7.5 Blinding

This is an open-label study and randomized in Part 2. Designated personnel of the Sponsor will have access to treatment and/or randomization assignments prior to database lock to facilitate data analysis (see Section 10.3.9), as well as the bioanalytical analysis of PK and immunogenicity samples. A bioanalytical scientist in the Bioanalytical Sciences department of BMS Research & Development (or a designee in the external central bioanalytical laboratory) will have access to the randomized treatment assignments in order to minimize unnecessary bioanalytical analysis of samples.

7.6 Dosage Modification

Intra-participant dose escalation/reduction of BMS-986218, nivolumab, or ipilimumab is not permitted in this study in order to allow better evaluation of the safety and efficacy at individual dose levels and schedules.

7.6.1 Dose-limiting Toxicities

For the purpose of guiding dose escalation, DLTs will be defined based on the incidence, intensity, and duration of AEs that are possibly related to study treatment. The DLT period will be 8 weeks (56 days) in both the BMS-986218 Monotherapy Dose Escalation (Part 1A) and the Safety Evaluation of Combination Doses of BMS-986218 with Nivolumab (Part 1B). Any toxicities that occur beyond the DLT period will be accounted for in making final dose level decisions.

Participants receiving 2 doses of BMS-986218 and have completed or who discontinued due to a DLT in the 8-week DLT period will be considered as DLT-evaluable participants for BMS-986218 monotherapy. Participants receiving either 2 doses each of BMS-986218 and nivolumab, or participants who discontinued due to a DLT in the 8-week combination treatment DLT period, will be considered as DLT-evaluable participants for combination treatment. Participants who withdraw from the study during the DLT evaluation period or have received less than 2 doses for reasons other than a DLT in both monotherapy and combination therapy will not be considered as DLT-evaluable participants and may be replaced with a new participant at the same dose level. Participants who have received 2 doses and withdraw from the study during the last week of the DLT evaluation period for reasons other than a DLT in both monotherapy and combination therapy may be considered as DLT-evaluable. Participants who are dose delayed during the DLT evaluation period for reasons other than a DLT in both monotherapy and combination therapy could be considered as DLT-evaluable participants if they received 2 doses and completed at least 2 full cycles of therapy 4 weeks each, with a maximum of 12 weeks for the total duration, including delays.

For the purpose of participant management, any AE that meets DLT criteria, regardless of the cycle in which it occurs, will lead to discontinuation of study treatment. Participants who withdraw from the study during the 8-week DLT evaluation period for reasons other than a DLT may be replaced with a new participant at the same dose level. The incidence of DLT(s) during the 8-week DLT evaluation period will be used in dose escalation decisions and to define the MTD. AEs occurring after the DLT period will be considered for the purposes of defining the RP2D upon agreement between the Sponsor, Medical Monitor (or designee), and Investigators.

Participants experiencing a DLT will not be re-treated with study treatment and will enter the Safety Follow-up Period of the study. DLTs occurring after the 8-week DLT observation period will be accounted for in determining the dose levels for expansion.

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

7.6.1.1 Gastrointestinal Dose-limiting Toxicity

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

- Grade 2 colitis that lasts longer than 5 days.

- Grade ≥ 3 diarrhea or colitis, regardless of duration.

7.6.1.2 Hepatic Dose-limiting Toxicity

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

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

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

- ALT or AST > 20 × ULN, regardless of duration.
- ALT or AST > 10 × ULN for greater than 2 weeks.
- Total bilirubin > 8 × ULN regardless of duration for participants with elevated bilirubin at study entry or > 5 × ULN for participants with normal bilirubin at study entry.
- ALT or AST > 3 × ULN and concurrent total bilirubin > 2 × ULN.

7.6.1.3 Hematologic Dose-limiting Toxicity

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

- Grade 4 neutropenia ≥ 7 days in duration.
- Grade 4 thrombocytopenia.
- Grade 3 thrombocytopenia with bleeding or any requirement for platelet transfusion.
- Febrile neutropenia that lasts longer than 48 hours.
- Grade 3 hemolysis (ie, requiring transfusion or medical intervention such as steroids).

7.6.1.4 Dermatologic Dose-limiting Toxicity

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

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

7.6.1.5 Other Dose-limiting Toxicities

Any of the following events will be considered a DLT:

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

7.6.2 Management Algorithms for Immuno-oncology Agents

I-O agents are associated with imAEs that can differ in severity and duration from AEs caused by other therapeutic classes. BMS-986218, ipilimumab, and nivolumab are considered I-O agents in this protocol. Early recognition and management of imAEs associated with I-O agents may mitigate severe toxicity. Management algorithms have been developed from extensive experience with ipilimumab and nivolumab to assist Investigators in assessing and managing the following groups of imAEs:

- GI
- Renal
- Pulmonary
- Hepatic
- Endocrinopathies
- Skin

- Neurological
- Myocarditis

The clinical nature of AEs noted with BMS-986218 will determine the role of the algorithms for use in toxicities related to its use in this study. The algorithms recommended for the management of imAEs in this protocol are in Appendix 10.

7.6.3 Dose Delays Due To Toxicity

Participants who experience the following due to any cause must have all study treatment(s) withheld:

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

Criteria for participants who are required to permanently discontinue study treatments is listed in Section 8.2. Participants not meeting guidelines for permanent discontinuation will be permitted to resume therapy based on the criteria specified below in Section 7.6.3.1. Participants eligible to resume study therapy will resume study therapy at the nominal treatment visit following their last received study medication dose.

The end of cycle tumor assessments, such as CT, magnetic resonance imaging (MRI), or positron emission tomography (PET), will continue on a Q8W schedule relative to the participant's first dose, regardless of any treatment delay incurred.

7.6.3.1 Criteria to Resume Treatment

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

Participants experiencing AEs not meeting criteria for permanent discontinuation as outlined in Section 8.2 may resume treatment with study medication under the following criteria:

- Participants may resume study treatment when the drug-related AE(s) resolve to Grade ≤ 1 or baseline value, with the following exceptions:
  - Participants may resume treatment in the presence of Grade 2 fatigue.

  - Participants who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
  - Participants with Grade 2 uveitis, episcleritis, iritis, eye pain, or blurred vision not meeting DLT criteria (Section 8.2) must resolve to baseline prior to resuming study therapy.
- For participants with Grade 2 AST, ALT, or total bilirubin elevations, dosing may resume when laboratory values return to baseline and management with corticosteroids (if needed) is complete.
- Participants with combined Grade 2 AST/ALT **and** total bilirubin values meeting DLT criteria (Section 7.6.1) should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed. Participants with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for re-treatment if discussed with, and approved by, the BMS Medical Monitor (or designee).
- Participants with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment.
- 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-PRC test result, or positive viral antigen test result, 2) resolution of acute symptoms (including at least 24 hours has passed since last fever without fever reducing medications), 3) evaluation by the investigator with confirmation that there are no sequelae that would place the participant at a higher risk of receiving investigational treatment, and 4) consultation by the medical monitor. For suspected cases, treatment may also resume if SARS-CoV-2 infection is ruled-out and other criteria to resume treatment are met.
  - Prior to re-initiating on-study treatment in a participant with a dosing delay lasting 8 weeks due to SARS-CoV-2 infection, the medical monitor/designee must be consulted.

7.6.4 Exceptions to Permanent Discontinuation Criteria

Any drug-related AE occurring at any time that meets DLT criteria as outlined in Section 7.6.1 will require permanent discontinuation, **with the exception of the following**:

- Grade 3, nausea, vomiting, or abdominal pain that returns to Grade 1 or baseline within or at 48 hours either spontaneously or with medical intervention.
- Grade 3 pruritus or rash that returns to Grade 1 or baseline within 7 days with medical intervention.
- Isolated Grade 3 or 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 3 days of their onset.
- Grade 4 neutropenia < 7 days in duration.
- Grade 4 lymphopenia or leukopenia.
- Grade 3 increase in amylase or lipase that is not associated with clinical or radiographic evidence of pancreatitis.
- Grade 3 infusion reactions that return to Grade 1 in < 6 hours.

- Grade 3 fever not associated with hemodynamic compromise (eg, hypotension, clinical, or laboratory evidence of impaired end-organ perfusion).
- Grade 3 tumor flare (defined as pain, irritation, or rash that localizes to sites of known or suspected tumor).
- Grade 3 fatigue.
- Grade 3 or 4 drug-related endocrinopathy AEs, such as adrenal insufficiency, adrenocorticotropic hormone, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS Medical Monitor (or designee).
- Any event that leads to delay in dosing, lasting > 8 weeks from the previous dose, requires discontinuation, with the exception of the following:
  - Dosing delays for prolonged steroid tapers to manage drug-related AEs are allowed. Prior to re-initiating treatment in a participant with a dosing delay lasting > 8 weeks from the previous dose, the BMS Medical Monitor (or designee) must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue Q4W, or more frequently if clinically indicated, during such dosing delays.
  - Dosing delays lasting > 8 weeks from the previous dose that occur for non-drug-related reasons may not require discontinuation, if approved by the BMS Medical Monitor (or designee). Prior to re-initiating treatment in a participant with a dosing delay lasting > 8 weeks, the BMS Medical Monitor (or designee) must be consulted.
- Any AE, laboratory abnormality, or concurrent illness, which, in the judgment of the Investigator, presents a substantial clinical risk to the participant with continued nivolumab dosing.

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

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

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

7.6.5 Management of Drug-related Infusion Reactions

Since BMS-986218, ipilimumab, and nivolumab contain only human Ig protein sequences, they are unlikely to induce hypersensitivity reactions. However, based on the non-clinical toxicology evaluation of BMS-986218, infusion reactions due to T-cell activation and cytokine release may occur in both monotherapy and combination with nivolumab. If such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgia, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the BMS Medical Monitor (or designee) and reported as an SAE. Infusion reactions should be graded according to NCI CTCAE v4.03 guidelines.

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

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

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

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

- Stop the study treatment infusion, begin an IV infusion of normal saline, and treat the participant with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor participant until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor participant closely. If symptoms recur, then no further BMS-986218, ipilimumab, or nivolumab will be administered at that visit.
- For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg should be administered at least 30 minutes before study treatment infusions. If necessary, corticosteroids (up to 25 mg of hydrocortisone or equivalent) may be used.

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

impairment, pulmonary infiltrates]; Grade 4: life-threatening; pressor or ventilatory support indicated):

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

In the 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).

7.7 Preparation/Handling/Storage/Accountability

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

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

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

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

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

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

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

7.7.1 Retained Samples for Bioavailability/Bioequivalence

Not applicable.

7.8 Treatment Compliance

Not applicable.

7.9 Concomitant Therapy

7.9.1 Prohibited and/or Restricted Treatments

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

- Immunosuppressive agents.
- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 6.2).
- Any concurrent anti-neoplastic therapy (ie, chemotherapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents for treatment of cancer). Palliative hormonal therapy will be permitted when indicated.
- Any botanical preparation (eg, herbal supplements or traditional Chinese medicines) intended to treat the disease under study or provide 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 treatment at the discretion of the investigator. See Section 6.2 Exclusion Criteria.
- Treatment of active SARS-CoV-2 infections or high risk exposures, including use of investigational therapies, is allowed and should be discussed with the medical monitor.

7.9.2 Other Restrictions and Precautions

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

7.9.3 Permitted Therapy

Participants are permitted the use of the following treatments:

- Topical, ocular, intra-articular, intra-nasal, and inhalational corticosteroids.
- Adrenal replacement steroid doses ≤ 10 mg daily prednisone equivalent.
- A brief (less than 3 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen).
- Palliative hormonal therapy will be permitted when indicated.

7.9.4 Palliative Radiation

Palliative radiation for disease-related symptoms may be offered to all participants on the study after the DLT evaluation period. Limited radiation therapy to control symptoms from isolated lesions is permitted for participants who have Investigator-assessed clinical benefit following consultation with the BMS Medical Monitor or designee. Participants should not receive study treatment during radiation, as the potential for overlapping toxicities with radiotherapy and BMS-986218, ipilimumab, or BMS-986218 in combination with nivolumab is currently not known. Anecdotal data suggest that radiotherapy administered to participants while receiving nivolumab therapy is tolerable; however, because concurrent radiotherapy and immunotherapies in cancer have not been formally evaluated, in cases where palliative radiotherapy is required for a tumor lesion, BMS-986218, ipilimumab, and/or nivolumab should be withheld for at least 1 week before, during, and 2 weeks after radiation. Participants should be closely monitored for any potential toxicity during and after receiving radiotherapy, and AEs related to radiotherapy should resolve to Grade 1 prior to resuming study treatment. Participants who have received palliative local therapy will be documented as having had disease progression for the purpose of efficacy analyses.

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

7.9.5 Surgery

Participants undergoing major surgery for any reason while on study should have BMS-986218, ipilimumab, and/or nivolumab held for at least 4 weeks after surgery, and these study treatments should not be resumed until wound healing has occurred and it is considered safe to do so in the assessment of the Investigator.

For participants who need to undergo surgery during the study, it is recommended to hold study treatment(s) for at least 2 weeks before (if elective or planned) and 3 weeks after surgery or until the participant recovers from the procedure, whichever is longer. Wound healing must be evaluated by surgeon prior to resuming study treatment. Prior to resuming study treatment, surgically related AEs should resolve to Grade 1 or baseline, and participants must meet relevant eligibility criteria as determined by the BMS Medical Monitor (or designee) in discussion with the Investigator.

7.9.6 Imaging Restriction and Precautions

It is the local imaging facility's responsibility to determine, based on participant attributes (eg, allergy history, diabetic history, and renal status), the appropriate imaging modality and contrast regimen for each participant. Imaging contraindications and contrast risks should be considered in this assessment. Participants with renal insufficiency should be assessed as to whether they should receive contrast and if so, what type and dose of contrast is appropriate.

Specific to MRI, participants with severe renal insufficiency (ie, estimated glomerular filtration rate < 30 mL/min/1.73 m^2) are at increased risk of nephrogenic systemic fibrosis. MRI contrast should not be given to this participant population. In addition, participants are excluded from MRI if they have tattoos, metallic implants, pacemakers, etc.

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

7.10 Treatment After the End of the Study

At the end of the study, BMS will not continue to provide BMS supplied study treatment to participants/Investigators unless BMS chooses to extend the study. The Investigator should ensure that the participant receives appropriate standard of care to treat the condition under study.

8 DISCONTINUATION CRITERIA

8.1 Discontinuation from Study Treatment

Participants MUST discontinue for any of the following reasons:

- Documented disease progression as defined by RECIST v1.1 (Appendix 5) or per PCWG 3 criteria for prostate (Appendix 12) unless participants meet criteria for treatment beyond progression (Section 8.1.1).
- Clinical deterioration while receiving active study therapy that, in the opinion of the Investigator, indicates that continued participation in the study is not in the best interest of the participant.
- Any drug-related AE occurring at any time that meets DLT criteria as outlined in Section 7.6.1 will require permanent discontinuation. Exceptions to permanent discontinuation are listed in Section 7.6.4.
- Participant's request to stop study treatment. Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information.
- Any clinical AE, laboratory abnormality or intercurrent illness that, in the opinion of the Investigator, indicates that continued participation in the study is not in the best interest of the participant.
- Termination of the study by BMS.
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness. (Note: Under specific circumstances, and only in countries where local regulations permit, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply and BMS approval is required.)
- Inability to comply with protocol.
- Discretion of the Investigator.
- Pregnancy.

- Individual participants with confirmed CR will be given the option to discontinue study therapy on a case-by-case basis after specific consultation and agreement between the Investigator and BMS Medical Monitor (or designee) in settings where benefit-risk justifies discontinuation of study therapy.
- Any event that leads to delay in dosing lasting > 8 weeks from the previous dose requires discontinuation, with the following exceptions:
  - Dosing delays for prolonged steroid tapers to manage drug-related AEs are allowed.
  - Dosing delays lasting > 8 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS Medical Monitor (or designee).
- If a participant in any of the nivolumab/BMS-986218 combination arms meets criteria for discontinuation, because it is not possible to determine whether the event is related to both or 1 study treatment, the participant should discontinue both nivolumab and BMS-986218 and be taken off the treatment phase of the study.

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

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

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

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

8.1.1 Treatment Beyond Progression

As described in Section 5.4.6, accumulating evidence indicates that a minority of patients with tumors treated with immunotherapy may derive clinical benefit despite initial evidence of progressive disease. Participants will be permitted to continue treatment beyond initial RECIST v1.1/PCWG 3-defined progressive disease (see Appendix 5 and Appendix 12), as long as they meet the following criteria:

- Investigator-assessed clinical benefit, and no rapid disease progression.
- Continue to meet all other study protocol eligibility criteria.
- Tolerance of study treatment.
- Stable performance status.

- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases).
- Participant provides written informed consent prior to receiving any additional nivolumab or BMS-986218 treatment, using an ICF describing any reasonably foreseeable risks or discomforts, or other alternative treatment options.

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

8.1.1.1 Discontinuation Due to Further Progression (Confirmed Progression)

Participants will continue to receive monitoring according to the on-treatment assessments in Section 2. Radiographic assessment, by CT (preferred) or MRI described in Section 9.3.1, is required when participants continue post-progression treatment and should be performed at each scheduled tumor assessment, no later than 8 weeks ± 7 days following initial disease progression, to determine whether there has been continued progressive disease. If the Investigator believes that the participant continues to achieve clinical benefit by continuing treatment, the participant should remain on the trial and continue to receive monitoring according to the Schedule of Activities (Section 2). Participants should permanently discontinue study therapy upon evidence of further progression, defined as an additional 10% or greater increase in tumor burden volume from time of initial progression (including all target lesions and new measurable lesions). This includes an increase in the sum of diameters of all target lesions and/or the diameters of new measurable lesions compared to the time of initial progressive disease.

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

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

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

For statistical analyses that include the Investigator-assessed progression date, participants who continue treatment beyond initial Investigator-assessed, RECIST v1.1/PCWG 3-defined progression will be considered to have Investigator-assessed progressive disease at the time of the initial progression event.

For participants who discontinue post progression treatment with study therapy, additional radiographic assessments will be required until a new tumor-directed therapy is initiated.

8.1.2 Post-treatment Follow-up

Post-treatment follow-up is of critical importance and is essential to preserving participant safety and the integrity of the study. Participants who discontinue study treatment must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with Section 2 until death or the conclusion of the study.

8.2 Discontinuation from the Study

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

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

8.3 Lost to Follow-Up

- All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant.
- Lost to follow-up is defined by the inability to reach the participant after a minimum of **3** documented phone calls, faxes, or emails, as well as lack of response by participant to 1 registered mail letter. All attempts should be documented in the participant's medical records.
- If it is determined that the participant has died, then the site will use permissible local methods to obtain date and cause of death.
- If Investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the participant's informed consent, then the Investigator may use a Sponsor retained third-party representative to assist site staff with obtaining participant's contact information or other public vital status data necessary to complete the follow-up portion of the study.
- The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information.

- If after all attempts, the participant remains lost to follow-up, then the last known alive date as determined by the Investigator should be reported and documented in the participant's medical records.

9 STUDY ASSESSMENTS AND PROCEDURES

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

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

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

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before randomization. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of 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.

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

If a participant shows pulmonary-related signs (hypoxia, fever) or symptoms (eg, dyspnea, cough, and fever) consistent with possible pulmonary AEs, the participant should be immediately evaluated to rule out pulmonary toxicity, according to the suspected pulmonary toxicity management algorithm in the BMS-936558 (nivolumab) IB.[27]

Some of the assessments referred to in this section may not be captured as data in the electronic CRF (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 Safety

Safety assessments will be based on reported AEs and the measurement results of vital signs, ECG, PEs, and clinical laboratory tests. AEs will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA) and the incidence of observed AEs will be tabulated and reviewed for potential significance and clinical importance. AEs will be assessed continuously during the study and for 100 days after the last dose of BMS-986218 in the case of

monotherapy, and the last dose of BMS-986218 and nivolumab for combination therapy. Local laboratory will perform the clinical laboratory tests and will provide reference ranges for these tests. Both AEs and laboratory tests will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03.

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

9.1.1 Physical Examinations

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

9.1.2 Vital signs

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

9.1.3 Electrocardiograms

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

The effect of BMS-986218 on the QTc interval will be evaluated by a central reader using ECG data collected in triplicate along with time-matched PK during the BMS-986218 Monotherapy Dose Escalation (Part 1A) only (eg, 1 ECG test equals 3 consecutive individual 12-lead ECGs performed 5 minutes apart). For the purposes of monitoring participant safety, the Investigators will review the 12-lead ECGs using their site's standard ECG machines throughout the study. The QTcF will be applied to each ECG reading.

9.1.4 Clinical Safety Laboratory Assessments

- Investigators must document their review of each laboratory safety report.
- A local laboratory will perform the analyses and will provide reference ranges for these tests. Results of clinical laboratory tests performed on Day -1 must be available prior to dosing.
- The laboratory tests that will be performed for study participants are shown in Table 9.1.4-1.
- Results of all laboratory tests required by this protocol must be provided to the Sponsor, recorded either on the laboratory pages of the CRF or by another mechanism as agreed upon between the Investigator and BMS (eg, provided electronically). If the units of a test result differ from those printed on the CRF, the recorded laboratory values must specify the correct units. Any abnormal laboratory test result considered clinically significant by the Investigator must be recorded on the appropriate AE page of the CRF.

Table 9.1.4-1: Clinical Laboratory Assessments

Hematology	
Hemoglobin and hematocrit	
Total leukocyte count, including differential	
Platelet count	
Prothrombin time, activated partial thromboplastin time and *international normalized ratio* (at screening only)	
Serum Chemistry	
Aspartate aminotransferase Alanine aminotransferase Total bilirubin Direct bilirubin (reflex)[a] Alkaline phosphatase Lactate dehydrogenase Creatinine Creatine kinase/ Creatine phosphokinase C-reactive protein Blood urea nitrogen Uric acid Glucose Lipase Amylase Gamma glutamyl transferase (reflex only)[b] Thyroid stimulating hormone Free T3 and T4 (screening and reflex only)[c]	Total protein Albumin Sodium Potassium Chloride Calcium Phosphorus Magnesium Creatinine clearance (Cockcroft-Gault method) (screening only) Troponin
Urinalysis	
Protein	
Glucose	
Blood	
Leukocyte esterase	
Specific gravity	
pH	
Microscopic examination of the sediment if blood, protein, or leukocytes esterase are positive on the dipstick	
Serology	
Serum for hepatitis C Ab, hepatitis B surface antigen, HIV-1 and HIV-2 Ab (at screening, and as mandated by local requirement)	
Other Analyses	
Pregnancy test (WOCBP only: screening, predose on Day 1 of each treatment cycle, discharge). FSH (screening only and women only)	

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

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

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

[redacted]

9.2 Adverse Events

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

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

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

Contacts for SAE reporting are specified in Appendix 3.

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

The collection of non-serious AE information should begin at initiation of study treatment until 100 days after the discontinuation of study treatment administration or until the start of a new anti-neoplastic treatment (whichever occurs first), at the timepoints specified in the Schedule of Activities (see Section 2).

Following the participant's written consent to participate in the study, all SAEs, whether related to study treatment or not, must be collected, including those thought to be associated with protocol-specified procedures.

- All SAEs that occur during the screening period and within 100 days after discontinuation of dosing must be collected, except in cases where a study participant has started a new anti-neoplastic treatment. However, any SAE occurring after the start of a new anti-neoplastic treatment that is suspected to be related to study treatment by the Investigator should be reported as an SAE.
- The Investigator must report any SAE that occurs after these time periods and that is believed to be related to study treatment or protocol-specified procedure.

- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the appropriate section of the CRF section.
- All SAEs will be recorded and reported to Sponsor or designee within 24 hours, as indicated in Appendix 3.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of this being available.
- 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 last dose of study treatment.
- With the exception of nonserious AEs related to SARS-CoV-2 infection, all nonserious AEs (not only those deemed to be treatment-related) should be collected from the time of first dose and continuously during the treatment period and for a minimum of 100 days following last dose of study treatment.

Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study and he/she considers the event reasonably related to the study treatment or study participation, then 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 judgment in the context of known AEs, when appropriate for the program or protocol.

9.2.3 Follow-up of AEs and SAEs

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

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and non-serious AEs (as defined in Section 9.1), including ones 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 IB and will notify the Independent Review Board (IRB)/Independent Ethics Committee, if appropriate according to local requirements.

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

9.2.5 Pregnancy

If, following initiation of the study treatment, it is subsequently discovered that a participant is pregnant or may have been pregnant at the time of study exposure, including during at least for 5 months for combination therapy and 3 months for BMS-986218 monotherapy after product administration, the Investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Appendix 3.

The study treatment will be permanently discontinued in an appropriate manner. Please call the BMS Medical Monitor (or designee) within 24 hours of awareness of the pregnancy.

If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, or re-initiation of study treatment, a discussion between the investigator and the BMS Medical Monitor/designee must occur.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form. Protocol-required procedures for study discontinuation and follow-up must be performed on the participant.

9.2.6 Laboratory Test Result Abnormalities

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

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

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

9.2.7 Immune-mediated Adverse Events

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

9.2.8 Potential Drug-induced Liver Injury

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a p-DILI event. All occurrences of p-DILIs meeting the defined criteria must be reported as SAEs (see Section 9.1 and Appendix 3 for reporting details).

Potential drug induced liver injury is defined as:

- ALT or AST elevation > 3 × ULN

AND

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

AND

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

The key responsibilities for Investigators during p-DILI assessment include: (i) Early detection, medical evaluation (including the exclusion of other potential causes) and rapid laboratory confirmation of liver-related abnormalities; and (ii) BMS notification of p-DILI cases via SAE forms. Following the gathering and assessment of relevant clinical information, BMS is responsible for: (i) Timely evaluation and triaging of p-DILI cases;

(ii) Expedited reporting of p-DILI cases; and (iii) Expanded review of p-DILI cases including a detailed assessment of all available clinical information, investigations, and biochemical data.

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

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

9.2.9 Other Safety Considerations

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

9.3 Efficacy Assessments

Efficacy assessments for the anti-tumor activity of BMS-986218, alone and in combination with nivolumab, will be based on tumor measurements using RECIST v1.1 or per PCWG 3 criteria for prostate with CT and/or MRI, as appropriate, at baseline, and during the treatment period. Tumor imaging assessments are to be performed prior to initiating next cycle of treatment.

[redacted]

Tumor assessments will occur every 8 weeks (Q8W) for participants receiving BMS-986218 and nivolumab for all study parts, except the Randomized BMS-986218 Monotherapy Cohort Expansion in Cutaneous Melanoma (Part 2A), where tumor assessment in participants receiving BMS-986218 or ipilimumab will occur at 12 weeks from first dose (± 1 week), prior to initiating the next cycle of treatment. After that, subsequent tumor imaging assessments are to be performed Q8W (± 1 week), prior to initiating the next cycle of treatment. Participants who remain free of subsequent therapy will undergo tumor imaging assessment Q8W (± 1 week) until subsequent

tumor-directed therapy is initiated or until 48 weeks after discontinuation of study treatment/EOT visit, and then Q12W (± 2 weeks) for a total duration of 2 years.

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

9.3.1 Imaging Assessment for the Study

Images will be submitted to an imaging core lab. Image acquisition guidelines and submission process will be outlined in the CA022001 Imaging Manual to be provided by the core lab.

Tumor assessment with contrast-enhanced CT scans acquired on dedicated CT equipment is preferred for this study. Contrast-enhanced CT of the chest, abdomen, pelvis, and other known/suspected sites of disease should be performed for tumor assessments.

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

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

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

CT and MRI scans 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.

Use of CT component of a PET/CT scanner: Combined modality scanning such as with 2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG)-PET/CT is increasingly used in clinical care, and is a modality/technology that is in rapid evolution; therefore, the recommendations outlined here may change rather quickly with time. At present, low dose or attenuation correction CT portions of a combined FDG-PET/CT are of limited use in anatomically-based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for anatomically-based RECIST v1.1/PCWG 3 measurements. However, if a site can document that the CT performed as part of a FDG-PET/CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the FDG-PET/CT can be used for RECIST v1.1 measurements. Note, however, that the FDG-PET portion of the CT introduces additional data which may bias an Investigator if it is not routinely or serially performed.

At screening, MRI without and with contrast of the brain is required if participant is symptomatic or has history of brain metastasis and has not had brain imaging within 30 days of anticipated first study drug administration. CT of the brain without and with contrast may be performed if MRI is contraindicated. CT and MRI scans should be acquired with a slice thickness of 5 mm or less with no intervening gap (contiguous). Participants with a history of brain metastasis should have a surveillance MRI if clinically indicated.

Participants with prostate cancer should have bone scans performed for each imaging timepoint. Other participants may have bone scans as clinically indicated.

Assessments will be performed at baseline and at the timepoints described per RECIST v1.1 criteria (see Appendix 5) or per PCWG 3 criteria for prostate (see Appendix 12). At the time of the EOT visit or at the time of study treatment discontinuation, all participants will continue to have radiologic tumor assessments Q8W (± 1 week) until subsequent tumor-directed therapy is initiated or until 48 weeks after discontinuation of study treatment/EOT visit, and then Q12W (± 2 weeks) for a total duration of 2 years.

Radiologic assessments for participants who have ongoing clinical benefit and remain free of subsequent therapy may continue to be collected after participants complete the Survival Follow-up Period of the study.

Scans will be submitted to an imaging core laboratory for review by BICR at a later date or at any time during the study at the Sponsor's discretion.

Tumor assessments at other timepoints may be performed if clinically indicated. Assessments of PR and CR must be confirmed at least 8 weeks after initial response. When participants are allowed to be treated beyond initial disease progression per RECIST v1.1 criteria, subsequent tumor assessment will continue Q8W until confirmation of tumor progression. Thereafter, participants will continue tumor assessment as described in the follow-up period. Changes in tumor measurements and tumor responses will be assessed by the Investigator per study design using RECIST v1.1 criteria or per PCWG 3 criteria for prostate. Investigators will also 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 or per PCWG 3 criteria for prostate. (See Appendix 5 and Appendix 12 for specifics of RECIST v1.1 criteria and PCWG 3 criteria to be utilized in this study, respectively.)

9.4 Overdose

For this study, any dose of BMS-986218 greater than the assigned dose will be considered an overdose.

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

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

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

2) Closely monitor the participant for AEs/SAEs and laboratory abnormalities until at least 5 times the projected elimination half-life of BMS-986218 (75 days), when it is considered safe to stop monitoring the participant.
3) Obtain a serum sample for PK if requested by the Medical Monitor/designee (determined on a case-by-case basis).
4) Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

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

9.5 Pharmacokinetic and Immunogenicity Assessments

The serum samples will be analyzed for BMS-986218 and Anti-BMS-986218 antibodies by two validated electrochemiluminescence (ECL) assays, respectively.

The PK of BMS-986218 will be derived from serum concentration vs time data. The PK parameters that will be assessed following serial PK collection, are shown in Table 9.5-1. Sparse ipilimumab and nivolumab concentration-time data will be collected and may be used in an integrated population PK or ER analysis along with data from other ipilimumab and nivolumab studies, which would be the subject of a separate report. Separate samples will be collected for PK and ADA assessments.

Table 9.5-1: Pharmacokinetic Parameters for BMS-986218

Parameters	Definition
Cmax	Maximum observed plasma serum concentration
Tmax	Time of maximum observed plasma serum concentration
AUC(0-T)	Area under the plasma serum concentration-time curve from time zero to time of last quantifiable concentration; may be calculated if concentrations are not quantifiable up to TAU across a treatment group
AUC(TAU)	Area under the serum concentration-time curve in 1 dosing interval
Ctau	Observed serum concentration at the end of a dosing interval
Ctrough	Trough observed serum concentrations (this includes predose concentrations [C0] and Ctau)
Parameters that May be Assessed Following the Dose Administration in Cycle 3	
CLT	Total body clearance
Css-avg	Average serum concentration over a dosing interval (AUC[TAU]/tau) at steady state
AI	Ratio of an exposure measure at steady state to that after the first dose (exposure measure includes AUC[TAU] and Cmax)
T-HALF	Terminal serum half-life if data permit

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

Table 9.5-2, Table 9.5-3, Table 9.5-4, and Table 9.5-5 list the sampling schedule to be followed for the assessment of PK. Detailed instructions for the PK blood collection, labeling, processing, storage, and shipping will be provided to the site in the procedure manual.

All predose samples should be taken within 30 minutes before the start of any dose infusion. On treatment PK samples are intended to be drawn relative to actual dosing days.

If a dose occurs on a different day within the cycle due to delays or minor schedule adjustments, PK samples should be adjusted accordingly. If it is known that a dose is going to be delayed, then the predose sample should be collected just prior to the delayed dose. However, if a predose sample is collected but the dose is subsequently delayed, then an additional predose sample should not be collected. Following consensus of the Investigator and the BMS Medical Monitor (or designee), a PK and ADA sample may be taken in the event of a Grade 3+ infusion reaction or hypersensitivity reaction using an 'Event Kit - GR3+ INF RXN'.

Table 9.5-2: Pharmacokinetic and Anti-Drug Antibody (ADA) Sampling Schedule for BMS-986218 Q4W Monotherapy in Dose Escalation (Part 1A) and Dose Expansion (Part 2A and Part 2B)

Study Day of Sample Collection (1 cycle = 4 weeks)	Event	Time (relative to initiation of BMS-986218 dose) Hour:Minute	BMS-986218 Blood Sample	BMS-986218 ADA Samples
C1D1	Predose[a]	00:00	X	X
	EOI	See note[b]	X	
C1D2		24:00	X	
C1D8[c]		168:00	X	
C1D15[c]		336:00	X	
C1D22[c]		504:00	X	
C2D1	Predose[a]	00:00	X	X
	EOI	See note[b]	X	
C2D8[c]		168:00	X	
C3D1	Predose[a]	00:00	X	X
	EOI	See note[b]	X	
C3D2		24:00	X	
C3D8[c]		168:00	X	
C3D15[c]		336:00	X	
C3D22[c]		504:00	X	
C4D1	Predose[a]	00:00	X	X
C5D1	Predose[a]	00:00	X	X

Table 9.5-2: Pharmacokinetic and Anti-Drug Antibody (ADA) Sampling Schedule for BMS-986218 Q4W Monotherapy in Dose Escalation (Part 1A) and Dose Expansion (Part 2A and Part 2B)

Study Day of Sample Collection (1 cycle = 4 weeks)	Event	Time (relative to initiation of BMS-986218 dose) Hour:Minute	BMS-986218 Blood Sample	BMS-986218 ADA Samples
Every fourth cycle after C5 until EOT (C9D1, C13D1, C17D1, etc. until EOT)	Predose[a]	00:00	X	X
EOT			X	X
30-day follow-up			X	X
60-day follow-up			X	X
100-day follow-up			X	X
Grade 3+ Infusion Reaction			X	X

[a] Predose: All predose samples should be taken prior to the start of the infusion.

[b] EOI PK should be collected when all the study drug has been infused. If a flush is administered to clear the IV lines of the drug and to ensure delivery of the entire drug dose, then draw the EOI PK sample within approximately 15 minutes after end of the flush. Do not draw EOI samples from the same IV access that the drug was administered. Refer to Table 7.3-1 for infusion duration. If the EOI is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.

[c] This sample may be collected ± 2 days from timepoint. The actual date and time of sampling must be recorded.

Abbreviations: C = cycle; D = day; EOI = end of infusion; IV = intravenous; PK = pharmacokinetic.

Table 9.5-3: Pharmacokinetic and Anti-Drug Antibody (ADA) Sampling Schedule for BMS-986218 Q2W Monotherapy in Dose Escalation (Part 1A)

Study Day of Sample Collection (1 cycle = 4 weeks)	Event	Time (relative to initiation of BMS-986218 dose) Hour:Minute	BMS-986218 Blood Sample	BMS-986218 ADA Samples
C1D1	Predose[a]	00:00	X	X
	EOI	See note[b]	X	
C1D2		24:00	X	
C1D8[c]		168:00	X	
C1D15	Predose[a]	00:00	X	
	EOI	See note[b]	X	
C1D16		24:00	X	
C1D22[c]		168:00	X	
C2D1	Predose[a]	00:00	X	X
	EOI	See note[b]	X	
C2D8[c]		168:00	X	
C2D15	Predose[a]	00:00	X	
	EOI	See note[b]	X	
C3D1	Predose[a]	00:00	X	X
	EOI	See note[b]	X	
C3D2		24:00	X	
C3D8[c]		168:00	X	
C3D15[c]	Predose[a]	00:00	X	
	EOI	See note[b]	X	
C3D16		24:00	X	
C3D22[c]		168:00	X	
C4D1	Predose[a]	00:00	X	X
C5D1	Predose[a]	00:00	X	X
Every fourth cycle after C5 until EOT (C9D1, C13D1, C17D1, etc. until EOT)	Predose[a]	00:00	X	X
EOT			X	X
30-day follow-up			X	X

Table 9.5-3: Pharmacokinetic and Anti-Drug Antibody (ADA) Sampling Schedule for BMS-986218 Q2W Monotherapy in Dose Escalation (Part 1A)

Study Day of Sample Collection (1 cycle = 4 weeks)	Event	Time (relative to initiation of BMS-986218 dose) Hour:Minute	BMS-986218 Blood Sample	BMS-986218 ADA Samples
60-day follow-up			X	X
100-day follow-up			X	X
Grade 3+ Infusion Reaction			X	X

[a] Predose: All predose samples should be taken prior to the start of the infusion.

[b] EOI PK should be collected when all the study drug has been infused. If a flush is administered to clear the IV lines of the drug and to ensure delivery of the entire drug dose, then draw the EOI PK sample within approximately 15 minutes after end of the flush. Do not draw EOI samples from the same IV access that the drug was administered. Refer to Table 7.3-1 for infusion duration. If the EOI is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.

[c] This sample may be collected ± 2 days from timepoint. The actual date and time of sampling must be recorded.

Abbreviations: C = cycle; D = day EOI = end of infusion; IV = intravenous; PK = pharmacokinetic.

Table 9.5-4: Pharmacokinetic and Anti-Drug Antibody (ADA) Sampling Schedule for Ipilimumab Q3W Monotherapy in Dose Expansion (Part 2A)

Study Day of Sample Collection (1 cycle = 3 weeks)	Event	Time (relative to initiation of Ipilimumab dose) Hour:Minute	Ipilimumab Blood Sample	Ipilimumab ADA Samples
C1D1	Predose[a]	00:00	X	X
	EOI	See note[b]	X	
C2D1	Predose[a]	00:00	X	X
	EOI	See note[b]	X	
C3D1	Predose[a]	00:00	X	X
	EOI	See note[b]	X	
C4D1	Predose[a]	00:00	X	X
EOT			X	X
30-day follow-up			X	X
60-day follow-up			X	X
100-day follow-up			X	X
Grade 3+ Infusion Reaction			X	X

[a] Predose: All predose samples should be taken prior to the start of the infusion.

[b] EOI PK should be collected when all the study drug has been infused. If a flush is administered to clear the IV lines of the drug and to ensure delivery of the entire drug dose, then draw the EOI PK sample within approximately 15 minutes after end of the flush. Do not draw EOI samples from the same IV access that the drug was administered. Refer to Table 7.3-1 for infusion duration. If the EOI is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.

Abbreviations: C = cycle; D = day; EOI = end of infusion; IV = intravenous; PK = pharmacokinetic; Q3W = every 3 weeks.

Table 9.5-5: Pharmacokinetic and Anti-Drug Antibody (ADA) Sampling Schedule for BMS-986218 Q4W in Combination with Nivolumab Q4W in Dose Escalation (Part 1B) and Dose Expansions (Part 2C and Part 2D)

Study Day of Sample Collection (1 cycle = 4 weeks)	Event	Time (Relative to Initiation of BMS-986218 and Nivolumab Dose) Hour:Minute	BMS-986218 Blood Sample	Nivolumab Blood Sample	BMS-986218 ADA Samples	Nivolumab ADA Samples
C1D1	Predose[a]	00:00	X	X	X	X
	EOI	See note[b]	X	X		
C1D2		24:00	X			
C1D8[c]		168:00	X			
C1D15[c]		336:00	X			
C1D22[c]		504:00	X			
C2D1	Predose[a]	00:00	X	X	X	X
	EOI	See note[b]	X	X		
C2D8[c]		168:00	X	X		
C3D1	Predose[a]	00:00	X	X	X	X
	EOI	See note[b]	X	X		
C3D2		24:00	X			
C3D8[c]		168:00	X			
C3D15[c]		336:00	X			
C3D22[c]		504:00	X			
C4D1	Predose[a]	00:00	X	X	X	X
C5D1	Predose[a]	00:00	X	X	X	X
Every fourth cycle after C5 until EOT (C9D1, C13D1, C17D1, etc. until EOT)	Predose[a]	00:00	X	X	X	X
EOT			X	X	X	X
30-day follow-up			X	X	X	X
60-day follow-up			X	X	X	X
100-day follow-up			X	X	X	X
Grade 3+ Infusion Reaction			X	X	X	X

[a] Predose: All predose samples should be taken prior to the start of the infusion.

[b] EOI PK should be collected when all the study drug has been infused. If a flush is administered to clear the IV lines of the drug and to ensure delivery of the entire drug dose, then draw the EOI PK sample within approximately 15 minutes after end of the flush. Do not draw EOI samples from the same IV access that the drug was administered. Refer to Table 7.3-1 for infusion duration. Separate EOI samples should be collected following administration of

BMS-986218 and nivolumab and recorded with the same collection time. If the EOI is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.

[c] This sample may be collected ± 2 days from timepoint. The actual date and time of sampling must be recorded.

Abbreviations: C = cycle; CXDY = Cycle X Day Y, as an example; D = day; EOI = end of infusion; IV = intravenous; PK = pharmacokinetic.

9.6 Pharmacodynamics

[redacted]

9.7 Pharmacogenomics

Not applicable.

9.7.1 Absorption, Distribution, Metabolism, and Excretion Sampling

Not applicable.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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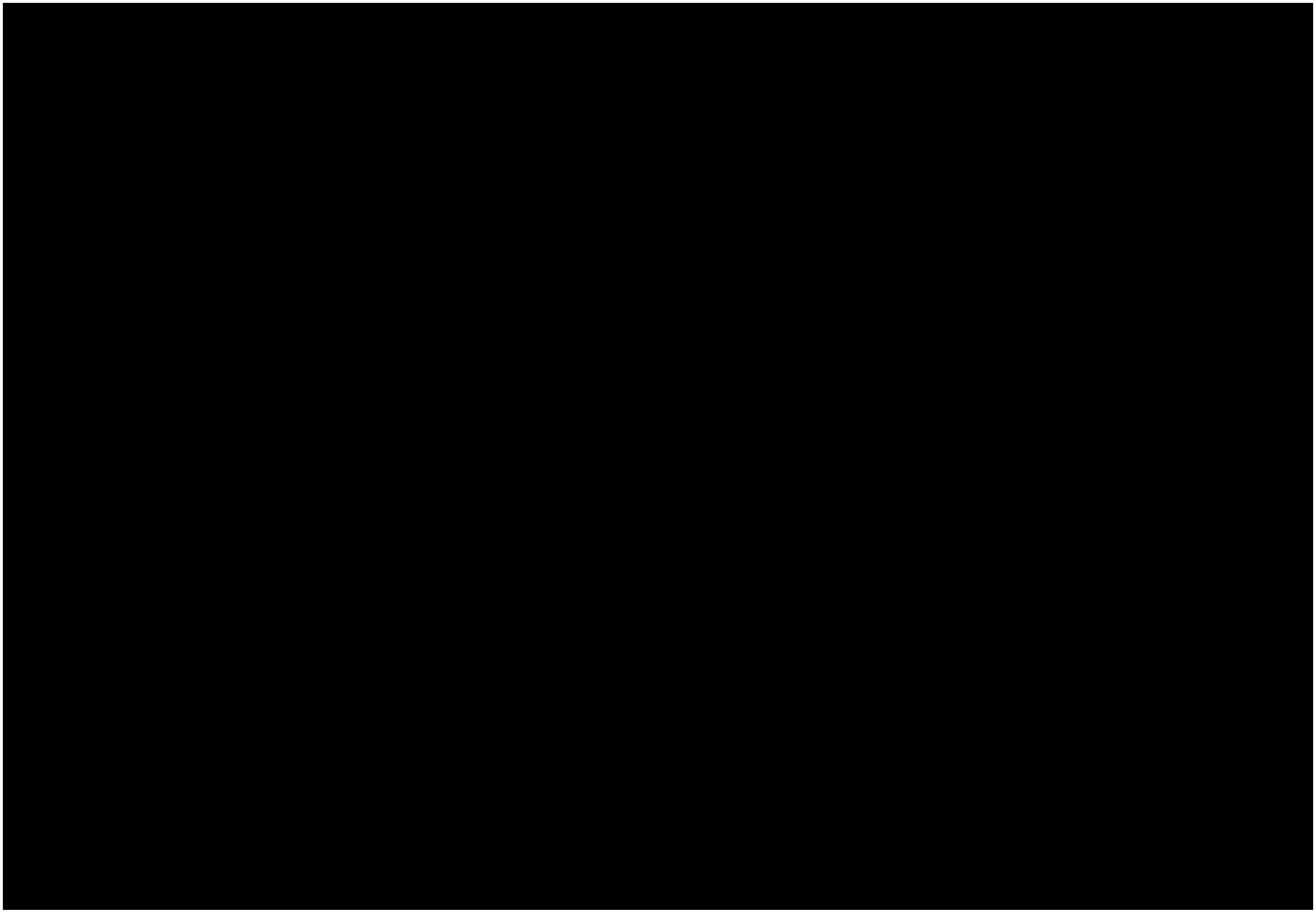

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[redacted]

9.10 Health Economics OR Medical Resource Utilization and Health Economics

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

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

10.1.1 Monotherapy Dose Escalation (Part 1A)

Dose escalation during the BMS-986218 Monotherapy Escalation (Part 1A) will be guided by BLRM employing the EWOC principle. The BLRM method is fully adaptive, makes use of all the information available at the time of each dose assignment, not just data from the current dose level, and directly addresses the ethical need to control the probability of overdosing. The targeted toxicity rate in this study is in the range of (16%, 33%). The use of the EWOC principle limits the risk of exposing patients in the next cohort to an intolerable dose by ensuring the posterior probability of the DLT rate at or exceeding 33% at any dose is capped at 35%.

In order to understand operational characteristics of the BLRM, the total maximum number of participants for the simulation will be set to 108. As indicated in Appendix 11, simulation studies with various scenarios show that the expected number of DLT-evaluable participants needed for BLRM is no more than approximately 29.

For the trial, approximately 3 participants will be treated at the starting dose levels of BMS-986218. While the BLRM will use DLT information from the DLT period only, clinical assessment will take into consideration of the totality of available data including PK/pharmacodynamics from all treated participants in assigning a dose level for the next cohort of 3 participants. At least 6 DLT-evaluable participants will be treated at the MTD. Without exceeding a total of 200 evaluable participants, across dose levels and schedules, additional

participants may be treated at any dose level below or at the estimated MTD for further evaluation of safety, PK, or pharmacodynamic parameters as required.

The model recommended MTD is the dose that satisfies the following 3 conditions:

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

The final recommended MTD/RP2D will be based on the recommendation from the BLRM and overall clinical assessment of all available safety, PK, pharmacodynamic, and efficacy data. Lower doses of BMS-986218 may be tested if none of the planned doses are found to be tolerable as monotherapy. Such decisions will be made after discussion and agreement between the Investigators and the BMS Medical Monitor (or designee).

In addition, in Part 1A PD cohort, approximately 20 evaluable participants will be treated with BMS-986218 Q2W or Q4W monotherapy. Evaluable participants for the PD cohort are participants with matching baseline [redacted] in order to evaluate PD changes, and additional safety and PK, in participants with advanced stage cutaneous melanoma, MSS CRC, NSCLC, or SCCHN. Assuming that the [redacted] interest is measured as a continuous variable, about 20 participants will be needed to provide ≥ 80% confidence that the estimate of the ratio of on-treatment to baseline values will be within 20% of the true value, assuming intra-subject variability of 49% at a specific dose level.

10.1.2 The Safety Evaluation of Combination Doses of BMS-986218 with Nivolumab (Part 1B)

In the Safety Evaluation Combination Doses of BMS-986218 with Nivolumab (Part 1B), the starting dose of BMS-986218 will be at least 1 dose level lower than the highest monotherapy dose level of BMS-986218 demonstrating an acceptable safety profile, and will be administered in combination with nivolumab at the flat dose of 480 mg Q4W. Dose escalation and determination of MTD for the Safety Evaluation of Combination Doses of BMS-986218 with Nivolumab (Part 1B) will be guided by BLRM-copula with EWOC principle. Subsequent dose selection of the combination will be based on evaluating the recommendation from BLRM-copula and an overall assessment of all available safety and PK/pharmacodynamic data. Safety evaluation and tumor assessment will be performed Q8W (2 cycles). BLRM-copula will incorporate historical information from ipilimumab and nivolumab studies and the DLT information from the DLT period from both combination arms to estimate dose-toxicity surface, and will provide guidance for dose adjustment of either drug as needed.

While guided by the BLRM-copula, clinical assessment will take into consideration of the totality of available data including PK/pharmacodynamic from all treated participants in assigning a dose level for the next cohort of 3 participants. Six to 12 DLT-evaluable participants will be treated at

each combination dose. Additional participants may be treated at any dose combination below or at the BLRM-copula recommended dose combination for further evaluation of safety, PK, or pharmacodynamic parameters as required. A combination with a higher dose level of either drug may be considered if recommended per BLRM-copula, after consideration of all available safety, and PK/pharmacodynamic data. At no time will the dose of BMS-986218 in the Safety Evaluation of Combination Doses of BMS-986218 with Nivolumab (Part 1B) exceed the highest tolerated dose in the BMS-986218 Monotherapy Escalation (Part 1A). Up to approximately 84 DLT-evaluable participants will be enrolled in Part 1B.

10.1.3 The Randomized BMS-986218 Monotherapy Cohort Expansion in Cutaneous Melanoma (Part 2A)

The primary purpose of the Randomized BMS-986218 Monotherapy Cohort Expansion in Cutaneous Melanoma (Part 2A) is to evaluate preliminary efficacy of BMS-986218 relative to ipilimumab 3 mg/kg. One hundred and thirty two response-evaluable participants will be randomized to BMS-986218 or ipilimumab evenly across study arms (eg, 33 participants to BMS-986218 at 7 mg Q4W; 33 participants to BMS-986218 at 20 mg Q4W; 33 participants to BMS-986218 at 70 mg Q4W; and 33 participants to ipilimumab) and stratified by the outcome (ie, progressed, relapsed) of previous anti-PD-1/PD-L1 immunotherapy. Additional response-evaluable participants may be randomized to further evaluate emerging data or subgroups of interest if needed but not to exceed 40 response-evaluable participants per arm. If additional participants are randomized, up to 160 response-evaluable participants (= 40 participants × 4 arms) may be randomized in Part 2A. The ORR of ipilimumab will serve as a control. With 33 treated participants in each BMS-986218 arm, the lower limit of the 1-sided 80% confidence interval for ORR difference from ipilimumab arm will be 12%, 7.3%, or 2.7%, assuming effect size of 20%, 15%, or 10%, respectively.

Although the above assumptions on the response rate were used for the purpose of sample size calculation, it should be noted that, to date, there are no anti-tumor response data available in this post anti-PD-1/PD-L1 population. The efficacy evaluation criteria may evolve by the time when the tumor data from this study are matured for evaluation.

10.1.4 The BMS-986218 Cohort Expansion - Monotherapy (Part 2B)

The purpose of the BMS-986218 Cohort Expansion - Monotherapy (Part 2B) is to gather additional safety, tolerability, preliminary efficacy as monotherapy, PK, and pharmacodynamic information. However, the sample size calculation will be based on the ORR.

The preliminary efficacy of BMS-986218 as a monotherapy in solid tumors, including NSCLC, in participants who have received, and then progressed on, relapsed, or have been intolerant to, at least 2 standard systemic therapies with proven survival benefit according to their tumor types for metastatic and/or unresectable disease will be evaluated. Sixty-six response-evaluable participants will be randomized evenly across study arms (eg, 22 participants to BMS-986218 at 7 mg Q4W; 22 participants to BMS-986218 at 20 mg Q4W; and 22 participants to BMS-986218 at 70 mg Q4W). Additional response-evaluable participants may be randomized to further evaluate emerging data or subgroups of interest if needed but not to exceed a total of 40 response-evaluable

participants per arm. If additional participants are randomized, up to 120 response-evaluable participants (= 40 participants × 3 arms) may be randomized in Part 2B.

With 22 treated participants in each BMS-986218 arm, the lower limit of the 2-sided 80% Clopper Pearson confidence interval for ORR estimate will be 8.2%, 5.1%, or 2.4%, assuming ORR estimate size of 18%, 13.6%, or 9.1%, respectively.

10.1.5 The BMS-986218 Combination-Therapy Cohort Expansion in NSCLC (Part 2C)

The purpose of the BMS-986218 Cohort Expansion - Combination Therapy (Part 2C) is to gather additional data including safety, tolerability, preliminary efficacy as combination therapy of BMS-986218 with nivolumab, in NSCLC. The sample size calculation will be based on the ORR.

Approximately 40 response-evaluable participants will be treated. Initial evaluation of efficacy signal (ORR) will be based on approximately the first 20 response-evaluable participants at a dose level, will be descriptive based on a point estimate and an 80% Clopper Pearson CI for ORR. In order for an 80% CI to exclude a 5.5% ORR (as reported for ipilimumab with nivolumab in similar population), at least 3 responders (15% ORR) will need to be observed in the first 20 participants evaluated at this dose. If 4 responders are observed (20% ORR), the 80% confidence interval will equal (9.0%, 36.1%). Based on the results of this initial evaluation, additional participants for a total of up to 40 participants may be treated at a dose level.

Furthermore, if 40 participants are evaluated at a dose level, there will be approximately 80% power to detect a difference between the null hypothesis assuming ORR of 5.5% and the alternative assuming ORR of 15%, based on a one group $\chi 2$ test with a 0.10 one-sided significance alpha level. If more than one dose level is evaluated, up to 80 response-evaluable participants (= 40 participants × 2 arms) may be treated.

10.1.6 The BMS-986218 Combination-Therapy Cohort Expansion in MSS CRC (Part 2D)

The purpose of the BMS-986218 Cohort Expansion - Combination Therapy (Part 2D) is to gather additional data including safety, tolerability, preliminary efficacy as combination therapy of BMS-986218 in combination with nivolumab, in participants with MSS CRC. The sample size calculation will be based on the ORR.

Approximately 40 response-evaluable participants will be treated in Part 2D, with the goal of treating approximately 20 participants each with either mutation or wild-type with respect to extended RAS status. As response to immunotherapy may differ substantially based on tumor genomics, ORR will be analyzed separately for participants with mutation and participants with wild-type.

With 20 treated participants with either mutation or wild-type, the lower limit of the 2-sided 80% Clopper Pearson confidence interval for ORR estimate will be 9%, 5.6%, or 2.7%, assuming ORR estimate size of 20%, 15%, or 10%, respectively.

10.2 Populations for Analyses

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

Table 10.2-1: Population for Analyses

Population	Description
Enrolled	All participants who sign informed consent and are registered into the IRT
Treated	All participants who take at least 1 dose of study treatment
Randomized	All participants who were randomized to study drug (Parts 2A or 2B)
Response-evaluable	All treated participants with measurable disease at baseline and 1 of the following: (a) at least 1 post baseline tumor assessment, (b) clinical progression, (c) death
Pharmacokinetic	All treated participants who have evaluable concentration-time data
Immunogenicity	All treated participants who have baseline and at least 1 post baseline pre-infusion immunogenicity assessment
[redacted]	

10.3 Statistical Analyses

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

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

10.3.1 Efficacy Analyses

The primary efficacy analyses (Table 10.3.1-1) will be performed on the randomized population in Parts 2A, and 2B, and on all treated participants in Part 1A, Part 1B, Part 2C, and Part 2D, for the final analysis. Supplemental analysis on All treated population may be provided in Parts 2A and 2B; Efficacy analyses based on the response-evaluable population may be performed for interim analyses when the minimum follow-up period is less than sufficient to warrant adequate interpretation of the result. Details of the censoring scheme on time-to-event endpoints such as DOR, progression-free survival rate (PFSR), PID, and overall survival rate (OSR) will be described in the Statistical Analysis Plan.

Table 10.3.1-1: Efficacy - Statistical Analyses

Endpoint	Statistical Analysis Methods
ORR is defined as the proportion of all treated participants whose BOR is either CR or PR by Investigator per RECIST v1.1 or per PCWG 3 criteria for prostate. BOR for a participant will be assessed per RECIST v1.1 by Investigator, unless otherwise specified.	Estimate of ORR and corresponding 2-sided exact 95% CI using the Clopper-Pearson method by treatment for each tumor type. For part 2A, estimate of difference in ORR between arms (using ipilimumab as reference) and corresponding 2-sided exact 95% CI using the Clopper-Pearson method by BMS treatment arms.
Median DOR DOR for a participant with a BOR of CR or PR is defined as the time between the date of first response and the date of the first objectively documented tumor progression per RECIST v1.1 or per PCWG 3 criteria for prostate, or death, whichever occurs first.	Estimate by the Kaplan-Meier method and corresponding 2-sided 95% CI using Brookmeyer and Crowley methodology (using log-log transformation) by treatment for each tumor type.
PFSR at 24, 36, and 48 weeks PFS for a participant is defined as the time from the first dosing date to the date of first objectively documented disease progression or death due to any cause, whichever occurs first.	Estimate PFSR by the Kaplan-Meier method and corresponding 2-sided 95% CI using Greenwood formula by treatment for each tumor type. For part 2A, estimate difference in PFSR between arms (using ipilimumab as reference) by the Kaplan-Meier method and corresponding 2-sided 95% CI using Greenwood formula by BMS treatment arms. Estimate median PFS by the Kaplan-Meier method and corresponding 2-sided 95% CI using Greenwood formula by treatment for each tumor type.

Abbreviations: BOR = best overall response; BMS = Bristol Myers Squibb; CI = confidence interval; CR = complete response; DOR = duration of response; ORR = objective response rate; PCWG 3 = Prostate Cancer Working Group; PFSR = progression-free survival rate; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors.

10.3.2 Safety Analyses

All safety analyses will be performed on the treated population.

Table 10.3.2-1: Safety - Statistical Analyses

Endpoint	Statistical Analysis Methods
Incidence of DLTs, AEs, SAEs, AEs leading to discontinuation, and death. AEs will be graded according to CTCAE v4.03.	DLT rate by dose level, frequency distribution of treated participants with AE using the worst CTC grade. Participants will only be counted (1) once at the PT level, (2) once at the system organ class level, and (3) once in the 'total participant' row at their worst CTC grade, regardless of system organ class or PT.
Toxicity Changes from Baseline. Laboratory values will be graded according to CTCAE v4.03.	Laboratory shift table using the worst CTC grade on-treatment per participant.

Abbreviations: CTC = common terminology criteria; PT = preferred term.

10.3.3 Pharmacokinetic Analysis for BMS-986218

Table 10.3.3-1: Pharmacokinetic - Statistical Analyses

Endpoint	Statistical Analysis Methods
Cmax, AUC(0-T), AUC(TAU), Ctau, CLT, Css-avg, AI_Cmax, AI_AUC, and T-HALF	Summary statistics: geometric means and coefficients of variation
Cmax, AUC(0-T), AUC(TAU)	Scatter plots vs dose for each cycle measured; dose proportionality based on a power model and a CI around the power coefficient
Tmax	Summary statistics: medians and ranges
Ctrough	Summary statistics to assess attainment of steady state: geometric means and coefficients of variation, by treatment and by day; plots vs time by dose

Abbreviations: AI_AUC = ratio of an exposure measure at steady state to that after the first dose (exposure measure includes AUC[TAU]); AI_Cmax = ratio of an exposure measure at steady state to that after the first dose (exposure measure includes Cmax); AUC(0-T) = area under the plasma serum concentration-time curve from time zero to time of last quantifiable concentration (may be calculated if concentrations are not quantifiable up to TAU across a treatment group); AUC(TAU) = area under the serum concentration-time curve in 1 dosing interval; CLT = total body clearance; Css-avg = average serum concentration over a dosing interval (AUC[TAU]/tau) at steady state; Ctau = observed serum concentration at the end of a dosing interval; Ctrough = trough observed serum concentrations (this includes predose concentrations [C0] and Ctau); T-HALF = terminal serum half-life; Tmax = time of maximum observed plasma serum concentration.

PK serum concentration-time data for BMS-986218, ipilimumab, and/or nivolumab may be pooled with data from other studies for integrated population PK and ER analyses, which will be presented in a separate report.

10.3.4 Immunogenicity

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

[a] Baseline sample is the last sample before initiation of the treatment.

[b] Details of the immunogenicity data analysis, including ADA titers, will be provided in the Statistical Analysis Plan.

[redacted]

[redacted]

10.3.9 Interim Analyses

Interim analyses will be performed for administrative purposes, internal decisions, or publications and they will be descriptive. No formal inferences requiring any adjustment to statistical significance level will be performed.

Preliminary efficacy may be assessed for Part 2 to determine an initial signal, and enrollment may be paused, prior to enrolling additional participants. Depending on enrollment rate and preliminary data there may not be a pause in enrollment. If an inadequate signal is detected from a preliminary analysis, then enrollment may be closed for that cohort.

11 REFERENCES

[1] Zitvogel L, Tesniere A, Kroemer G. Cancer despite immunosurveillance: immunoselection and immunosubversion. Nat Rev Immunol 2006;6:715-27.

[2] Dunn GP, Bruce AT, Ikeda H, et al. Cancer immunoediting: from immunosurveillance to tumor escape. Nat Immunol 2002;3:991-8.

[3] Greenwald RJ, Freeman GJ, Sharpe AH. The B7 family revisited. Annu Rev Immunol 2004;23:515-48.

[4] Selby MJ, Engelhardt JJ, Quigley M, et al. Anti-CTLA-4 antibodies of IgG2a isotype enhance antitumor activity through reduction of intratumoral regulatory T cells. Cancer Immunol Res 2013;1:32-42.

[5] Simpson TR, Li F, Montalvo-Ortiz W, et al. Fc-dependent depletion of tumor-infiltrating regulatory T cells co-defines the efficacy of anti-CTLA-4therapy against melanoma. J Exp Med 2013;210:1695-710.

[6] BMS-986218; Investigator Brochure Version 3. Bristol-Myers Squibb Company; 2019. Document Control No. 930110515.

[7] Leach DR, Krummel MF, Allison JP. Enhancement of antitumor immunity by CTLA-4 blockade. Science 1996;271:1734-6.

[8] Leabman MK, Meng YG, Kelley RF, et al. Effects of altered FcγR binding on antibody pharmacokinetics in cynomolgus monkeys. MAbs 2013;5(6):896-903.

[9] Feng Y, Masson E, Dai D, et al. Model-based clinical pharmacology profiling of ipilimumab in patients with advanced melanoma. Br J Clin Pharmacol 2014;78(1):106-17.

[10] Physicochemical Characterization of MDX-010 (Study MDX-010-011-R); Report. Medarex Inc.; 18-Jan-2007. Document Control No. 930020111.

[11] Ipilimumab Toxicology Written Summary. Bristol-Myers Squibb Company; 2010. Document Control No. 930043843.

[12] BMS-986218: One-Month Intermittent-Dose (QW) Intravenous Toxicity Study in Monkeys with a 6-Week Recovery (Study DN16107); Report. Bristol-Myers Squibb Company; 2017. Document Control No. 930109559.

[13] Repeated-dose toxicity study of anti-CTLA-4/10D1 administered via intravenous injection to cynomolgus monkeys (Study 126-002); Report. Redfield Laboratories; 2000. Document Control No. 930009967.

[14] A 2-week toxicity study of human anti-CTLA-4 administered by intravenous injection to cynomolgus monkeys (Study 0919-128); Report. Sierra Biomedical; 2000. Document Control No. 930009982.

[15] 14-day intravenous toxicity study with mAb 10D1 in cynomolgus monkeys (Study 7114-100); Report. Covance Laboratories; 2000. Document Control No. 930009970.

[16] BMS-663513 and BMS-734016: One-month intravenous combination toxicity study in monkeys (Study DS06064); Report. Bristol-Myers Squibb Company; 2007. Document Control No. 930021064.

[17] A repeated dose toxicity and efficacy study of MDX-010 or MDX-010-HYB in combination with HBsAg and SKMel vaccines in cynomolgus monkeys (Study 1416-128); Report. Sierra Biomedical; 2003. Document Control No. 930009973.

[18] An immunogenic study following combined intravenous/ intramuscular administration of MAb10D1/HBsAg, respectively, to cynomolgus monkeys (Study 0992-128); Report. Sierra Biomedical; 2001. Document Control No. 930009968.

[19] MDX-CTLA-4: A 6-month intravenous toxicity study in cynomolgus monkeys (Study 01-3460); Report. Huntingdon Life Sciences; 2002. Document Control No. 930009980.

[20] BMS-986218: In vitro cytokine release and lymphocyte activation assessment using whole blood in a soluble assay format (Study DN16263); Report. Bristol-Myers Squibb Company; 2017. Document Control No. 930110258.

[21] BMS-986218: In vitro cytokine release and lymphocyte activation assessment using human peripheral blood mononuclear cells (Study DN16149); Report. Bristol-Myers Squibb Company; 2017. Document Control No. 930109567.

[22] BMS-986012: Anti-fucosyl GM1 Investigator Brochure Version 02. Bristol-Myers Squibb Company; 2015. Document Control No. 930073880.

[23] BMS-663513 and Ipilimumab: Exploratory in vitro proliferation and cytokine release assessment using human peripheral-blood mononuclear cells. Study Report 930034490. Bristol-Myers Squibb Research and Development. 2009. Document Control No. 930034490.

[24] Effect of Combined MDX-1106 and Ipilimumab Treatment on Ex Vivo Cytokine Expression in Human Peripheral Blood Cells (Study MDX-1106/010-008-R), Report. Medarex, 2009. Document Control No. 930036361.

[25] Ipilimumab Summary of Clinical Safety. Bristol-Myers Squibb Company; 2010. Document Control No. 930028133.

[26] Nivolumab (Opdivo) US Prescribing Information. Bristol-Myers Squibb Company; Revised May 2016.

[27] Nivolumab (BMS-936558) Investigator Brochure Version 18. Bristol-Myers Squibb Company; 2019. Document Control No. 930038243.

[28] Note for guidance on nonclinical evaluation for anticancer pharmaceuticals EMEA/CHMP/ICH/646107/2008.

[29] Ipilimumab (BMS-734016, MDX0110) Investigator Brochure Version 22. Bristol-Myers Squibb Company; 2019. Document Control No. 930017531.

[30] Sharma P, Allison JP. The future of immune checkpoint therapy. Science 2015;348(6230):56-61.

[31] Restifo NP, Smyth MJ, Snyder A. Acquired resistance to immunotherapy and future challenges. Nat Rev Cancer 2016;16(2):121-6.

[32] Ngiow SF, Young A, Jazquelot N, et al. A threshold level of intratumor CD8+ T-cell PD-1 expression dictates therapeutic response to anti-PD-1. Cancer Res 2015;75(18):3800-11.

[33] Koyama S, Akbay EA, Li YY, et al. Adaptive resistance to therapeutic PD-1 blockade is associated with upregulation of alternative immune checkpoints. Nat Commun 2016;7:10501.

[34] Hugo W, Zaretsky JM, Sun L, et al. Genomic and transcriptomic features of response to anti-PD-1 therapy in metastatic melanoma. Cell 2016;165(1):35-44.

[35] 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. Oral presentation presented at: American Association for Cancer Research (AACR) Annual Meeting; April 1-5, 2017; Washington, DC, USA.

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

[37] Spigel DR, et al. Randomized results of continuous vs 1-year fixed-duration in patients with advanced non-small cell lung cancer. Oral presentation at the European Society of Medical Oncology Annual Meeting. 2017 Sep 8-12; Madrid, Spain. Abstract 1297O.

[38] Bates GJ, Fox SB, Han C, et al. Quantification of regulatory T cells enables the identification of high-risk breast cancer patients and those at risk of late relapse. J Clin Oncol 2006;24:5373-80.

[39] Merlo A, Casalini P, Carcangiu ML, et al. FOXP3 expression and overall survival in breast cancer. J Clin Oncol 2009;27:1746-52.

[40] Hiraoka N, Onozato K, Kosuge T, et al. Prevalence of FOXP3+ regulatory T cells increases during the progression of pancreatic ductal adenocarcinoma and its premalignant lesions. Clin. Cancer Res 2006;12:5423-34.

[41] Ino Y, Yamazaki-Itoh R, Shimada K, et al. Immune cell infiltration as an indicator of the immune microenvironment of pancreatic cancer. Br. J. Cancer 2013;108:914-923.

[42] BMS-986218: Binding Affinity for Human FcγRs by Surface Plasmon Resonance (Study Report BDX-010NF-006). Bristol Myers Squibb Company; 2017. Document Control No. 930105087.

[43] BMS-986218: Validation Report for the Quantification of BMS-986218 in Cynomolgus Monkey Serum by Chemiluminescence Enzyme-Linked Immunosorbent Assay (ELISA). Bristol-Myers Squibb Company; 2016. Document Control No. 930106252.

[44] Ipilimumab Population Pharmacokinetic and Exposure - Response Analyses in Previously Treated or Untreated Subjects with Advanced Melanoma. Bristol-Myers Squibb Company; 2014. Document Control No. 930082362.

[45] Stebbings R, Eastwood D, Poole S, et al. After TGN1412: Recent developments in cytokine release assays. J of Immunotoxicology 2013;10(1):75–82.

[46] Saber H, Gudi R, Manning M, et al. An FDA oncology analysis of immune activating products and first-in-human dose selection. Reg Tox and Pharm 2016;81:448-456.

[47] BMS-986218: In Vitro Fc Effector Function of BMS-986218, (Study BDX-010NF-005). Bristol-Myers Squibb Company; 2017. Document Control No.930109701.

[48] BMS-986218: Evaluation of BMS-986218 in Functional Assays (Study BDX-1804-004). Bristol-Myers Squibb Company; 2016. Document Control No. 930109403.

[49] Wang DD, Zhang S, Zhao H, et al. Fixed dosing versus body size-based dosing of monoclonal antibodies in adult clinical trials. J Clin Pharmacol 2009;49(9):1012-1024.

[50] Bai S, Jorga K, Xin Y, et al. A guide to rational dosing of monoclonal antibodies. Clin Pharmacokinet 2012;51(2):119-135.

[51] Momtaz P, Park V, Panageas KS, et al. Safety of infusing ipilimumab over 30-minutes. J Clin Oncol 2015;33(30):3454-3458.

[52] Waterhouse D, Horn L, Reynolds C, et al. Safety Profile of Nivolumab Administered as 30-Minute Infusion: Analysis of Data from CheckMate 153. ASCO poster #3059.

[redacted]

12. APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
Ab	antibody
ADA	anti-drug antibody
ADCC	antibody-dependent cellular cytotoxicity
AE	adverse event
AI	accumulation index
AI_AUC	accumulation index ratio of AUC at steady state to that after the first dose
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC(0-xh)	area under the concentration-time curve from time zero to x hours
AUC(0-T)	area under the concentration-time curve from time zero to the time of the last quantifiable concentration
AUC(TAU)	area under the concentration-time curve in 1 dosing interval
Avg	average
BLRM	Bayesian Logistic Regression Model
BMS	Bristol-Myers Squibb
BOR	best overall response
BRAF	v-raf murine sarcoma viral oncogene homolog B1
BUN	blood urea nitrogen
C	cycle
Cavg	average concentration
Cavgss	average steady state concentration
CD	cluster differentiation
cHL	classical Hodgkin Lymphoma
CI	confidence interval
CL	clearance
CLT	total body clearance

Term	Definition
CLTp	total plasma clearance
Cmax	maximum observed plasma concentration
CNS	central nervous system
COVID-19	Coronavirus Disease 2019
CR	complete response
CRC	colorectal cancer
CrCl	creatinine clearance
CRF	case report form
Css-avg	average concentration over a dosing interval (AUC[TAU]/tau) at steady state
CT	computed tomography
CTAg	Clinical Trial Agreement
Ctau	observed concentration at the end of a dosing interval
CTC	common terminology criteria
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
Ctrough	trough observed plasma concentration
D	day
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
EAU_{50}	area-under-the-concentration-time curve producing 50% of the maximum effect
EC50	concentration required for 50% efficacy
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EGFR	epidermal growth factor receptor
EMAX	maximum effect
EOI	end of infusion
[redacted]	[redacted]

Term	Definition
[redacted]	
EOT	end of treatment
[redacted]	[redacted]
ER	exposure response
EWOC	escalation with overdose control
FcR	Fc receptor
FDA	Food and Drug Administration
FDG	2-deoxy-2-[^{18}F]fluoro-D-glucose
[redacted]	[redacted]
FIH	first-in-human
FNR	false negative rate
FPR	false positive rate
FSH	Follicle stimulating hormone
GI	gastrointestinal
GE	gastroesophageal
GnRH	gonadotropin-releasing hormone
HCC	hepatocellular carcinoma
hCG	human chorionic gonadotropin
hIgG1	human immunoglobulin G1
HIV	human immunodeficiency virus
HNSTD	highest non-severely toxic dose
[redacted]	[redacted]
IB	Investigator Brochure
ICF	informed consent form
IFN-γ	interferon gamma
Ig	immunoglobulin
[redacted]	[redacted]
[redacted]	[redacted]
IL	interleukin

Term	Definition
IMP	investigational medicinal product
IND	Investigational New Drug
I-O	immuno-oncology
IP	investigational product
IPRES	Innate PD-1 RESistance
irAE	immune-related adverse event
IRR	infusion-related reaction
IRT	Interactive Response Technology
IV	intravenous
Kd	constant of dissociation
KRAS	Kirsten rat sarcoma viral oncogene homolog
LHRH	luteinizing hormone releasing hormone
mAb	monoclonal antibody
MAP	meta-analytic predictive
mCRPC	metastatic castration-resistant prostate cancer
mDOR	median duration of response
[redacted]	[redacted]
[redacted]	[redacted]
MRI	magnetic resonance imaging
MSS	microsatellite stable
[redacted]	[redacted]
MTD	maximum tolerated dose
NF	non-fucosylated
NK	natural killer (cell)
NRAS	neuroblastoma rat viral oncogene homolog
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
OSR	overall survival rate
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction

Term	Definition
PCWG 3	Prostate Cancer Working Group 3
PD	pharmacodynamic
PD-1	programmed cell death 1
PDAC	pancreatic ductal adenocarcinoma
PD-L1	programmed death ligand 1
PD-L2	programmed death ligand 2
p-DILI	potential drug-induced liver injury
PE	physical examination
PET	positron emission tomography
PrEE	probability of early efficacy
PrET	probability of early termination
PFS	progression-free survival
PFSR	progression-free survival rate
PI	prediction interval
PID	patient identification number
PK	pharmacokinetic/s
PPK	population pharmacokinetics
PR	partial response
[redacted]	[redacted]
PT	preferred term
Q2W	every 2 weeks
Q3W	every 3 weeks
Q4W	every 4 weeks
Q8W	every 8 weeks
Q12W	every 12 weeks
[redacted]	[redacted]
[redacted]	[redacted]
QTcF	QT interval corrected for heart rate using Fridericia's formula
RAS	rat sarcoma
RCC	renal cell carcinoma

Term	Definition
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
[redacted]	[redacted]
RP2D	recommended Phase 2 dose
RP2D-1	1 dose level below the recommended Phase 2 dose of BMS 986218
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
[redacted]	[redacted]
SCC	squamous cell carcinoma
SCCHN	squamous cell carcinoma of the head and neck
SD	stable disease
SMT	Safety Management Team
[redacted]	[redacted]
SPR	surface plasmon resonance
T3	triiodothyronine
T4	thyroxine
[redacted]	[redacted]
TGI	tumor growth inhibition
T-HALF	terminal serum half-life
Tmax	time of maximum observed concentration
TNBC	triple-negative breast cancer
TNF-α	tumor necrosis factor alpha
Treg	T-regulatory cell
TSH	thyroid stimulating hormone
ULN	upper limit of normal
US	United States
[redacted]	[redacted]
Vss	steady-state volume of distribution
WOCBP	women of childbearing potential

Term	Definition
WWPS	Worldwide Patient Safety

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

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

REGULATORY AND ETHICAL CONSIDERATIONS

GOOD CLINICAL PRACTICE

This study will be conducted in accordance with:

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

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

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

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

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

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

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

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

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

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

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

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

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

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

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

FINANCIAL DISCLOSURE

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

INFORMED CONSENT PROCESS

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

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

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

Investigators must:

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

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

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

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

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

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

SOURCE DOCUMENTS

The investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original and attributable, whether the data are hand written on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic

devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records (EMRs/EHRs), adverse event tracking/reporting, protocol required assessments, and/or drug accountability records).

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

STUDY TREATMENT RECORDS

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

If	Then
Supplied by BMS (or its vendors):	Records or logs must comply with applicable regulations and guidelines and should include: • amount received and placed in storage area • amount currently in storage area • label identification number or batch number • amount dispensed to and returned by each participant, including unique participant identifiers • amount transferred to another area/site for dispensing or storage • nonstudy disposition (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 SOPs/standards of the sourcing pharmacy.

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

CASE REPORT FORMS

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

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

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

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

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

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

MONITORING

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

Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and

requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

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

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

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities and promptly forward copies of inspection reports to 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, institution procedures, or for the period specified by BMS or designee, whichever is longer. The investigator (or head of the study site in Japan) must contact BMS prior to destroying any records associated with the study.

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

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

RETURN OF STUDY TREATMENT

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

If	Then
Study treatments supplied by BMS (including its vendors)	Any unused study treatments supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless study treatments containers must be immediately destroyed as required for safety or to meet local regulations (eg, cytotoxics or biologics). If study treatments will be returned, the return will be arranged by the responsible Study Monitor.

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

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

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor, must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

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

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

STUDY AND SITE START AND CLOSURE

The Sponsor/designee reserves the right to close the study site or to terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed. The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination. Reasons for the early closure of a study site by the Sponsor or investigator may include, but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local Health Authorities, the Sponsor's procedures, or GCP guidelines

- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

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

DISSEMINATION OF CLINICAL STUDY DATA

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

CLINICAL STUDY REPORT

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

For each CSR related to this protocol, the following criterion will be used to select the signatory investigator:

- Study steering committee chair or their designee

SCIENTIFIC PUBLICATIONS

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

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

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

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

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

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

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

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

ADVERSE EVENTS

Adverse Event Definition:

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

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

Events Meeting the AE Definition

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

Events NOT Meeting the AE Definition

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

DEFINITION OF SAE

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

SERIOUS ADVERSE EVENTS

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
Requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below) NOTE: The following hospitalizations are not considered SAEs in BMS clinical studies: • a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event) • elective surgery, planned prior to signing consent • admissions as per protocol for a planned medical/surgical procedure • routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy) • medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases • admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason) • admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)
Results in persistent or significant disability/incapacity
Is a congenital anomaly/birth defect
Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 9.2.8 for the definition of potential DILI.)

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

Any component of a study endpoint that is considered related to study therapy should be reported as SAE (e.g., death is an endpoint; if death occurred due to anaphylaxis, anaphylaxis must be reported).

EVALUATING AES AND SAES

Assessment of Causality

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

Follow-up of AEs and SAEs

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

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

All SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

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

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

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

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

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

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

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

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

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

Note: Females treated with hormone replacement therapy (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. Suggested guidelines for the duration of the washout periods for HRT tryes 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.

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

One of the highly effective methods of contraception listed below is required during study duration and until the end of relevant systemic exposure, defined as 3 months after the end of study treatment for monotherapy treatment with BMS-986218 or with monotherapy with ipilimumab, and 5 months after completion of combination therapy treatment with BMS-986218 and nivolumab.* Less than highly effective contraception methods are not acceptable.

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

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*[a]
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation. (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
• 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 (IUD)

- 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

A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP, and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

- Sexual abstinence

Sexual abstinence is considered a highly effective contraception only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

- Continuous abstinence must begin at least 30 days prior to initiation of study therapy.
- It is not necessary to use any other method of contraception when complete abstinence is elected.
- WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 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 participating in clinical studies.

[b] Hormonal contraception may be susceptible to interaction with the study drug, 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 7.9.1 PROHIBITED AND/OR RESTRICTED TREATMENTS of the protocol.

[c] IUSs are acceptable methods of contraception in the absence of definitive drug interaction studies or 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 7.9.1 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, symptothemral, post-ovulation methods) • Withdrawal (coitus interruptus) • Spermicide only • Lactation amenorrhea method (LAM)

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

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of pregnancy information and outcome of pregnancy on the pregnancy surveillance form is provided in Section 9.2.5 and the Appendix for Adverse Events and Serious Adverse Events Definitions and procedures for Evaluating, Follow-up and Reporting.

APPENDIX 5 RECIST 1.1 CRITERIA

1 ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

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

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable.

1.1 Measurable Lesions

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

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

1.2 Non-measurable Lesions

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

1.3 Special Considerations Regarding Lesion Measurability

1.3.1 Bone Lesions

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

1.3.2 Cystic Lesions

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor nonmeasurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above in Section 1.1. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

1.3.3 Lesions with Prior Local Treatment

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

1.4 Specifications by Methods of Measurements

1.4.1 Measurement of Lesions

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

1.4.2 Method of Assessment

The **same method of assessment and the same technique should be used** to characterize each identified and reported lesion at baseline and during follow-up. Unless the lesions being followed cannot be imaged, and are assessable only by clinical examination, imaging-based evaluation should always be done.

1.4.2.1 CT/MRI Scan

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

1.4.2.2 Chest X-ray

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

1.4.2.3 Clinical Examination

Lesions identified by clinical examination will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers. For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is

suggested. As previously noted, when lesions can be evaluated by both clinical examination and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

1.4.2.4 Ultrasound

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

1.4.2.5 Endoscopy, Laparoscopy

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

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

2.1 Target Lesions

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

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

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

2.1.1 Lymph Nodes

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

2.2 Non-target Lesions

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

3 TUMOR RESPONSE EVALUATION

3.1 Evaluation of Target Lesions

Complete Response (CR): **Disappearance of all target lesions.** Any pathological lymph nodes (whether target or non-target) must also have reduction in the short axis to < 10 mm.

Partial Response (PR): At least a **30% decrease in the sum of the diameters of target lesions**, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a **20% increase in the sum of the diameters of target lesions, taking as reference the *smallest sum on study*** (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an **absolute increase of at least 5 mm**. (*Note:* The appearance of 1 or more new lesions is also considered progression.)

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

3.1.1 Special Notes on the Assessment of Target Lesions

3.1.1.1 Lymph Nodes

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

3.1.1.2 Target Lesions That Become 'Too Small to Measure'

All lesions (nodal and nonnodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation. If the radiologist is able to provide an actual measurement, even if it is below 5 mm it should be recorded.

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

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

3.1.1.3 Target Lesions That Split or Coalesce on Treatment

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

3.2 Evaluation of Non-Target Lesions

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

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

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

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

3.2.1 Special Notes on Assessment of Non-Target Lesions

The concept of progression of non-target disease requires additional explanation.

3.2.1.1 When the Subject Also Has Measurable Disease

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

3.2.1.2 When the Subject Has Only Non-Measurable Disease

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

3.2.1.3 Tumor Markers

Tumor markers *alone* cannot be used to assess objective tumor responses. If markers are initially above the upper normal limit, however, they must normalize in order for a subject to be considered as having attained a CR.

3.3 New Lesions

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

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

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

3.3.1 FDG-PET Evaluation

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

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

4 RESPONSE CRITERIA

4.1 Timepoint Response

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

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

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

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

Abbreviation: NE =not evaluable

Missing Assessments and Not Evaluable Designation

When no imaging/measurement is done at all at a particular timepoint, the subject is **not evaluable** at that timepoint. If only a subset of lesion measurements are made at an assessment, the subject is also considered NE at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not have changed the assigned timepoint response.

4.1.1 Confirmation Scans

- **Verification of Response:** Confirmation of PR and CR is required at least 4 weeks following initial assessment to ensure responses identified are not the result of measurement error.

4.2 Best Overall Response: All Timepoints

The *best overall response* is determined once all the data for the subject are known. It is the best response recorded from the start of the study treatment until the date of objectively documented PD based on RECIST v1.1, taking into account any requirement for confirmation or the date of subsequent anti-cancer therapy, whichever occurs first in the study. The subject's best overall

response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

The best overall response is defined as the best response across all timepoints with subsequent confirmation. CR or PR may be claimed only if the criteria for each are met at a subsequent timepoint as specified in the protocol (generally 4 weeks later).

In this circumstance, the best overall response can be interpreted as specified in Table 4.2-1. When SD is believed to be best response, it must meet the protocol specified minimum time from baseline. Measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6 to 8 weeks) that is defined in the study protocol.

Table 4.2-1: Best Overall Response When Confirmation of CR and PR Is Required

Overall Response First Timepoint	Overall Response Subsequent Timepoint	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

[a] If a CR is truly met at the first timepoint, then any disease seen at a subsequent timepoint, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since the disease must have reappeared after CR). The best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may

be claimed when subsequent scans suggest small lesions were likely still present and in fact the subject had PR, not CR at the first timepoint. Under these circumstances, the original CR should be changed to PR and the best response is PR.

4.3 Duration of Response

4.3.1 Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or PD is objectively documented (taking as reference for PD the smallest measurements recorded on study).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

4.3.2 Duration of Stable Disease

SD is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

CR (Complete Remission)

The designation of CR requires all of the following:

1) Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms, if present before therapy.
   a) Typically FDG-avid lymphoma: in patients without a pre-treatment PET scan or if the pre-treatment PET scan was positive, a post-treatment residual mass of any size is permitted as long as it is PET negative.
   b) Variably FDG-avid lymphomas/FDG avidity unknown: in patients without a pre-treatment PET scan, or if a pre-treatment PET scan was negative, all lymph nodes and nodal masses must have regressed on CT scan to normal size (≤ 1.5 cm in their greatest transverse diameter for nodes > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their long axis and > 1.0 cm in their short axis before treatment must have decreased to ≤ 1.0 cm in their short axis after treatment.
2) The spleen and/or liver, if considered enlarged before therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies, and nodules related to lymphoma should disappear. However, determination of splenic involvement is not always reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma.
3) If the bone marrow was involved by lymphoma before treatment, the infiltrate must have cleared [redacted]. The [redacted] sample on which this determination is made must be adequate (with a goal of > 20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry, but demonstrates a small population of clonal lymphocytes by flow

cytometry, will be considered a CR until data become available demonstrating a clear difference in patient outcome.

PR (Partial Remission)

The designation of PR requires all of the following:

1) At least a 50% decrease in the sum of the product of the diameters (SPD) of up to 6 of the largest dominant nodes or nodal masses. These nodes or nodal masses should be selected according to all of the following: they should be clearly measurable in at least 2 perpendicular dimensions; if possible, they should be from disparate regions of the body; and they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
2) No increase should be observed in the size of other nodes, liver, or spleen.
3) Splenic and hepatic nodules must regress by ≥ 50% in their SPD or, for single nodules, in the greatest transverse diameter.
4) With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable, and no measurable disease should be present.
5) Bone marrow assessment is irrelevant for determination of a PR, if the sample was positive before treatment. However, if positive, the cell type should be specified (eg, large-cell lymphoma or small neoplastic B cells). Patients who achieve a CR by the above criteria but have persistent morphologic bone marrow involvement will be considered partial responders. When the bone marrow was involved before therapy and a clinical CR was achieved but with no bone marrow assessment after treatment, patients should be considered partial responders.
6) No new sites of disease should be observed.
7) FDG:
   a) Typically FDG-avid lymphoma: for patients without a pre-treatment PET scan or if the pre-treatment PET scan was positive, the post-treatment PET scan should be positive in at least 1 previously involved site.
   b) Variably FDG-avid lymphomas/FDG avidity unknown: for patients without a pre-treatment PET scan, or if a pre-treatment PET scan was negative, CT criteria should be used. In patients with follicular lymphoma or mantle-cell lymphoma, a PET scan is only indicated with 1 or at most 2 residual masses that have regressed by > 50% on CT; those with more than 2 residual lesions are unlikely to be PET negative and should be considered partial responders.

SD (Stable Disease)

1) The designation of SD requires all of the following: A patient is considered to have SD when he or she fails to attain the criteria needed for a CR or PR but does not fulfill those for PD (see Relapsed Disease [after CR]/PD [after PR, SD]).
2) Typically FDG-avid lymphomas: the PET should be positive at prior sites of disease with no new areas of involvement on the post-treatment CT or PET scan.

3) Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pre-treatment PET scan or if the pre-treatment PET was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.

PD: Relapsed Disease (after CR)/PD (after PR, SD)

Lymph nodes should be considered abnormal if the long axis is > 1.5 cm, regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if its short axis is > 1.0. Lymph nodes ≤ 1.0 × ≤ 1.0 cm will not be considered abnormal for relapse or progressive disease.

1) Appearance of any new lesion > 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or PD after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET scan without histologic confirmation.
2) At least a 50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (eg, splenic or hepatic nodules). To be considered PD, a lymph node with a diameter of the short axis of < 1.0 cm must increase by ≥ 50% and to a size of 1.5 × 1.5 cm or > 1.5 cm in the long axis.
3) At least a 50% increase in the longest diameter of any single previously identified node > 1 cm in its short axis.
4) Lesions should be PET positive if observed in a typical FDG-avid lymphoma or the lesion was PET positive before therapy, unless the lesion is too small to be detected with current PET systems (< 1.5 cm in its long axis by CT).

Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these assessments, the spleen is considered nodal disease. Disease that is only assessable by physical examination (eg, pleural effusions, bone lesions) will be recorded as present or absent only, unless, while an abnormality is still noted by imaging studies or physical examination, it is found to be histologically negative.

In clinical trials where PET is unavailable to the vast majority of participants, or where PET is not deemed necessary or appropriate for use (eg, a trial in patients with mucosa-associated lymphoid tissue lymphoma), response should be assessed as above, but only using CT scans. However, residual masses should not be assigned CRu status but should be considered a PR.

Reference: Cheson BD, Pfisner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol 2007;25:579-86.

APPENDIX 6 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 7 NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION

Heart failure is usually classified according to the severity of the patient's symptoms. The table below describes the most commonly used classification system, the New York Heart Association (NYHA) functional classification. It places patients in 1 of 4 categories based on how much they are limited during physical activity.

Class	Patient Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, or dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Class	Objective Assessment
A	No objective evidence of cardiovascular disease. No symptoms and no limitation in ordinary physical activity.
B	Objective evidence of minimal cardiovascular disease. Mild symptoms and slight limitation during ordinary activity. Comfortable at rest.
C	Objective evidence of moderately severe cardiovascular disease. Marked limitation in activity due to symptoms, even during less-than-ordinary activity. Comfortable only at rest.
D	Objective evidence of severe cardiovascular disease. Severe limitations. Experiences symptoms even while at rest.

APPENDIX 8 COUNTRY SPECIFIC REQUIREMENTS

Argentina, Czech Republic, France, Germany, Italy, Spain, and Any Other Countries Where Exclusion of HIV Positive Participants Is Locally Mandated

	Country-specific language
Section 9.1.4 Clinical Safety Laboratory Assessments, Table 9.1.4-1: Clinical Laboratory Assessments	Add "HIV" to the list of laboratory tests
Section 6.2 Exclusion Criteria, Exclusion criterion: 3), e), vii)	"Known human immunodeficiency virus (HIV) positive with an acquired immunodeficiency syndrome (AIDS) defining opportunistic infection within the last year, or a current CD4 count < 350 cells/uL. Participants with HIV are eligible if: they have received antiretroviral therapy (ART) for at least 4 weeks prior to treatment assignment as clinical indicated while enrolled on study; they continue on ART as clinically indicated while enrolled on study; CD4 counts and viral load are monitored per standard of care by a local health care provider" to be replaced with "Positive test for HIV." **Argentina Only:** "Positive human immunodeficiency virus (HIV) with an acquired immunodeficiency syndrome (AIDS) defining opportunistic infection within the last year, or a current CD4 count <350 cells/uL. Participants with HIV are eligible if: they have received antiretroviral therapy (ART) for at least 4 weeks prior to treatment assignment as clinically indicated while enrolled on study; they continue on ART as clinically indicated while enrolled on study; CD4 counts and viral load are monitored per standard of care by a local health care provider"

Norway contraception requirements:

	Country-specific language
Additional pregnancy testing information to Table 2-5	Pregnancy testing will continue beyond the 100 day follow-up visit until the end of the protocol-specified contraception requirement (ie, 5 months).

APPENDIX 9 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 10 MANAGEMENT ALGORITHMS FOR STUDIES UNDER CTCAE VERSION 4.0

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology agents and regimens.

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

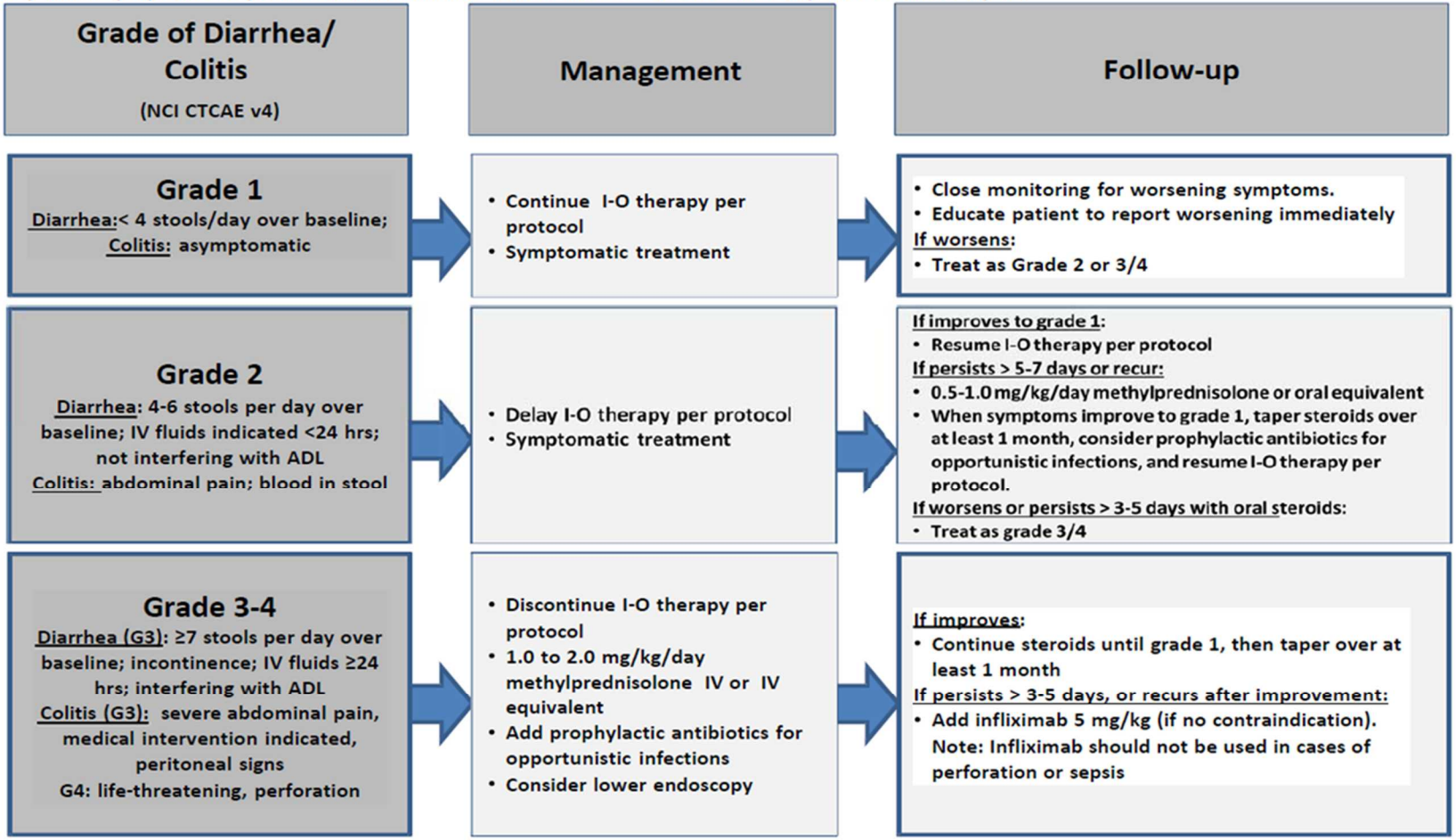
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

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

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

GI Adverse Event Management Algorithm

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

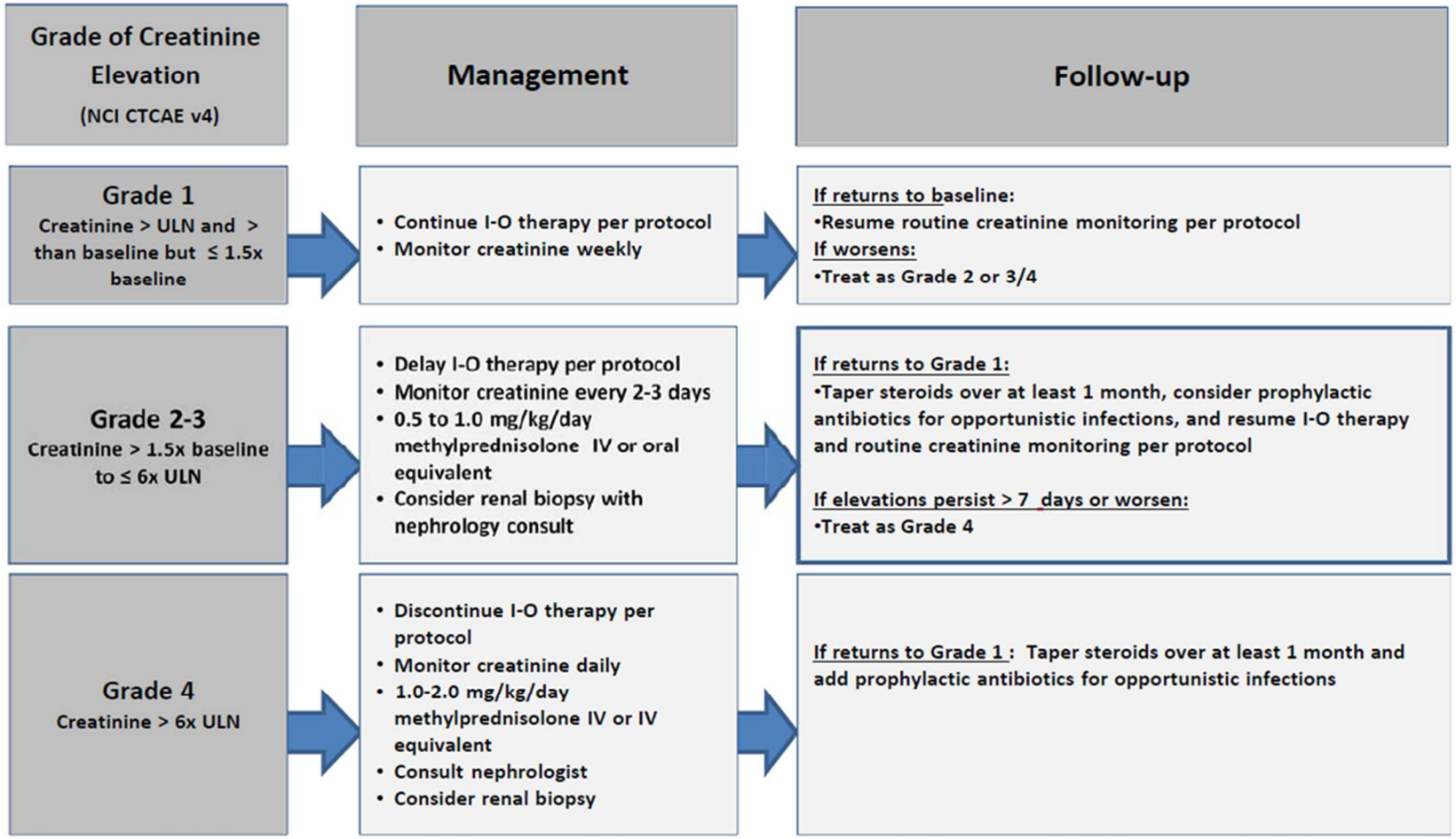


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

28-Sep-2020

Renal Adverse Event Management Algorithm

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

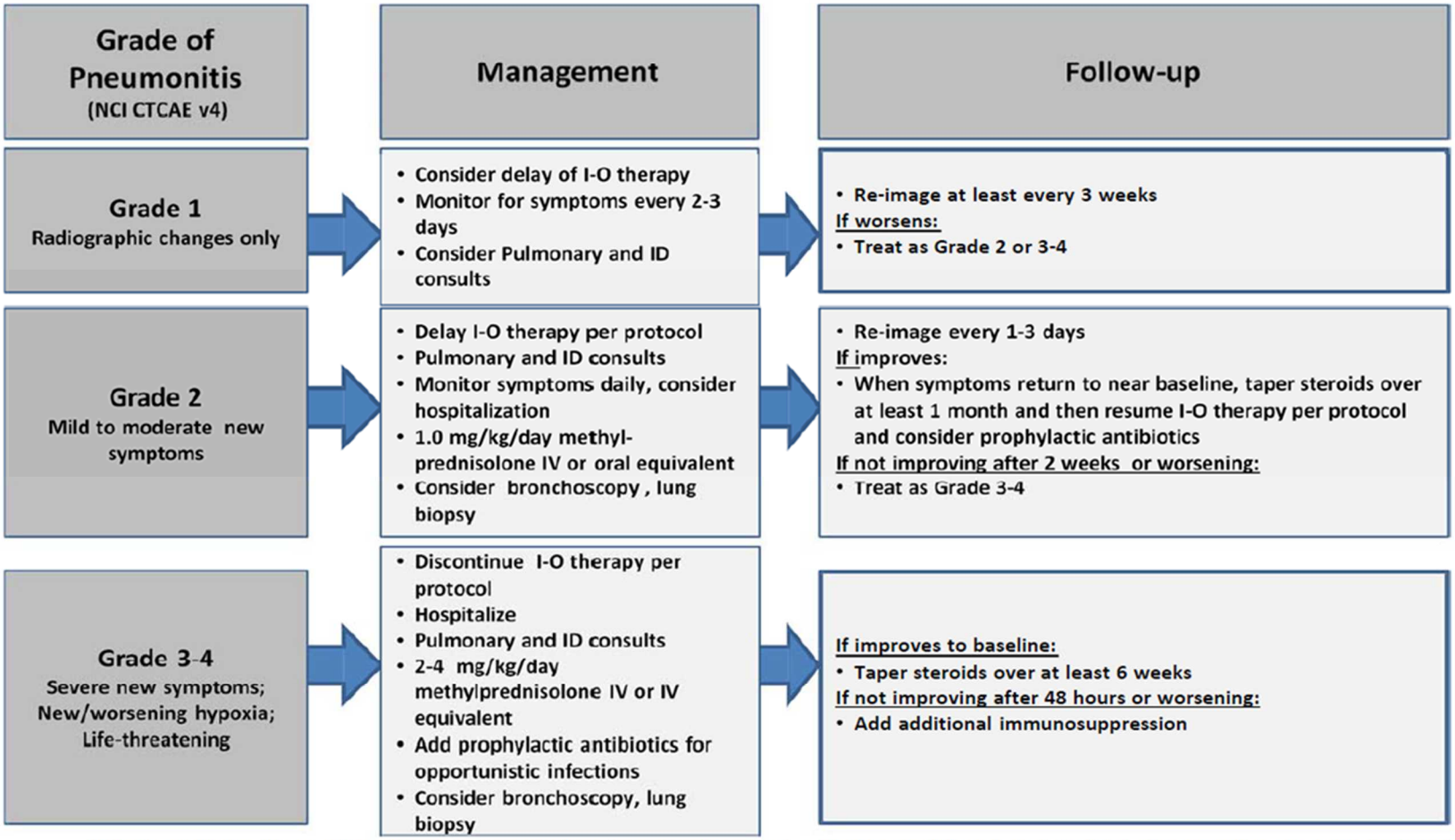


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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.

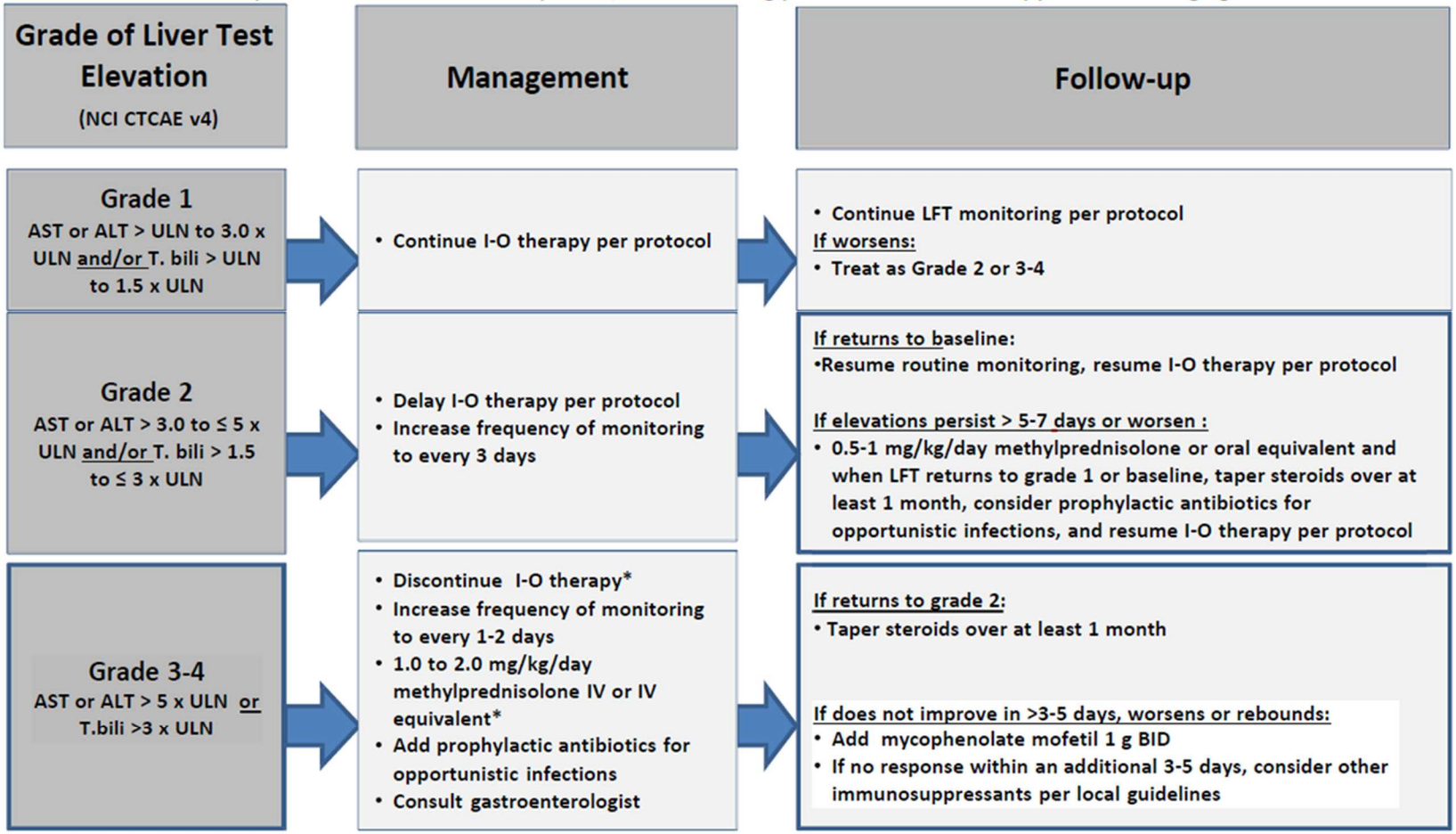


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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.



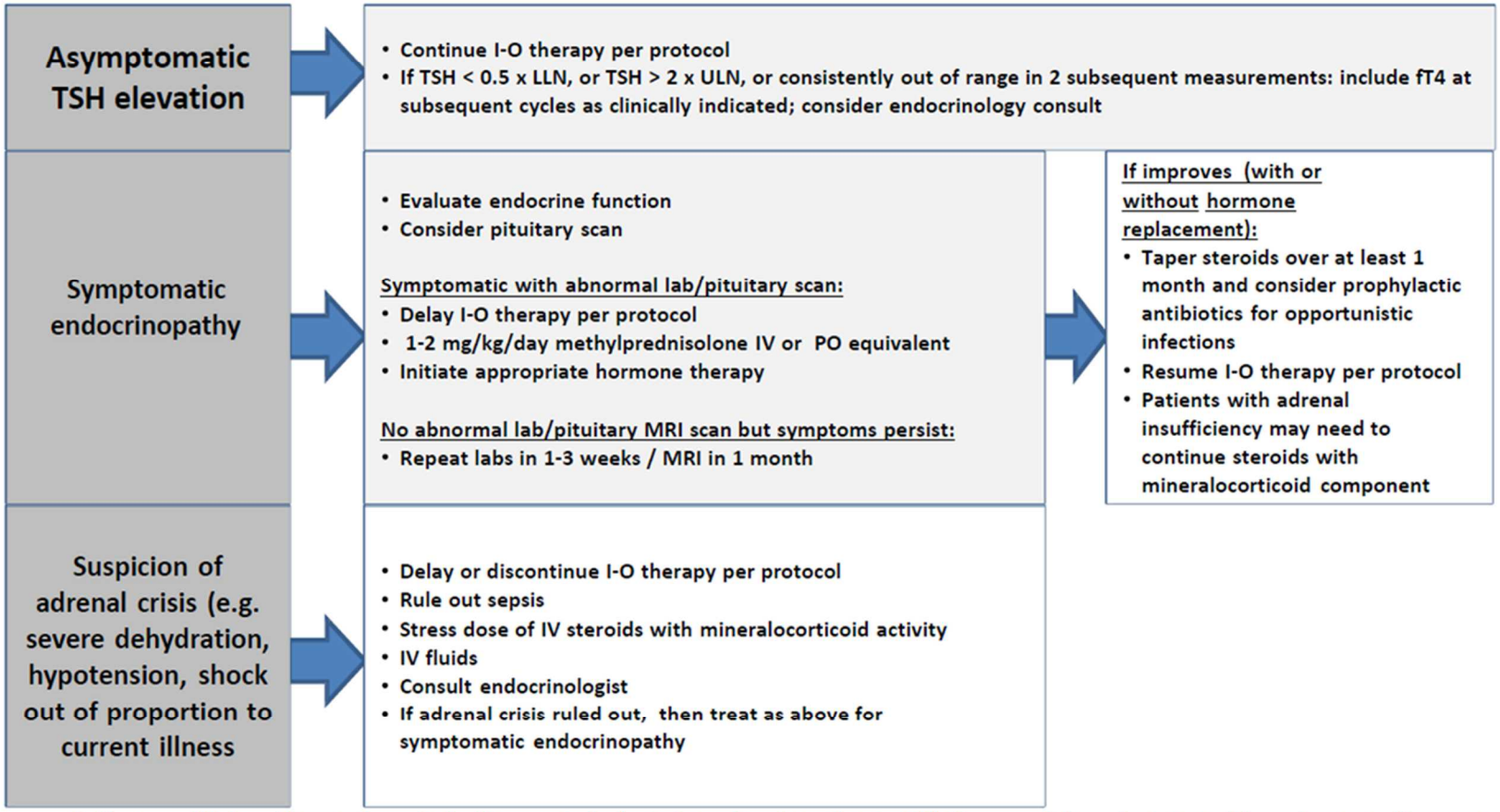
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

*The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

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.

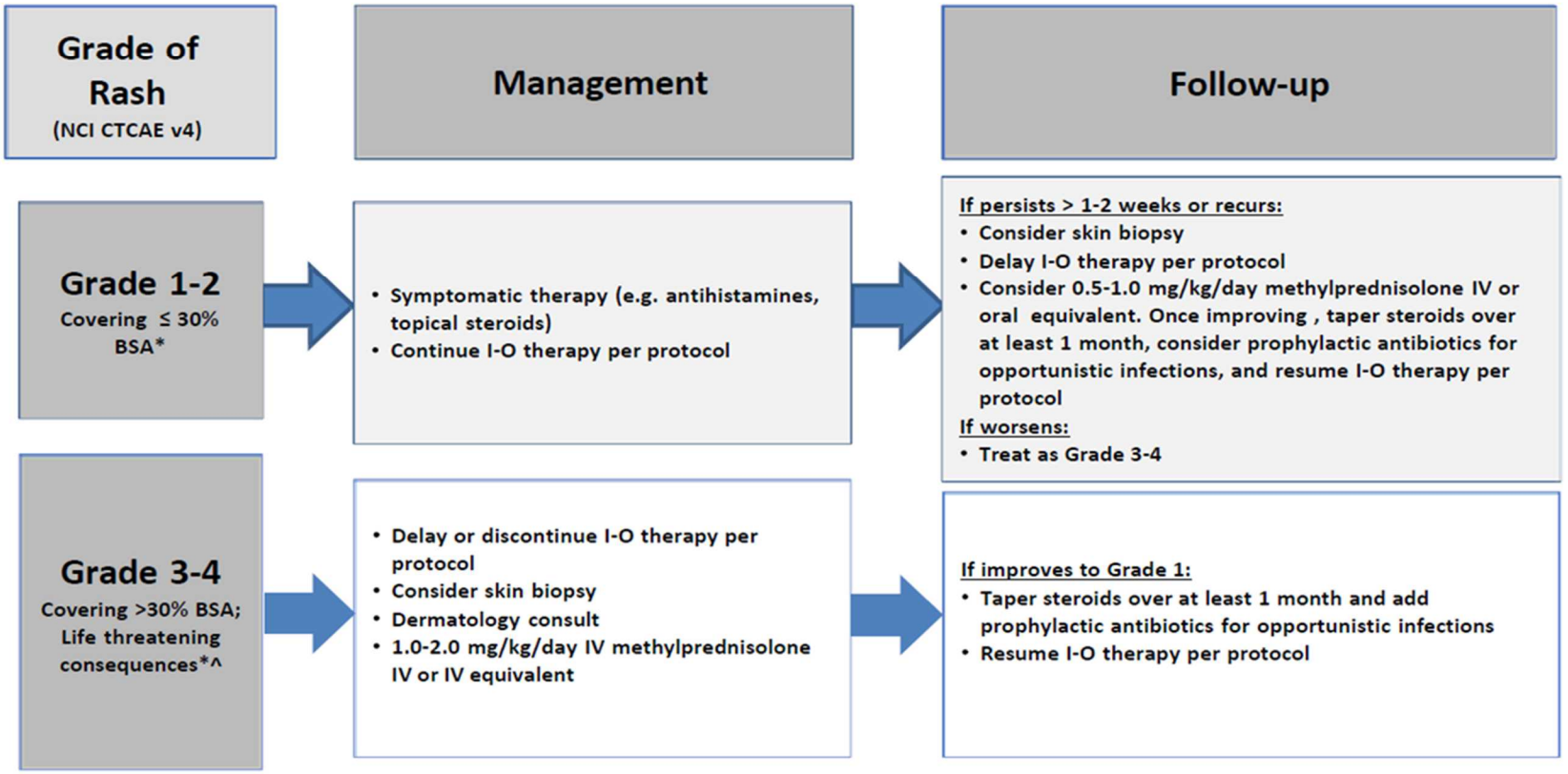


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

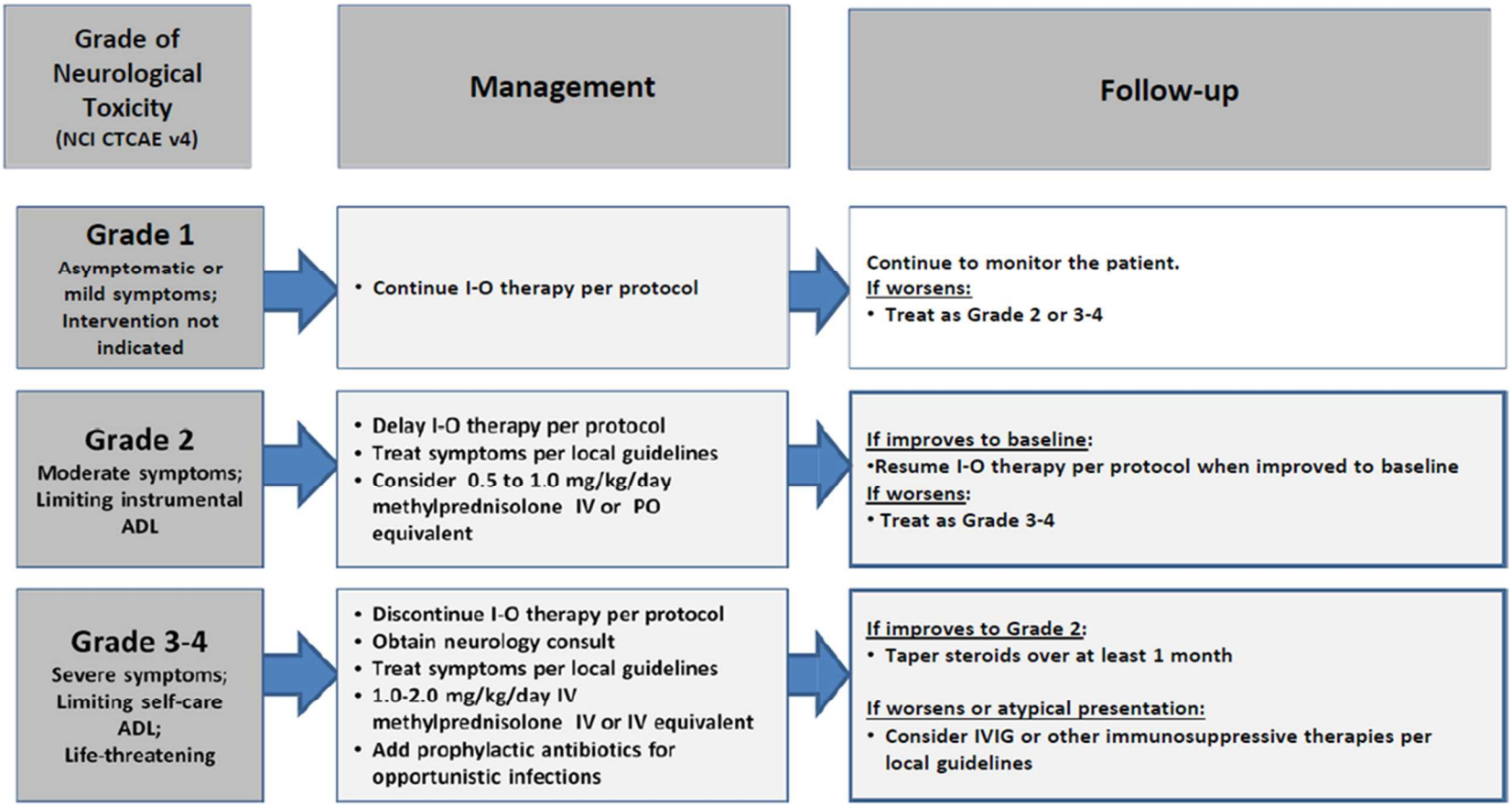
*Refer to NCI CTCAE v4 for term-specific grading criteria.

^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

28-Sep-2020

Neurological Adverse Event Management Algorithm

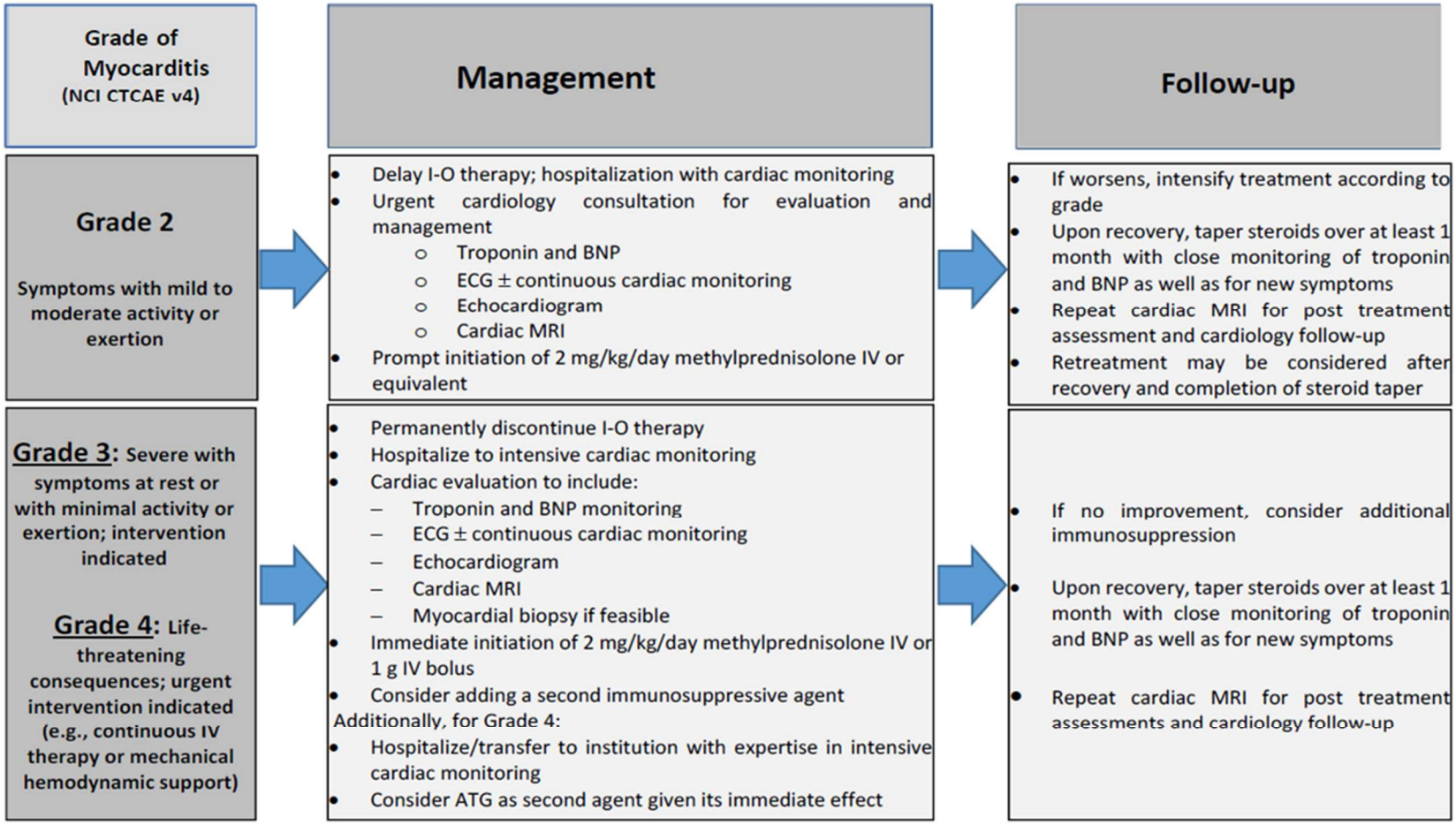
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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

28-Sep-2020

Myocarditis Adverse Event Management Algorithm



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.
ATG = anti-thymocyte globulin; BNP = B-type natriuretic peptide; ECG = electrocardiogram; IV = intravenous; MRI = magnetic resonance imaging

28-Sep-2020

APPENDIX 11 STATISTICAL METHODOLOGY

STATISTICAL DETAILS FOR BAYESIAN LOGISTIC REGRESSION MODEL (BLRM AND BLRM-COPULA)

1 MODEL SETUP FOR BMS-986218 MONOTHERAPY

1.1 Monotherapy Methodology Description

An adaptive 2-parameter Bayesian Logistic Regression Model (BLRM) guided by the escalation with overdose control (EWOC) principle[1,2,3] will be used for dose recommendation during the monotherapy dose escalation phase.

The BLRM will be fitted on the dose-limiting toxicity (DLT) data during the first 8 weeks of treatment accumulated throughout the dose escalation to model the dose-toxicity relationship of BMS-986218 in the monotherapy dose escalation phase.

The dose-toxicity relationships for BMS-986218 monotherapy is assumed to follow a logistic model:

$$logit(p_i) = log(\alpha_1) + \beta_1 log(^{d_{1i}}/_{d_1^*}),$$

where p_i is the probability of toxicity at dose level d_{1i}. Note that the α_1 and β_1 parameters are assumed positive, and d_1^* is the reference dose for BMS-986218 (please refer to the meaning of α_1 and β_1 in Section 1.2.1 for detailed implementation).

1.2 Prior Specification for BMS-986218 Monotherapy

The Bayesian approach requires the specification of prior distributions for model parameters, which include parameters (α_1, β_1) for BMS-986218. A mixture prior will be used for parameters (α_1, β_1) for BMS-986218. There are two bivariate normal components in generating this mixture prior:

- Meta-analytic predictive (MAP) component: Obtained based on the clinical safety and exposure profiles of ipilimumab using the MAP approach, because BMS-986218 is the nonfucosylated form of ipilimumab.
- Weakly informative prior for BMS-986218 component: Reflecting the potential higher toxicity of BMS-986218 than ipilimumab and allowing for considerable prior uncertainty.

Derivation of prior distribution of these parameters is provided in the following subsections.

1.2.1 Meta-analytic Predictive Component

The MAP component provides a prediction of the dose-toxicity curve for BMS-986218 based on prior data from ipilimumab. This dose-toxicity curve combines a weakly informative prior for ipilimumab with toxicities from a range of doses observed in a set of ipilimumab studies and adds an extra layer of variability to account for heterogeneity among ipilimumab studies. Note that this weakly informative prior is for ipilimumab and is different from the weakly informative prior for BMS-986218 described in Section 1.2.

Since DLT information from ipilimumab studies was not available, incidence of treatment-related Grade 3 to 4 adverse events (AEs) from various Phase 2 to 3 ipilimumab studies at Bristol-Myers Squibb (BMS) in participants with previously treated or untreated advanced melanoma was used in lieu of DLT rate in order to derive the prior for the BLRM parameters corresponding to the effect of BMS-986218, ($\log(\alpha_1)$,$\log(\beta_1)$).

- Weakly informative prior for ipilimumab is as follows:
  - The median toxicity rate at the ipilimumab reference dose (10 mg/kg every 3 weeks) was assumed to be 30%, that is, mean ($\log(\alpha_1)$) = logit(0.30) = -0.847.
  - A doubling in dose was assumed to double the odds of DLT, that is, mean ($\log(\beta_1)$) = 0.
  - The standard deviation of $\log(\alpha_1)$ was set to 2, and the standard deviation of $\log(\beta_1)$ was set to 1, which allows for considerable prior uncertainty for the dose-toxicity profile.
  - The correlation between $\log(\alpha_1)$ and $\log(\beta_1)$ was assumed to be 0 (assuming independence of $\log(\alpha_1)$ and $\log(\beta_1)$).
- Dose-toxicity data for ipilimumab are as follows:
  - Phase 3 study of ipilimumab administered at 3 mg/kg versus 10 mg/kg (Study CA184169, N=360 per arm)
  - Phase 2 study of multiple doses of ipilimumab monotherapy (Study CA184022, N=71 per arm)
  - Phase 3 study in HLA-A*0201 positive participants (Study MDX010-20, ipilimumab 3 mg/kg monotherapy arm with N=131)
  - Data from other various Phase 2 studies (N=111 for pooled 3 mg/kg; N=325 for pooled 10 mg/kg; from Clinical Overview of a Common Technical Document for ipilimumab).

Based on the exposure-response analysis, BMS-986218 appeared to be 10-fold more potent than ipilimumab, and therefore, toxicity of BMS-986218 at 0.3 mg/kg that was converted to 20 mg flat dose for the study was assumed to be similar to that of 3 mg/kg of ipilimumab. Similarly, toxicity of BMS-986218 at 70 mg and 2 mg was mapped to that of ipilimumab 10 mg/kg and 0.3 mg/kg, respectively. The data are summarized in Table 1.

Table 1: Data from Phase 2 and 3 Ipilimumab Studies at BMS in Participants with Previously Treated or Untreated Advanced Melanoma

Dose of BMS-986218 (mg)	Dose of Ipilimumab (mg/kg*)	Toxicity (percentage [number of participants/total participants])[a]
2	0.3	10% (7/72)
7		
20	3	18% (119/675)
70	10	32% (242/760)
200		

[a] % of participants with treatment-related Grade 3-4 AEs

In addition, heterogeneity between the historical study and the current study was incorporated using a MAP by defining between-trial standard deviations τ1 and τ2 for log(α_1) and log(β_1), respectively. The between-trial variability is assumed to be moderate. Therefore, τ1 and τ2 were set to follow a log-normal distribution with mean log(0.25) and log(0.125), respectively, with a common standard deviation log(2)/1.96.

1.2.2 Weakly Informative Prior for BMS-986218 Component

1) The median DLT rate at the reference dose (BMS-986218 at 150 mg every 4 weeks [Q4W]) was assumed to be 30%, that is, mean ($\log(\alpha_1)$) = logit(0.3) = log(0.3/(1-0.3)) = -0.847.
2) A doubling in dose was assumed to double the odds of DLT, that is, mean ($\log(\beta_1)$) = 0.
3) The standard deviation of $\log(\alpha_1)$ was set to 1.53 using the following steps:

- If the toxicity probability range was set to be [1%, 99%], then the toxicity interval would be logit (0.99)-logit (0.01) = 9.19.
- To cover 99.7% of the variance, the toxicity interval will cover 6*sd ($\log(\alpha_1)$), which results in sd ($\log(\alpha_1)$) = 9.19/6 = 1.53.

4) The standard deviation of $\log(\beta_1)$ was set to 2, which allows for considerably large prior uncertainty for the dose-toxicity relationship.
5) The correlation between $\log(\alpha_1)$ and $\log(\beta_1)$ was set to 0.
6) $\log(\alpha_1)$ and $\log(\beta_1)$ follow a bivariate normal distribution.

1.2.3 Mixture Prior

To obtain the mixture prior, 50% weight is assigned to the MAP component (described in Section 1.2.1), and 50% weight is assigned to the weakly informative component (described in Section 1.2.2) to balance the previous experience with ipilimumab and potential unknown toxicity profile of BMS-986218.

The mixture prior will be fitted into EAST® v6.3.1 Dose Escalation Module by Cytel for the Monotherapy Escalation (Part 1A) as stated in model setup section.

The mixture prior with both MAP and weakly informative components for the BLRM parameters of BMS-986218 is generated using R v3.3.2, the R2WinBUGS package v2.1-21, and WinBUGS v14 and is summarized in Table 2.

Table 2: Prior Distribution for Model Parameters of BMS-986218

Parameter	Means	Standard Deviations	Correlation
MAP component	(-0.39, -0.62)	(0.305, 0.231)	0.463
Weakly informative prior for BMS-986218 component	(-0.847, 0)	(1.53, 2)	0
Mixture priors for BMS-986218: ($\log(\alpha_1)$, $\log(\beta_1)$)	(-0.619, -0.304)	(1.123, 1.464)	-0.036

2 MODEL SETUP FOR BMS-986218 AND NIVOLUMAB COMBINATION

2.1 Methodology Description for Combination Therapy

Toxicity profiles of both BMS-986218 monotherapy and nivolumab monotherapy will be incorporated to develop the combination model framework. A copula-type model will be used to cover all general combination cases, including additive and synergistic effects. The combination of the 2 treatments will be explored using a Bayesian hierarchical model by utilizing the toxicity profiles of both BMS-986218 (Part 1A) and nivolumab studies in advanced solid tumors, ie, the single agents as prior marginal profiles for the combination. The following copula-type model[4] will be used to describe the probability p_{ij} of toxicity when dose level i of agent A and dose level j of agent B are administered in combination:

$$p_{ij} = 1 - exp(-\left[\{-log(1-{p_i}^m)\}^{1/\gamma_1} + \{-log(1-{q_j}^n)\}^{1/\gamma_1}\right]^{\gamma_1}),$$

where p_i is the prespecified best guess toxicity probability for agent A, q_j is the prespecified best guess toxicity probability for agent B, m, and n characterize the individual drug effects, and γ_1 characterizes the drug-drug interactive effect.

The joint toxicity framework models the toxicity rates of both agents as well as their interaction effects in a 7-parameter hierarchical model, where each monotherapy dose-toxicity relationship will be characterized by a 2-parameter BLRM (see Section 1.1). There are 3 additional parameters for the copula-type model, 1 for each agent (m and n) as well as 1 for the interaction term (γ_1). A dose-toxicity surface will be characterized for different dose combinations of these 2 agents.

As there are currently no historical data or prior knowledge to indicate how much information is to be borrowed for each of the single agents, parameters m and n are both set to be 1, meaning borrowing 100% of the information from the 2 agents. The above formula is then simplified into a 5-parameter model as follows:

$$p_{ij} = 1 - exp(-\left[\{-log(1-p_i)\}^{1/\gamma_1} + \{-log\big(1-q_j\big)\}^{1/\gamma_1}\right]^{\gamma_1}.$$

One dose for nivolumab (480 mg) and 7 doses for BMS-986218 (7, 20, 40, 70, 100, 150, and 200 mg) will be used in the BMS-986218 and nivolumab combination arms for simulation purposes. The joint toxicity probability surface will be simplified into a 2-dimensional dose-toxicity curve for each of the different dose combinations that can be evaluated for the purpose of safety. Posteriors for the corresponding 5 parameters (2 logistic regression parameters $[\alpha_1, \beta_1]$ for BMS-986218 and 2 logistic regression parameters $[\alpha_2, \beta_2]$ for nivolumab, as well as 1 interaction parameter for the copula-type model [γ_1, which will be discussed in detail in the following section]) will be fitted into the in-house developed model. It implements the above-described theoretical setup.

2.2 Prior Specification for Combination Therapy

2.2.1 Marginal Prior for BMS-986218

Posterior information on log(α_1) and log(β_1) from the monotherapy part of the study will be used as marginal BMS-986218 prior for combination with nivolumab. This prior information is not prespecified and will be continuously updated when additional DLT information from the monotherapy is available. In the simulation (see Section 3), the posterior prior of BMS-986218 using DLT from monotherapy part of the study and prior of BMS-986218 as described in Section 1.2.3 (Table 2) is used for illustration purposes as

- log(α_1): mean -1.421 and standard deviation 0.637
- log(β_1): mean -1.041 and standard deviation 0.832
- Correlation: 0.624

2.2.2 Marginal Prior Derivation for Nivolumab Parameters (log(α_2), log(β_2))

Similar to BMS-986218 monotherapy, the logistic model for nivolumab is as follows:

$$logit(q_j) = log(\alpha_2) + \beta_2 log(^{d_{2j}}/_{d_2^*}),$$

where q_j is the probability of toxicity at dose level d_{2j}. Note that the α_2 and β_2 parameters are assumed positive, and d_2^* is the reference dose for nivolumab.

The toxicity profile of nivolumab has been studied in several studies. A bivariate normal prior for the nivolumab model parameters (log(α_2), log(β_2)) was obtained by extracting a posterior of nivolumab using incidence of treatment-related Grade 3 to 4 AEs from a Phase 1 dose-escalation study and several Phase 3 nivolumab studies, which are used later as the MAP prior for nivolumab. These include a Phase 1 dose-escalation study of nivolumab (Study CA209003, N=306 in doses of 0.1, 0.3, 1, 3, and 10 mg/kg across multiple tumor types), a randomized Phase 3 study in advanced melanoma participants progressing post anti-CTLA-4 therapy (Study CA209037, N=268 in a dose of 3 mg/kg), a Phase 3 study in previously treated participants with squamous cell NSCLC (Study CA209017, N=131 in a dose of 3 mg/kg), a Phase 3 study in previously treated participants with non-squamous cell NSCLC (Study CA209057, N=287 in a dose of 3 mg/kg), and a Phase 3 study in previously treated participants with clear-cell RCC (Study CA209025, N=406 in a dose of 3 mg/kg). The results from the simulation of nivolumab flat dose exposures, the corresponding exposure-response analyses, and review of nivolumab safety support nivolumab flat dose and the overall distributions of nivolumab exposures are comparable after treatment with either 3 mg/kg Q2W or 240 mg Q2W nivolumab. In addition, dose proportionality of nivolumab exposures supports nivolumab 240 mg Q2W being comparable to 480 mg Q4W.

The MAP prior for the model parameters (log(α_2), log(β_2)) was obtained in the following steps.

First, a prior distribution for nivolumab was developed:

- The median DLT rate at the reference dose (3 mg/kg every 2 weeks) was assumed to be 10%, that is, mean (log(α_2)) = logit(0.10) = log(0.1/0.9) = -2.197.

- A doubling in dose was assumed to double odds of DLT, that is, mean(log(β_2)) = 0.
- The standard deviation of log(α_2) was set to 2, and the standard deviation of log(β_2) to 1, which allows for considerable prior uncertainty for the dose-toxicity profile.
- The correlation between log(α_2) and log(β_2) is assumed to be 0 (assuming independence of log(α_2) and log(β_2)).
- In addition, heterogeneity between the historical study and current study was incorporated using a MAP by defining between-trial standard deviations τ_1 and τ_2 for log(α_2) and log(β_2), respectively. The between-trial variability is assumed to be moderate. Therefore, τ_1 and τ_2 were set to follow a log-normal distribution, with mean log(0.25) and log(0.125), respectively, with a common standard deviation log(2)/1.96.

With this prior, the clinical trial data below (Table 3) were used to generate the posterior for nivolumab, which is then used as the MAP prior for this study (Table 4).

Table 3: Data from Nivolumab Studies

Nivolumab Flat Dose (mg), Q4W	Dose of Nivolumab (mg/kg), Q2W	Toxicity[a]
	0.1	29% (5/17)
	0.3	17% (3/18)
160	1	14% (12/86)
480	3	13% (150/1146)
	10	16% (21/131)

[a] % of participants with treatment-related Grade 3-4 AEs

Abbreviation: Q2W = every 2 weeks.

Table 4: Marginal Prior Distribution for Model Parameters for Nivolumab (ie, Posterior from MAP Method)

Parameter	Means	Standard Deviations	Correlation
log(α_2), log(β_2)	(-1.856, -2.131)	(0.404, 0.546)	-0.009

2.2.3 Prior for Interaction Parameters for Joint Toxicity of BMS-986218 and Nivolumab Combination

A gamma prior distribution for the interaction parameter γ_1 is derived to reflect the current uncertainty about the toxicity profile of the combination of BMS-986218 and nivolumab. Although no pharmacokinetic (PK) drug-drug interaction is expected, the possibility of a significant positive interaction between BMS-986218 and nivolumab cannot be totally excluded. The interaction parameter γ_1 was chosen accordingly but with a degree of uncertainty to allow for the possibility that the interaction may be positive or negative. Therefore, the following assumptions are made for the interaction parameter:

- γ_1 follows a gamma distribution with a mean centered at 1.1, which means the combination of 2 agents is likely to have only a small synergistic effect.
- The standard deviation of γ_1 is 0.5, such that there is a 52% prior probability that γ_1 is larger than 1.

This model assigns the highest probability to there being small synergistic interaction and also allows for the potential of larger synergism of the toxic profiles. It also does not completely ignore the possibility of antagonism because there is a 48% prior probability that γ_1 is less than 1.

3 DOSE-ESCALATION PROCESS AND SIMULATION IN MONOTHERAPY

3.1 Dose-escalation Process

Dose escalation recommendations for BMS-986218 monotherapy will be based on the inference from the Bayesian posterior and the probability that the true DLT rate for each dose lies in 1 of the following categories:

- (0%, 16%) under-dosing
- (16%, 33%) targeted toxicity
- (33%, 100%) excessive toxicity

These boundaries are similar to the toxicity boundaries used by a rule-based design (ie, 3 + 3 design) in that a minimum is set at 16% (~ 1 in 6) DLT rate and a maximum at 33% (~ 2 in 6) DLT rate. Following the principle of EWOC, dose recommendations for the next cohort will be based on the Bayesian model after DLT information becomes available during the DLT period, accounting for all of the available data from the administered doses, and the candidate doses for the next cohort are the ones fulfilling the overdose criterion that there is no greater than 35% chance of excessive toxicity. Only the candidate doses will be considered for the next cohort. While the Bayesian model will use DLT information from the DLT period only, clinical assessment will take into consideration the totality of available data including PK/pharmacodynamics from all treated participants.

Stopping Rules:

The following are the general stopping rules of BLRM during monotherapy dose escalation:

- If all of 108 DLT-evaluable participants are treated.
- If all of the current prespecified doses are considered intolerable according to the prespecified cutoff (ie, EWOC criteria), then the model will recommend stopping the current dose level, and a new intermediate dose level lower than the current lowest dose level will need to be identified.
- The maximum number of participants in a dose level will be 12. This limit is set to avoid instances in which the model could recommend adding subjects indefinitely to a specific dose level due to uncertainty in the tolerability profile.

- If, for a specific dose level, 6 subjects have been treated and the chance of determining that the dose level to be the "target" dose is > 50%, then the model will suggest to stop and declare the current dose level to be the maximum tolerated dose (MTD).

Model-recommended MTD:

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

(1) The empirical posterior probability that the 'DLT rate of 16% to < 33%' is greater than 50%,

(2) This probability needs to be the largest among the dose levels that satisfy the EWOC condition (ie, the probability that 'DLT rate ≥ 33%' must be no greater than 35%);

(3) Minimum number of participants (ie, 6), were treated at this dose level.

Final MTD/RP2D:

The final recommended MTD/RP2D will be based on the recommendation from the BLRM and overall clinical assessment of all available safety, PK/pharmacodynamic, and efficacy data. Lower doses of BMS-986218 may be tested if none of the planned doses are found to be tolerable as monotherapy or in combination with nivolumab. Such decisions will be made after discussion and agreement between the investigators and the BMS Medical Monitor.

3.2 Simulation Parameters

Simulation study was done for monotherapy dose escalation using various hypothetical scenarios.

Ten thousand trial simulations were used for each scenario. All simulations were run using EAST 6.4.1® software BLRM module for BMS-986218 monotherapy. The number of participants to be treated in each cohort in a specific dose level and the stopping rules used to declare MTD are defined as:

- Fixed cohort size: 3
- Probability of overdosing: ≤ 35%
- Target probability of toxicity: 0.33, the upper boundary of the targeted toxicity interval
- Probability of achieving the target toxicity: > 50%
- Maximum number of participants treated: 108
- Prior specification on model parameters (based on mixture prior in Table 2 from Section 1.2.3):
  - log(α_2): mean -0.619 and standard deviation 1.123
  - log(β_2): mean -0.304 and standard deviation 1.464
  - Correlation: -0.036
- Posterior sampling method: Metropolis Hastings
- Minimum number of participants treated at a given dose level in order to declare MTD: 6
- Maximum number of participants at a dose:12

The provisional dose levels for BMS-986218 monotherapy are 2, 4, 7, 20, 40, 70, 100, 150 and 200 mg, with 150 mg as the reference dose.

3.3 Operating Characteristics of BLRM for Monotherapy

Three scenarios were investigated by selecting (1) dose-DLT relationship derived by the prior, (2) dose-DLT curve flatter than the 1 by the prior; (3) narrow safety window in order to explore how EWOC limits the risk of exposing participants from a toxic dose level, (4) all doses below the target toxicity, and (5) all doses above the target toxicity. Simulations were performed using EAST v6.4.1 BLRM with no dose skipping option.

For scenario (1), the % DLT by prior was derived using the model solving for the probability, p_i at the ith dose as follows:

$$\text{logit}(p_i) = \log(\alpha_1) + \beta_1 \log(d_{1i} / d_1^*)$$

The model can be re-written as follows:

$$p_i = \frac{exp(\log(\alpha_1) + \beta_1 \log(d_{1i} / d_1^*)}{1 + exp(\log(\alpha_1) + \beta_1 \log(d_{1i} / d_1^*)}$$

Using the estimates in Section 3.2, the prior probability of DLTs at doses of 2, 4, 7, 20, 40, 70, 100, 150, and 200 mg is 0.02, 0.04, 0.05, 0.11, 0.17, 0.23, 0.29, 0.35, and 0.40.

The simulation results are shown in Table 5 below.

Table 5: Simulation Results of BLRM for Monotherapy

Scenario	BMS-986218 Dose	2	4	7	20	40	70	100	150	200	MTD not Selected (%)	Fitted Median MTD	Avg Toxicity Observed (%)	Avg # Pts
By prior	% DLT	2	4	5	11	17[a]	23[a]	29[a]	35	40	0.3	125.4	15.0	25.8
	% MTD	0.1	0.2	1	8.6	23.7	31.1	26.7	6.9	1.4				
	# Pts	3.1	3.1	3.2	3.7	4.4	5	5.8	5.1	5.1				
	# DLTs	0.1	0.1	0.2	0.4	0.8	1.1	1.7	1.8	2.1				
Flatter than the one by the prior	% DLT	7	8	10	12	16[a]	17[a]	21[a]	23[a]	25[a]	2.9	147.9	15.8	26.1
	% MTD	1.1	1.3	4.5	12.1	18.1	19.1	20.4	11.3	9.3				
	# Pts	3.4	3.3	3.5	3.9	4.3	4.6	5.4	5.5	7.2				
	# DLTs	0.2	0.3	0.4	0.5	0.7	0.8	1.1	1.3	1.8				
Narrow safety window	% DLT	2	4	6	8	9	16[a]	18[a]	32[a]	80	0.3	156.5	13.3	28.6
	% MTD	0.1	0.2	0.9	4	9.9	23.1	42.9	18.5	0.2				
	# Pts	3.1	3.1	3.2	3.5	3.8	4.5	6.3	5.5	3.5				
	# DLTs	0.1	0.1	0.2	0.3	0.3	0.7	1.1	1.8	2.8				
All low	% DLT	2	4	6	8	14	16[a]	18[a]	20[a]	25[a]	0.4	165.8	12.6	28.7
	% MTD	0.1	0.2	0.9	5.7	14.4	19.8	26.1	19.2	13.3				
	# Pts	3.1	3.2	3.2	3.5	4.1	4.4	5.5	6	7.4				
	# DLTs	0.1	0.1	0.2	0.3	0.6	0.7	1	1.2	1.8				
All high	% DLT	55	60	65	70	75	80	82	84	86	95.4	0.5	64.2	5.1
	% MTD	3.6	0.8	0.3	0	0	0	0	0	0				
	# Pts	3.9	3.7	3.8	3.4	3	0	0	0	0				
	# DLTs	2.1	2.2	2.5	2.7	3	NA	NA	NA	NA				

[a] Doses with true target toxicity within the target toxicity interval (16%, 33%).

Note: % DLT, true DLT rate; % MTD, proportion of the dose selected as the MTD; # Pts, average number of patients given the dose was tried; # DLTs, average number of DLTs given the dose was tried; Fitted MTD: fitted MTD at 33% as the target toxicity rate; % toxicity observed, average proportion of DLTs.

Abbreviation: Avg = average; NA = not applicable; Pts = participants.

The average sample size was no more than 29 participants. Most scenarios have a fitted median MTD that is close to the reference dose, and the 100 mg dose was chosen as the MTD most frequently in all scenarios, except the all high and by prior scenarios. The results for the all high scenarios show how the EWOC principle limits the risk of exposing participants from a toxic dose level by not selecting an MTD in 95.4% of the simulations. The model performs well in the by prior, flat, narrow safety window and all low scenarios by correctly identifying the MTD within the target toxicity interval, (16%, 33%) at least 82%, 78%, 85%, and 78% of the time, respectively. Overall, the scenarios illustrated above demonstrate that the model performs satisfactorily in the hypothetical scenarios investigated by correctly identifying the MTD while limiting participants from receiving excessive/unacceptable toxic dose levels.

4 DOSE-ESCALATION PROCESS AND SIMULATION IN COMBINATION THERAPY

4.1 Dose-escalation Process

Similar to the dose escalation process for BMS-986218 monotherapy (Section 3.1), the dose-escalation recommendations for BMS-986218 and nivolumab combination therapy will be based on the inference from the Bayesian posterior and the probability (obtained from the BLRM-Copula model) that the true DLT rate for each dose lies in 1 of the following categories:

- (0%, 16%) under-dosing
- (16%, 33%) targeted toxicity
- (33%, 100%) excessive toxicity

While the Bayesian model will use DLT information of all available data from the DLT period only, clinical assessment will take into consideration the totality of available data including PK/PD from all treated participants.

Following the principle of EWOC, after gaining information of each cohort of participants, the candidate doses are the ones fulfilling the overdose criterion that there is less than 35% chance of excessive toxicity. Only the candidate doses will be considered for the next dose decision by Investigators and BMS study personnel based on a synthesis of all relevant data available from all dose levels evaluated in the ongoing study.

A combination with a lower, intermediate, or higher dose level of BMS-986218 may be considered and tested if the model recommends it. Such decisions will be made after discussion and agreement between the investigators and the BMS Medical Monitor.

Stopping Rules:

The following are the general stopping rules of BLRM during combination therapy dose escalation:

- If all of 84 DLT-evaluable participants are treated.

- If all of the current prespecified doses are considered intolerable according to the prespecified cutoff (ie, EWOC criteria), then the model will recommend stopping the current dose level, and a new intermediate dose level lower than the current lowest dose level will need to be identified.
- The maximum number of participants in a dose level will be 12. This limit is set to avoid instances in which the model could recommend adding subjects indefinitely to a specific dose level due to uncertainty in the tolerability profile.
- If, for a specific dose level, 6 participants have been treated and the chance of determining that the dose level to be the "target" dose is > 50%, then the model will suggest to stop and declare the current dose level to be the maximum tolerated dose (MTD).

Model-recommended MTD:

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

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

Final recommended MTD for combination therapy:

The final recommended MTD for combination therapy will be based on the recommendation from the BLRM and overall clinical assessment of all available safety, PK/pharmacodynamic, and efficacy data. Lower doses of BMS-986218 may be tested if none of the planned doses are found to be tolerable as monotherapy or in combination with nivolumab. Such decisions will be made after discussion and agreement between the Investigators and the BMS Medical Monitor.

4.2 Simulation Parameters

A simulation study was done for combination dose escalation using various hypothetical scenarios.

For each scenario, 1000 trial simulations were used. All simulations were run using in house-developed code via Rv3.1.2 and R2OpenBugs v3.2 software. The number of participants to be treated in each cohort in a specific dose level, the stopping rules used to identify the model recommeneded MTD, and other simulation parameters are defined as:

- Fixed cohort size: 3
- Probability of overdosing: ≤ 35%
- Target probability of toxicity: 0.33, the upper boundary of the targeted toxicity interval
- Probability of achieving the target toxicity: > 50%
- Maximum number of participants treated: 84
- Prior specification on model parameters are as follows :
  - BMS-986218 (based on marginal prior from Section 2.2.1):

- log(α_2): mean -1.421 and standard deviation 0.637
- log(β_2): mean -1.041 and standard deviation 0.832
- Correlation: 0.624

– Nivolumab (based on marginal prior in Table 4 from Section 2.2.2):

- log(α_2): mean -1.856 and standard deviation 0.404
- log(β_2): mean -2.131 and standard deviation 0.546
- Correlation: -0.009

– Interaction parameter (from Section 2.2.3)

- γ_1 : mean 1.1 and standard deviation 0.5

- Posterior sampling method: Metropolis Hastings
- Minimum number of participants treated at a given dose level in order to declare MTD: 6
- Maximum number of participants at a dose:12

The provisional dose levels for BMS-986218 in combination with nivolumab are 7, 20, 40, 70, 100, 150, and 200 mg, with 150 mg as the reference dose.

4.3 Operating Characteristics of BLRM-Copula for Combination Therapy

To demonstrate the performance of the model, the following 5 scenarios are examined below:

- Scenario 1 - Additive: General dose-DLT relationship derived by the prior with the assumption that higher doses will have higher DLT rates.
- Scenario 2 - Synergistic Effect: Toxicity rates 25% higher than the additive Scenario 1 along with increased dose levels, with the highest dose toxicity level above 33%.
- Scenario 3 - Strong Synergistic Effect: Toxicity rates 50% higher than the additive Scenario 1 along with increased dose levels, with the highest dose toxicity level above 33%.
- Scenario 4 - Sub-additive or Cancellation Effect: All dose levels with toxicities 25% lower than the additive Scenario 1.
- Scenario 5 - Strong Sub-additive or Cancellation Effect: All dose levels with toxicities 50% lower than the additive Scenario 1.
- For Scenario 1, the % DLT was derived using the BLRM-Copula model with the assumption that m = 1, n =1 and γ=1 (Additive model)

$$p_{ij} = 1 - exp(-\left[\{-log(1-p_i{}^m)\}^{1/\gamma} + \{-log(1-q_j{}^n)\}^{1/\gamma}\right]^{\gamma})$$

- where p_i and q_i at the ith dose are computed using the model for the marginal probability,

$$p_i = \frac{exp(\log(\alpha_1) + \beta_1 \log(d_{1i}/d_1^*)}{1 + exp(\log(\alpha_1) + \beta_1 \log(d_{1i}/d_1^*)}$$

$$q_i = \frac{exp(\log(\alpha_2) + \beta_2 \log(d_{2i}/d_2^*)}{1 + exp(\log(\alpha_2) + \beta_2 \log(d_{2i}/d_2^*)}$$

- Using the prior in Section 4.2 as estimates, the marginal probabilities for BMS-986218 (p_i) and nivolumab (q_i) are 0.08, 0.11, 0.13, 0.16, 0.17, 0.19, 0.21 for BMS-986218 and 0.14 for nivolumab, and therefore prior probability of DLTs (p_{ij}) are 0.20, 0.23, 0.25, 0.27, 0.28, 0.30 and 0.32 for BMS-986218 in combination with nivolumab at dose 7, 20, 40, 70, 100, 150, and 200 mg, with 150 mg as the reference dose.

The simulation results are shown in Table 6 below. The model seems to work as expected.

Table 6: Simulation Results of BLRM-Copula for BMS-986218 in Combination With Nivolumab

Scenario	BMS-986218 Dose	7	20	40	70	100	150	200	MTD not Selected (%)	Fitted Median MTD	Avg Toxicity Observed (%)	Avg # Pts
Additive	% DLT	20[a]	23[a]	25[a]	27[a]	28[a]	30[a]	32[a]				
	% MTD	32.1	18.7	24.4	17.1	3.5	0.2	0.1	3.9	206.8	26.8	13.4
	# Pts	4.5	3.7	3.2	1.6	0.4	0.0	0.0				
	# DLTs	0.9	0.8	0.8	0.5	0.1	0.0	0.0				
Synergistic (25% more tox than additive)	% DLT	25[a]	28[a]	31[a]	33	35	37	40				
	% MTD	43.0	22.8	17.1	8.0	1.2	0.0	0.0	7.9	151.3	32.4	12.0
	# Pts	4.8	3.6	2.5	0.9	0.2	0.0	0.0				
	# DLTs	1.2	1.0	0.7	0.3	0.1	0.0	0.0				
Strong Synergertic (50% more tox than additive)	% DLT	30[a]	34	37	40	42	45	48				
	% MTD	54.4	18.3	10.0	3.2	0.4	0.0	0.0	13.7	110.3	37.8	10.8
	# Pts	5.2	3.2	1.8	0.5	0.1	0.0	0.0				
	# DLTs	1.6	1.1	0.6	0.2	0.0	0.0	0.0				
Sub additive (25% less tox than additive)	% DLT	15	17[a]	19[a]	20[a]	21[a]	22[a]	24[a]				
	% MTD	17.3	15.4	24.2	27.4	13.6	0.4	0.3	1.4	330.4	20.4	15.5
	# Pts	4.0	3.8	3.8	2.7	1.1	0.1	0.0				
	# DLTs	0.6	0.6	0.7	0.6	0.2	0.0	0.0				
Strong sub additive (50% less tox than additive)	% DLT	10	11	12	13	14	15	16[a]				
	% MTD	6.9	6.2	17.2	30.8	33.9	1.6	3.1	0.3	664.2	13.6	18.0
	# Pts	3.4	3.5	4.1	3.8	2.6	0.4	0.2				
	# DLTs	0.3	0.4	0.5	0.5	0.4	0.1	0.0				

[a] Doses with true target toxicity within the target toxicity interval (16%, 33%).

Note: % DLT, true DLT rate; % MTD, proportion of the dose selected as the MTD; # Pts, average number of patients given the dose was tried; # DLTs, average number of DLTs given the dose was tried; Fitted MTD: fitted MTD at 33% as the target toxicity rate; % toxicity observed, average proportion of DLTs

Abbreviation: Avg = average; NA = not applicable; Pts = participants.

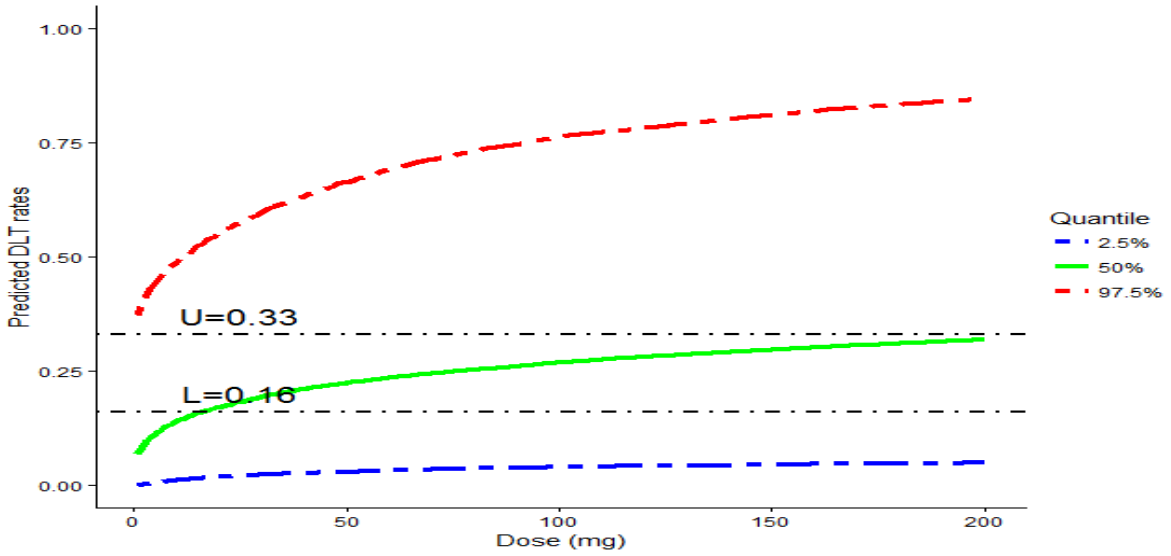
5 INTERIM MONITORING EXAMPLE TO ILLUSTRATE PROVISION OF DOSE RECOMMENDATIONS DURING DOSE-ESCALATION IN MONOTHERAPY

In order to provide a comprehensive view of the dynamics of the models, different hypothetical scenarios exploring all possibilities are examined. For the simplicity of illustration purposes, a static cohort size of 3 subjects is applied for dose levels 2 mg, 7 mg, 20 mg, 70 mg, and 200 mg in the BMS-986218 monotherapy. This cohort size could vary during the actual clinical trial, and the BLRM models are designed to fit various different cohort sizes, adaptively. In general, there are 4 possible scenarios for a specific dose level; these are 0 DLT observed in 3 total subjects in that cohort (denoted as 0/3), 1 DLT observed in 3 subjects (1/3), 2 DLTs observed in 3 subjects (2/3), and 3 DLTs observed in 3 subjects (3/3).

During interim monitoring, posterior probabilities will be updated when there is new DLT information available. The following 3 visualization plots will be produced to reflect the real-time dose-DLT relationship, to quantify benefit (in the form of target dosing) and risk (in the form of overdosing and underdosing) during model's recommendation process, and to facilitate clinical team's interpretation of the model recommendations for a decision making:

- Dose-DLT profile for the doses ranging between 0 mg and 200 mg (Figure 1).
- Stacking histograms displaying predictive probabilities on DLT rates classified into 3 different categories (Underdosing, Target dosing and Overdosing) (Figure 2).
- Box plots summarizing the Markov Chain Monte Carlo samples of predicted DLT rates for the 5 prespecified dose levels (Figure 3).

Figure 1: Updated Dose-DLT Profile After Incorporating Prior Information and All Previous and Current DLT Information



Abbreviations: L = lower DLT boundary; U = upper DLT boundary.

Interpretation and Use of Figure 1:

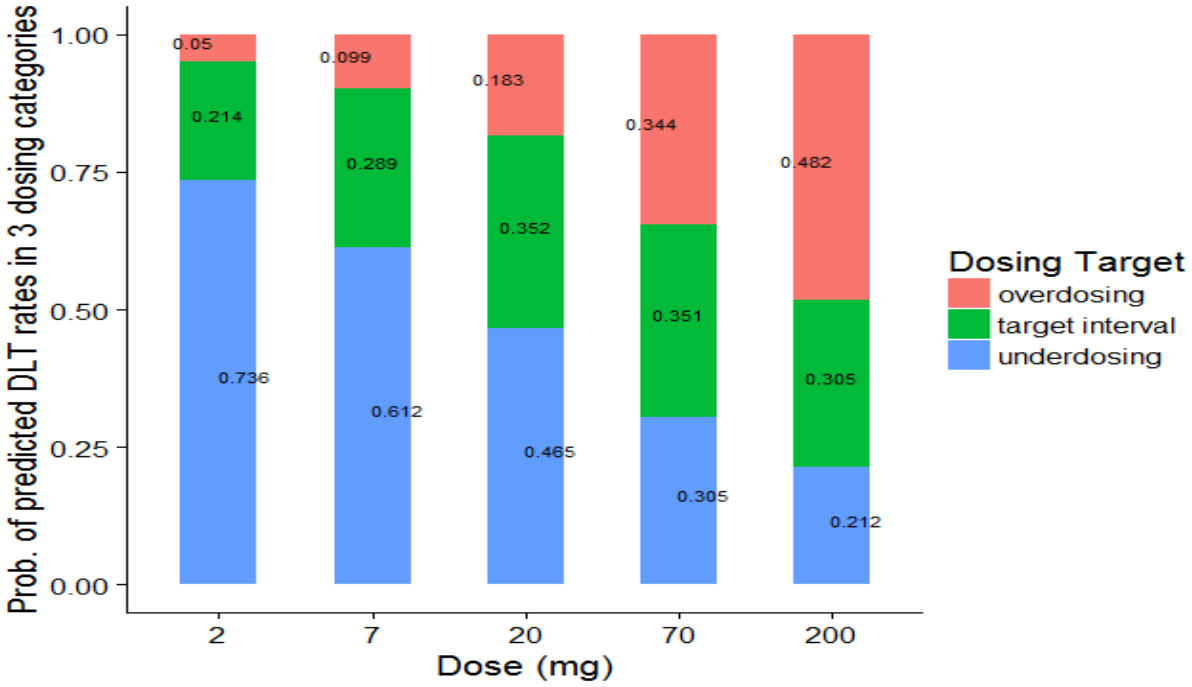
Figure 1 is a snapshot of an updated dose-DLT profile with DLT information available at dose level 2 mg for monotherapy. The dose-DLT profile is captured with a continuous dose spectrum ranging from 0 to 200 mg. For each dose within the range, there is a corresponding distribution of the predicted DLT rates calculated from the posterior samples of the model parameters. This figure will be updated each time new DLT information becomes available from the study.

In Figure 1, there are 3 different quantiles (2.5%, 50%, and 97.5%) plotted to characterize the current trend of the toxicity profile (as shown by the 50% quantile), as well as the variation of the dose-DLT profile (as shown by the 2.5% percentile and the 97.5% percentile), according to the accumulation of DLT data from all previous and current dose levels. The toxicity boundaries (0.16 and 0.33) are illustrated in two dotted horizontal lines to benchmark the way in which the dose-DLT profile is trending.

Intermediate dose levels can be identified using different boundary cutoffs. For example, using the 50% percentile curve (green highlight), which represents the nearly average DLT distribution for each dose level, the 13 mg-dose could be a potential intermediate dose level corresponding to the lower prespecified DLT rate boundary of 0.16, and the 205 mg dose could be a fitted MTD dose level associated with the upper boundary of 0.33.

Moreover, if all of the current pre-specified doses are considered intolerable (overdosing probabilities > 0.3 for monotherapy, a case not shown on the current Figure 1), the model will recommend to stop the current dose level, and the clinical team can leverage the current updated dose-DLT curve to pinpoint a new dose, which is lower than pre-specified lowest dose (2 mg) by using the DLT-rate boundaries.

Figure 2: **Updated Stacking Histogram After Incorporating Prior Information and All Previous and Current DLT Information to Classify Predicted DLT Rates into 3 Categories (Underdosing, Target Dosing, and Overdosing)**



Interpretation and Use of Figure 2:

Figure 2 is a snapshot of stacking histogram with DLT information available at dose level 2 mg. This figure will be updated each time new DLT information becomes available.

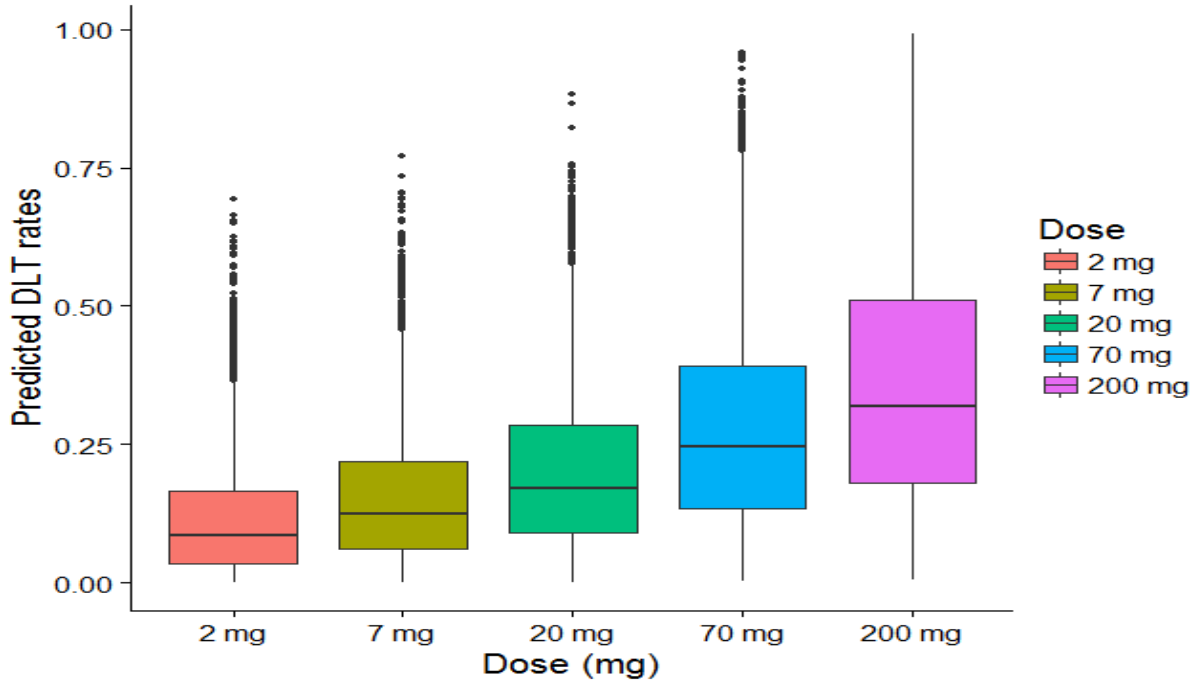
When recommending the next dose level, the model will first exclude doses that are intolerable (with overdosing probabilities > 30%, the rate that has been specified for BMS-986218 in combination with nivolumab). Among those qualified candidate doses that are considered "tolerable", the model will select the dose that maximizes the probability of being within the target toxicity range (DLT rate of 16% up to 33%). However, there will be no dose skipping during the dose-escalation monotherapy phase of the study.

As illustrated in Figure 2, the distribution of predicted DLT rates will be characterized into possibilities falling into 3 different categories. First, dose levels of 70 and 200 mg for BMS-986218 are excluded according to the higher-than-cutoff (0.3 for combination therapy) overdosing probabilities (0.344 for 70 mg and 0.482 for 200 mg). Among the remainder of tolerable dose levels, the BLRM recommends the dose that maximizes the probability of being within the target dosing interval. Therefore, the model's recommendation would be to escalate to 20 mg, which is associated with the highest target dosing probability of 0.352 compared with that of 2 mg (0.214) and 7 mg (0.289).

Similarly (although not shown on Figure 2), according to the rules specified above, the model could possibly recommend to de-escalate to a lower dose level than the current treated dose level,

extend the current dose level, or even recommend to stop and identify a new dose level lower than 2 mg, the lowest pre-specified dose level. Please refer to the description of Figure 1 for details on how to specify the new dose levels.

Figure 3: Updated Box Plot After Incorporating Prior Information and All Previous and Current DLT Information



Interpretation and Use of Figure 3:

Figure 3 is a snapshot with DLT information available at dose level 2 mg. The dose-DLT distributions calculated from the posterior samples of the model parameters are characterized in the format of boxplots for the pre-specified dose levels. This figure will be updated each time there is new DLT information available.

This plot supplements the information provided in Figure 1. It allows for a more in-depth and focused visualization of general trend of dose-DLT relationship, as well as the magnitude and variability in the DLT rates for each pre-specified dose level.

REFERENCES

1 Babb J, Rogatko A, Zacks S. Cancer Phase I clinical trials: efficient dose escalation with overdose control. Stat Med 1998;17:1103-20.

2 Neuenschwander B, Branson M, Gsponer T. Critical aspects of the Bayesian approach to Phase I cancer trials. Stat Med 2008;27:2420-39.

3 Neuenschwander B, Capkun-Niggli G, Branson M, et al. Summarizing historical information on controls in clinical trials. Clin Trials 2010;7:5-18.

4 Yin G, Yuan Y. Bayesian dose finding in oncology for drug combinations by copula regression. J R Stat Soc Ser C Appl Stat 2009;58(2):211-24.

APPENDIX 12 PROSTATE CANCER WORKING GROUP 3 (PCWG3) GUIDELINES (WITH MODIFIED RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) CRITERIA FOR SOFT TISSUE LESION ASSESSMENT)

1 EVALUATION OF LESIONS

Bone lesions should be evaluated with Technecium-99m based radionuclide bone scan as per PCWG3[1].

At baseline, soft tissue lesions/lymph nodes will be categorized as measurable or non-measurable as follows.

1.1 Measurable

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

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

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

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

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

1.2 Non-Measurable

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

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

1.3 Special considerations regarding bone lesions

Bone lesions will be assessed with Technecium-99m based radionuclide bone scans as per PCWG3.

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

When more than one measurable lesion is present at baseline all lesions up to a maximum of 20 lesions total (and a maximum of 5 lesions per organ system) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

Note: A maximum of 5 lesions can be selected per organ system. For example, a maximum of 5 lung lesions can be selected. A maximum of 5 lymph nodes can be selected at baseline, as the lymphatic system is considered one organ.

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

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

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Pelvic lymph nodes and extrapelvic lymph nodes (retroperitoneal, mediastinal, thoracic and other) may be reported separately, per PCWG3. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g., 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

2 RESPONSE CRITERIA

2.1 Evaluation of Target Lesions

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

2.1.1 Special Notes on the Assessment of Target Lesions

2.1.1.1 Lymph nodes

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

2.1.1.2 Target lesions that become 'too small to measure'

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

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

2.1.1.3 Lesions that split or coalesce on treatment

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

2.2 Evaluation of Non-Target Lesions

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

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

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

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

2.2.1.1 When the patient also has measurable disease

In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy (see examples in Appendix 2 and further details below). A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. Pleural effusions, pericardial effusions and ascites will not be followed as target or non-target lesions and will not contribute to response or progression. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

2.2.1.2 When the patient has only non-measurable disease

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

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

2.2.2 New Lesions

New bone lesions

New bone lesions should be evaluated as per PCWG3 criteria. Bone lesions will be assessed by radionuclide bone scan only. Radiographic progression on bone scan is defined by the following criteria:

- At least 2 new lesions on the first posttreatment bone scan, with at least 2 additional lesions on the next scan (performed at least 6 weeks later) as compared to baseline bone scan. Date of progression is then the date of first post-treatment scan,
- For scans after the first post-treatment scan, at least 2 new lesions relative to the first post-treatment scan AND confirmed on a subsequent scan (performed at least 6 weeks later). Date of progression is the date of the scan that first documents at least 2 new lesions relative to the first post-treatment scan.

New soft tissue lesions

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

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

he/she did not have brain imaging at baseline. A lesion identified on Chest X-Ray that was not present in prior CT can be considered a new lesion and will result in Progressive Disease (PD).

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

2.3 Response Assessment

2.3.1 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until disease progression per PCWG3 criteria, or the last response recorded, taking into account any requirement for confirmation and censoring rules regarding subsequent therapy. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement.

2.3.2 Time Point Response

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

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

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

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease and NE = inevaluable

Table 2.3.2-2: Time Point Response: Patients with Non-target Disease Only		
Non-Target Lesions	**New Lesions**	**Overall Response**
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD
CR = complete response, PD = progressive disease and NE = inevaluable		

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

2.3.3 Best Overall Response

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

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

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

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

Table 2.3.3-1: Best Overall Response (Confirmation of CR&PR Required)		
Overall Response First Time Point	**Overall Response Subsequent Time Point**	**BEST Overall Response**
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE
CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable		

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

2.3.4 Confirmation Scans

Verification of Response: To be assigned a status of CR or PR, changes in tumor measurements must be confirmed by consecutive or subsequent repeat assessments that should be performed no less than 28 days after the criteria for response are first met. Subsequent documentation of a CR may provide confirmation of a previously identified CR even with an intervening NE or PR (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] Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3. Scher et al. J Clin Oncol 2016, 34(12):1402-1418

APPENDIX 13 REVISED PROTOCOL SUMMARY OF CHANGE HISTORY

Overall Rationale for Protocol Amendment 06, 22-Dec-2020

This study has been revised to update the contraception language for women of child-bearing potential (WOCBP) participants and male participants, and their WOCBP partners. In addition, the protocol was revised to incorporate feedback from Investigators [redacted] around pregnancy testing and contraception requirements, respond to the Coronavirus Disease 2019 (COVID-19) pandemic, and to align with nivolumab program standards. [redacted]

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title page	Updated medical monitoring contact information and added clinical scientist contact information.	Administrative update. Medical Monitor has changed from [redacted] to [redacted] and [redacted] has been added as Clinical Scientist.
Synopsis, Table 1-1 Section 2, Schedule of Activities, Table 2-1, Table 2-2, Table 2-3, Table 2-4, and Table 2-5 Section 3.3, Benefit-Risk Assessment Section 4, Objectives and Endpoints, Table 4-1 Section 6.2, Exclusion Criteria 3(g) and 3(h) Section 6.4.1, Retesting During Screening Section 7.6.3, Dose Delays Due to Toxicity Section 7.6.3.1, Criteria to Resume Treatment Section 7.9.1, Prohibited and/or Restricted Treatments Section 9.2.1, Time Period and Frequency for Collecting AE and SAE Information Section 9.2.3, Follow-up of AEs and SAEs [redacted]	Changes were made throughout the protocol to [redacted] add the risks associated with SARS-CoV-2 infection and study participation; and clarify the collection and following of adverse events (AEs) and serious adverse events (SAEs).	For consistency with BMS standards, in the face of the rapidly evolving COVID-19 pandemic.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Synopsis, Number of Participants Section 5.2, Number of Participants Section 7.4, Method of Treatment Assignment	Added language to continue enrollment in selected arms in Part 2A and Part 2B.	To allow flexibility to better assess an initial efficacy signal.
Section 6.1, Inclusion Criteria	The following contraception requirement updates were made: • Updated wording in criterion 4c • Criterion 4e is no longer applicable • The first sentence in criterion 4f is no longer applicable (the second sentence pertaining to WOCBP is still applicable) • Removed text related to male contraception in the last paragraph and added a statement regarding transmission of study drug to a developing fetus • Added criterion 4g	These changes were made to: • Provide clarification and additional details regarding inclusion and contraception requirements for both WOCBP and for women who are not of childbearing potential • Remove contraceptive requirements for male participants based on current safety information
Section 6.2, Exclusion Criteria	• Revised eligibility for participants with human immunodeficiency virus (HIV) infection • Added criterion 3i to exclude participants with leptomeningeal metastases	Aligned with current nivolumab program standards.
Section 8.1, Discontinuation from Study Treatment	Revised text on reporting pregnancy.	Aligned with BMS standards.
Section 9.2.5, Pregnancy	Added a statement about the benefit/risk ratio of continuation of study treatment for pregnant participants.	Aligned with BMS standards.
Section 9.5, Pharmacokinetic and Immunogenicity Assessments, Table 9.5-2, Table 9.5-3, Table 9.5-4, Table 9.5-5	Added text on serum sample bioanalytical assay and updated table footnote text on end of infusion pharmacokinetic (PK) collection.	To clarify end of infusion (EOI) sample collection.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 10.1.3, The Randomized BMS-986218 Monotherapy Cohort Expansion in Cutaneous Melanoma (Part 2A) Section 10.1.4, The BMS-986218 Cohort Expansion Monotherapy (Part 2B)	Clarified sample size considerations for the expansion.	Updated information [redacted]
Section 10.3.1, Efficacy Analyses, Table 10.3.1-1	Clarified efficacy analysis for the expansion.	To align with current BMS standards.
Appendix 4, Women of Childbearing Potential Definitions and Methods of Contraception	Revised Appendix 4.	To align with current BMS standards and remove male contraception.
Appendix 8, Country Specific Requirements	• Updated country-specific HIV language. • Added Norway-specific additional pregnancy testing language to Table 2-5.	Revised Appendix 8 to align with current BMS standards [redacted].
Appendix 10, Management Algorithms for Studies Under CTCAE Version 4.0	Updated Appendix 10.	To align with current BMS standards.
All	Minor formatting and typographical corrections.	Minor, therefore have not been summarized.

Overall Rationale for Revised Protocol 05, 14-Aug-2019

The primary reasons for the changes outlined below are to specify the doses and schedules for expansions Part 2A and Part 2B and to include a subgroup of additional participants with advanced stage cutaneous melanoma in Part 1A.

Summary of key changes for Revised Protocol 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
All	Removed reference to Q3W dosing for BMS-986218.	Q3W schedule is not being studied in the expansion Part 2A.
Synopsis	Synopsis was updated.	Synopsis was updated to reflect the changes in the body of the protocol as summarized below.
2.0 Schedule of Activities Table 2-3	Corrected symptom directed physical examination.	To correct and clarify directions provided in the Schedule of Activities.
2.0 Schedule of Activities Table 2-4	Added note to Vital Signs.	To correct and clarify directions provided in the Schedule of Activities.
3.2.1 BMS 986218	Updated text with information from current IB.	To refer the reader to the IB.
3.2.2 Nivolumab	Updated text with information from current IB.	To refer the reader to the IB.
3.2.3 Ipilimumab	Updated text with information from current IB.	To refer the reader to the IB.
5.1 Overall Design	Revised text to reflect updated dosing regimen.	To specify dose in the expansion and provide additional details in Part 1.
5.1 Overall Design Figure 5.1-1	Updated study schematic and associated footnotes.	To specify dose in the expansion and provide additional details in Part 1 To add subgroup of participants with cutaneous melanoma.
5.1 Overall Design Figure 5.1-2	Removed reference to Q3W dosing for BMS-986218.	Q3W schedule is not being studied in the expansion Part 2A.
5.1.2 Treatment Period	Revised text to remove Q3W dosing for BMS-986218. Added text detailing dosing instructions for participants receiving BMS-986218 with nivolumab or ipilimumab.	To specify dose in the expansion and provide additional details in Part 1. To clarify dosing procedures.
5.1.2.1 The BMS-986218 Monotherapy Escalation (Part 1A)	Revised text to include 100 and 150 mg doses of BMS-986218. Updated number of participants. Added text to provide for up to 20 additional evaluable participants with advanced stage cutaneous melanoma.	Additional intermediate doses and participants added to study safety and tolerability. To assess additional clinical safety, PK and pharmacodynamic evaluation of participants with a single tumor type (advanced stage cutaneous melanoma).

Summary of key changes for Revised Protocol 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
5.1.2.2 The Safety Evaluation of Combination Doses of BMS-986218 with Nivolumab (Part 1B)	Updated number of participants.	Additional participants added to reflect planned number of dose levels under study.
5.1.2.4 The Randomized BMS 986218 Monotherapy Cohort Expansion in Cutaneous Melanoma (Part 2A), the BMS-986218 Cohort Expansion Monotherapy (Part 2B), and the BMS-986218 Cohort Expansion Combination Therapy (Part 2C) Cohort Expansions	Deleted text related to the Sentinel Participant rule. Revised text to reflect changes in dosing for Part 2.	The Sentinel participant rule is not required in expansion (Part 2A and Part 2B) as the doses have cleared safety in escalation (Part 1A). Doses and schedule to be studied are specified.
5.2 Number of Participants	Updated number of participants.	Additional participants added to reflect planned number of dose levels under study.
5.4.1 Rationale for the BMS-986218 Monotherapy Escalation (Part 1A) and the Safety Evaluation of Combination Doses of BMS-986218 with Nivolumab (Part 1B) Design	Revised text to replace MTD/RP2D with specific doses.	Doses and schedule to be studied are specified.
5.5.2 Rationale for Dose Selection and Dosing Schedule Table 5.5.2-1	Revised table to remove references to MTD/RP2D, and to replace Q2W and Q3W dosing of BMS-986218 with Q4W dosing.	Doses and schedule to be studied are specified.
6.1 Inclusion Criteria	Deleted Inclusion Criterion 4e stating women must not be breastfeeding (note this criterion is included as Exclusion criterion 3f). Added Inclusion Criterion 2.c.iv.1 providing for the addition of subgroup for participants with advanced stage cutaneous melanoma under certain conditions. Added Inclusion Criterion 2.c.vi, describing conditions under which participants with advanced stage cutaneous melanoma may be enrolled. Removed Inclusion Criterion 2.J.i.1.a to remove option of replacement of participants with TMB < 10 mutations per	To meet current protocol model document standards. To include evaluation of participants with advanced stage cutaneous melanoma. To clarify treatment of participants with cutaneous melanoma. Analysis of TMB data is not part of primary objectives and therefore it is not driving the sample size.

Summary of key changes for Revised Protocol 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
	megabase and PD L1 < 1% for purposes of statistical analyses.	
6.2 Exclusion Criteria	Revised Exclusion Criterion 5a stating incarcerated individuals may participate in the study in countries where local regulations permit under strict conditions.	To meet current protocol model document standards.
7.1 Treatments Administered Table 7.1-1	Updated Packaging/Appearance.	To reflect current drug supply characteristics.
7.3 Schedule of Dose for Each Investigational Product Table 7.3-1	Updated dosing for BMS-986218, added detail regarding infusion times.	Doses and schedule to be studied are specified.
7.4 Method of Treatment Assignment	Revised to remove references to MTD/RP2D, and to update dosing for BMS-986218.	Doses and schedule to be studied are specified.
7.6.2 Management Algorithms for Immuno-oncology Agents	Replaced Cardiac with Myocarditis in list of treatment algorithms.	To provide current treatment-related adverse event management algorithms.
8.1 Discontinuation from Study Treatment	Updated text with regards to incarcerated individuals who may participate in the study in countries where local regulations permit under strict conditions.	To meet current protocol model document standards.
9.5 Pharmacokinetic and Immunogenicity Assessments Table 9.5-4	Revised table to remove PK sample collections for BMS-986218 Q3W.	Q3W dosing schedule is not being studied in the Part 2A and Part 2B expansion.
[redacted]		
10.1.1 Monotherapy Dose Escalation (Part 1A)	Updated number of participants.	Additional participants added to reflect dose levels under study.

Summary of key changes for Revised Protocol 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
	Added text describing analysis of pharmacodynamic changes in participants in the cutaneous melanoma tumor subgroup.	To describe evaluation of participants with advanced stage cutaneous melanoma.
10.1.3 The Randomized BMS 986218 Monotherapy Cohort Expansion in Cutaneous Melanoma (Part 2A)	Revised to remove references to MTD/RP2D, and to update dosing for BMS-986218.	Doses and schedule to be studied are specified.
10.1.4 The BMS-986218 Cohort Expansion Monotherapy (Part 2B)	Revised to remove references to MTD/RP2D, and to update dosing for BMS-986218. Deleted paragraph referring to the Gehan design as a guide for the derivation of sample size in the Part 2B monotherapy expansion cohorts.	Doses and schedule to be studied are specified. Use of the Gehan design is no longer applicable. The derivation of sample size is provided in subsequent text.
Appendix 2 Study governance considerations	Replaced with current version of the Appendix.	To meet current standards.
Appendix 3 Adverse events and serious adverse events: definitions and procedures for recording, evaluating, follow-up, and reporting	Replaced with current version of the Appendix.	To meet current standards.
Appendix 4 Women of childbearing potential definitions and methods of contraception	Revised text to match most current version of the Appendix.	To meet current standards.
Appendix 10 Management algorithms for immuno-oncology agents	Replaced with current version of the Appendix, including algorithm for myocarditis.	To meet current standards.
All	Minor formatting and typographical corrections.	Minor, therefore have not been summarized.

Overall Rationale for Revised Protocol 04, 25-Dec-2018

The primary reasons for the changes outlined below are to:

1) Update pharmacokinetic (PK) and immunogenicity assessments sampling schedules to add and/or clarify blood and anti-drug antibody (ADA) samples.

Clarify relevant systemic exposure of study drugs for male participant contraceptive guidance.

Summary of key changes for Revised Protocol 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 9.5 Pharmacokinetic and Immunogenicity Assessments	Section 9.5 was modified as follows: • Table 9.5-2, Table 9.5-3, and Table 9.5-5 were updated to include additional ADA samples. • Table 9.5-4 was updated to include separate columns for BMS-986218 and ipilimumab blood samples and ADA samples.	PK and ADA sampling schedules were updated to add and/or clarify blood and ADA sample collections.
Appendix 4 Women of Childbearing Potential Definitions and Methods of Contraception	Relevant systemic exposure was updated in the third bullet of Contraception Guidance for Male Participants with Partner(s) of Childbearing Potential to until 165 and 215 days after the end of treatment for monotherapy and combination therapy, respectively.	Relevant systemic exposure was updated to ensure consistency throughout guidance on contraceptive methods for male participants with partner(s) of childbearing potential.

Overall Rationale for Revised Protocol 03, 24-Oct-2018

The primary reason for these changes are to update the study design as follows:

- Part 1A: Inclusion of alternative every-2-weeks (Q2W) dosing schedule to study BMS-986218 in the context of rapid T-regulatory cell (Treg) depletion and recovery.
- Part 1B: Inclusion of Bayesian Logistic Regression Model (BLRM) using the escalation with overdose control (EWOC) principle, and a starting dose 1 at dose level below the current safety-cleared monotherapy cohort (to allow initiation of this study part prior to declaring the RP2D and evaluation of different doses in combination in select tumor types).
- Part 2A: Inclusion of several dose levels and/or schedules to study BMS-986218 monotherapy and ipilimumab monotherapy in a randomized setting in participants with cutaneous melanoma
- Part 2B: Inclusion of several dose levels and/or schedules to study BMS-986218 monotherapy in a randomized setting in participants with non-small cell lung cancer (NSCLC).

Other key changes include [redacted] clarification of expectations and timing of scheduled activities, updates to eligibility criteria, [redacted] to the study. Additional amendments, including to sections of the Synopsis, have been made to align the protocol with respect to these changes.

Summary of key changes for Revised Protocol 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	Updated Study Director/Medical Monitor and contact information.	Incorporated contact information updates per Administrative Letter 02 and Administrative Letter 03.
Title Page; 1: Synopsis	Short Title added.	Short Title added for clarity and alignment with Short Title provided on ClinicalTrials.gov.
1: Synopsis	Added "Data Monitoring Committee" (DMC) sub-section at the end of the Synopsis section.	Clarified that a DMC is not used for this study and provided BMS process to ensure safety monitoring.
2: Schedule of Activities	The following modifications were made for Section 2 tables: • Moved footnotes, as appropriate, to corresponding rows in Notes columns. • Updated notes throughout tables for clarity (eg, defined collection windows, added details for tumor assessments). • Updated table titles to align with study design updates described below.	These changes were made to improve table readability, clarify expectations and timing of scheduled activities, and align the schedule of activities with the study design and sampling schedule updates described below.

Summary of key changes for Revised Protocol 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
3.1: Study Rationale; 3.2.1: BMS-986218 3.3: Benefit/Risk Assessment	The following modifications were made: • Updated descriptions of clinical experience with BMS-986218 and nivolumab in combination with ipilimumab. [redacted]	These changes were made to: • Align the description of clinical experience with study treatments with currently available data. [redacted]
4: Objectives and Endpoints	Added Prostate Cancer Working Group (PCWG 3) criteria to efficacy assessment endpoints and secondary [redacted] to objectives and endpoints.	Updated objectives and endpoints to clarify that PCWG 3 criteria is used in some cases for efficacy assessments [redacted].
5.1 Overall Design	The following modifications were made: • Part 1A o Added alternative Q2W dosing for BMS-986218 to further characterize safety and PK in participants with selected tumor types that may be more likely to have higher T-regulatory cell (Treg) levels at baseline. • Part 1B o Updated design from a 2-arm randomized design to a BLRM design employing the EWOC principle. • Part 2A o Updated participant population from RCC, urothelial carcinoma, and advanced-stage pancreatic ductal adenocarcinoma to cutaneous melanoma. o Added language describing the 3 dose levels and/or schedules of BMS-986218 that may explored in addition to ipilimumab.	These changes were made to: • Incorporate additional dose levels or schedules that may be explored, including Q2W dosing in Part 1A and/or Part 2, which may be the more relevant dosing frequency to achieve the pharmacodynamic goals of the program, given that Tregs are depleted within the first few days of BMS-986218 dosing and recover rapidly during the second week, as observed in preclinical models. The decision on which dose levels or schedules (eg, Q2W, Q3W) will be evaluated in Part 2 will be made prior to initiating Part 2A and Part 2B of the study. The rationale for evaluating multiple dose levels or schedules is to optimize the benefit-risk ratio for the participant. • Update the Safety Evaluation of Combination Doses of BMS-986218 with Nivolumab to a BLRM with EWOC principle study design.

Summary of key changes for Revised Protocol 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
5.1 Overall Design (cont)	• Part 2B o Updated population to focus on participants with NSCLC in a randomized setting. o Added language clarifying prior immunotherapy requirements. o Added language describing the 3 dose levels and/or schedules of BMS-986218 that may be explored. • Part 2C o Replaced description of study design with the statement "A future amendment will include 2 to 3 indications to evaluate this combination in a Phase 2 randomized setting."	• Update and clarify participant population and treatments to be explored in the expansion parts of the study. Tumor indications and prior therapies revised based on mechanism of action of BMS-986218 and study now includes tumor types that are likely to have enriched Tregs in tumor microenvironment. The number of lines of treatment was revised to take into account that patients who have progression of disease on 2 lines of treatment have poor prognosis and may not have significant benefit from additional lines of treatment. • Update and clarify that further details on the study design of Part 2C will be provided in a future amendment.
5.1: Overall Design; 5.1.2: Treatment Period; 5.1.3: Follow-up Period	Updated duration of treatment to be a maximum of 2 calendar years for BMS-986218 Q4W ± nivolumab Q4W or BMS-986218 Q2W, and a maximum of 4 doses for ipilimumab and BMS-986218 Q3W within text and Figure 5.1-2.	Aligned the maximum duration of BMS-986218 Q3W and ipilimumab Q3W with the current standard of care for ipilimumab.
5.1.2: Treatment Period (including subsections 5.1.2.1, 5.1.2.2, 5.1.2.3, and 5.1.2.4)	The following modifications were made: • Added language to clarify every-12-weeks (Q12W) tumor assessments in Part 2A. • Updated description of participant populations for each study part, as needed to align with changes to study design noted above. • Added language providing dose level and schedule details for alternative Q2W dosing schedule for Part 1A, Part 2A, and Part 2B, and alternative Q3W dosing schedule for Part 2A and Part 2B. • Aligned Part 1B with change to design from a 2-arm randomized design to a BLRM design employing the EWOC principle. • Added description of sentinel participant rule for Part 1B, Part 2A, Part 2B, and Part 2C.	There changes were made to: • Clarify timing and expectations for treatment period and tumor assessments. • Update the description of the BMS-986218 monotherapy and expansion parts of the study to align with the changes made to the Overall Design.
5.1.3.2: Response Follow-up Period	Added window of ± 1 week for every-8-weeks (Q8W) tumor assessments.	Clarified expectations and timing for follow-up tumor assessments.

Summary of key changes for Revised Protocol 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
5.1.4: Data Monitoring Committee and Other External Committees	Updated rationale for no DMC and language describing BMS multi-layered process to ensure safety monitoring during the study.	Clarified BMS process to ensure safety monitoring.
5.2: Number of Participants	Updated participant numbers per changes to Overall Study Design noted above.	Aligned planned number of participants with updated study design outlined above.
5.4.5: Rationale for Two Years Fixed Duration of Treatment with Checkpoint Blockade	Updated text describing the justification for 2-year fixed duration of treatment with checkpoint blockade per recently reported data.	Aligned justification of 2-year fixed duration of checkpoint blockade per currently available information.
5.4.6: Rationale for Treatment Beyond Progression	Removed last paragraph describing scenarios in which treatment beyond progression may be appropriate.	Removed text not related to this section (ie, rationale) for clarity.
5.5.2: Rationale for Dose Selection and Dosing Schedule	Updated Tumor Types and Dose columns in Table 5.5.2-1 to reflect changes to study design for each study part, as described above.	Aligned dosing schedule with updated study design outlined above.
5.5.2.1: BMS-986218	Added paragraph describing rationale for alternative Q2W and Q3W dosing schedules that may be explored to characterize the safety and PK of BMS-986218.	Provided rationale for inclusion of alternative Q2W and Q3W dosing schedules for BMS-986218 in updated study design.
5.5.2.2 Nivolumab	Updated text to align description of BMS-986218 and nivolumab doses and permitted dose reductions with updated study design for Part 1B.	Aligned BMS-986218 and nivolumab doses with updated study design outlined above.

Summary of key changes for Revised Protocol 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
6.1: Inclusion Criteria	The following modifications were made: • 2) c) i) no longer applicable; replaced with 2) c) iii) revised to limit permission of all solid tumor histologies to the Q4W dosing schedule in Part 1A. • 2) c) iv): added criterion on permitted tumor histologies for Q2W dosing schedule in Part 1A. • 2) c) ii) no longer applicable; replaced with 2) c) v) revised to received, and then progressed, relapsed or intolerant to at least 2 standard treatment regimens with proven survival benefit, and clarified prior therapy criteria for hormone-sensitive and prostate cancers. • 2) d) i) no longer applicable; replaced with 2) h) i) to clarify included histologies. • 2) d) ii) and 2) e) i) no longer applicable; replaced with 2) h) ii) and 2) i) i) to clarify scenarios for prior systemic therapy. • 2) f) i) (1), (2), (3) no longer applicable; replaced with 2) j) i) (1) and (2) to update and clarify permitted tumor histologies for Part 2B. • 2) g) and accompanying subbullets no longer applicable. • 3) f): added criterion on expectations for toxicities related to prior systemic therapy.	Updated and clarified eligibility criteria in alignment with updated study design outlined above. Tumor indications and prior therapies revised based on mechanism of action of BMS-986218 and study now includes tumor types that are likely to have enriched Tregs in tumor microenvironment. The number of lines of treatment was revised to take into account that patients who have progression of disease on 2 lines of treatment have poor prognosis and may not have significant benefit from additional lines of treatment.
6.2: Exclusion Criteria	The following modifications were made: • 2) e): added criterion on expectations for prior radiation therapy. • 2 f): added criterion on expectations for LHRH/GnRH agonist therapy in male participants. • 2) g): added criterion on expectations for botanical preparations prior to study treatment, including use of marijuana and its derivatives. • 3) e) ix) no longer applicable; replaced with 3) e) xii) clarifying expectations for prior vaccinations.	Updated and clarified eligibility criteria in alignment with updated study design outlined above.
6.4: Screen Failures	Added phrase “as applicable” to Consolidated Standards of Reporting Trials (CONSORT) statement.	Clarified requirements for screen failure information.
7.1: Treatments Administered	Added new subsections, Section 7.1.1 BMS-986218, Section 7.1.2 Nivolumab, and Section 7.1.3 Ipilimumab to provide additional details for administration of each study drug.	Provided additional details on administration of BMS-986218, nivolumab, and ipilimumab.
7.3: Schedule of Dose for Each	Updated Table 7.3-1 for consistency with study design updates.	Aligned the selection and timing of doses for all study parts with updated study design outlined above.

Summary of key changes for Revised Protocol 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Investigational Product		
7.4: Method of Treatment Assignment	Removed paragraphs describing randomization of Part 1B and updated/added text describing randomization of Part 2A and Part 2B.	Aligned treatment assignment methods with updates to study design outlined above.
7.5: Blinding	Added new section related to blinding.	Clarified expectations for access to treatment and/or randomization assignments prior to database lock.
7.6.1.1: Gastrointestinal Dose-limiting Toxicity; 7.6.1.5: Other Dose-Limiting Toxicities;	Added "regardless of duration" to bullet for Grade ≥ 3 diarrhea or colitis, and updated list of Grade 3 or 4 events not considered to be a DLT to add that a confirmatory laboratory test is required for conclusions related to electrolyte abnormalities and to remove diarrhea.	Updated expectations for treatment-related events considered to be dose-limiting toxicities (DLTs).
7.6.3: Dose Delays Due to Toxicity	Added "due to any cause" to first sentence.	Clarified expectations for events considered reasons for withholding all study treatments.
7.6.4: Exceptions to Permanent Discontinuation Criteria	Updated list of drug-related AEs meeting DLT criteria not requiring permanent discontinuation to: • Update first bullet to remove diarrhea and update duration from 3 days to 48 hours either spontaneously or with medical intervention. • Remove Grade 4 increase in amylase or lipase that is not associated with clinical or radiographic evidence of pancreatitis.	Updated expectations for events requiring permanent discontinuation.
7.9.1: Prohibited and/or Restricted Treatments	Added botanical preparations, marijuana and its derivatives, and live/attenuated vaccines to list of prohibited and/or restricted treatments.	Updated list of restricted and/or prohibited treatments to include botanical preparations, marijuana, and live/attenuated vaccines.
7.9.4: Palliative Radiation	Added new section describing scenarios in which palliative radiation for disease-related symptoms is permitted for participants on the study.	Provided details on scenarios in which palliative radiation for disease-related symptoms is permitted for participants on the study.
7.9.5: Surgery	Added new section describing scenarios in which study treatment should be held for participants undergoing surgery during the study.	Provided details on expectations for holding study treatment for participants who undergo surgery during the study.
7.10: Treatment After the End of the Study	Updated section to note that BMS will not continue to provide BMS-supplied study treatment to participants/Investigators unless BMS chooses to extend the study.	Clarified expectations for treatment after the end of the study.
8.1: Discontinuation from Study Treatment	Added Grade 4 amylase or lipase elevation as a reason for discontinuation.	Updated reasons for discontinuation from study treatment to include Grade 4 amylase or lipase elevation.
8.1: Discontinuation from Study	Updated language to clarify that, in the case of pregnancy, study treatment will be permanently continued in an appropriate manner, and removed	Clarified expectations and scenarios for reporting and discontinuation of study treatment in the case of pregnancy.

Summary of key changes for Revised Protocol 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Treatment; 9.2.5: Pregnancy	text related to scenarios for continuing study treatment in the context of pregnancy.	
8.1.1: Treatment Beyond Progression	Added text "prior to treatment beyond progression" to last paragraph.	Clarified that all decisions to continue treatment beyond initial progression must be discussed with the BMS Medical Monitor or designee prior to treatment beyond progression.
[redacted]		
9.3: Efficacy Assessments; 9.3.1: Imaging Assessment for the Study	Added text describing the timing of efficacy assessments and imaging modalities for imaging assessments in the context of each study part.	Clarified timing and expectations of efficacy/imaging assessments across study parts and in alignment with changes made to the Overall Design.
9.4: Overdose	Updated text describing overdose event and monitoring actions in the event of an overdose.	Clarified the definition and monitoring expectations for overdose.
9.5: Pharmacokinetics and Immunogenicity Assessments	The following modifications were made: • Table 9.5-2 and Table 9.5-5 o Updated footnote b to include reference to Table 7.3-1 for information on infusion duration. o Added footnote c providing time windows for sample collections for C1D8, C1D15, C1D22, C3D8, C3D15, and C3D22 in Table 9.5-2 and Table 9.5-4. • Added new Table 9.5-3 Table 9.5-4 for Q2W and Q3W dosing schedules, respectively.	These changes were made to: • Clarify timing details for end-of-infusion samples. • Clarify time windows for PK and immunogenicity sample collections for C1D8, C1D15, and C1D22 timepoints. • Align PK and immunogenicity sampling schedules with alternative Q2W and Q3W dosing schedules added to the study design.
[redacted]		

Summary of key changes for Revised Protocol 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
10.1: Sample Size Determination (including subsections)	Updated description of study design, planned number of participants, and/or target populations across study parts per updates made to the study design.	Aligned description of sample size determination with updated study design outlined above.
[redacted]		
11: References	Updated references as needed per literature supporting newly added text and current versions of Investigator Brochures.	Provided references to the most current versions of Investigator Brochures for nivolumab and ipilimumab.
Appendix 2: Study Governance Considerations	Modified Good Clinical Practice section in Appendix 2 to: • Add bullet to clarify that the study will also be conducted in accordance with ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines Good Clinical Practice. • Align with revised definition of serious breach to Regulation No 536/2014 of the European Parliament and of the Council.	Modified text to align with statement in the informed consent form and TransCelerate Common Protocol Template.
Appendix 3: Adverse Events and Serious Adverse Events Definitions and Procedures for Recording, Evaluating, and Follow-up and Reporting	Added new sections for Events Meeting the AE Definition, Events Not Meeting the AE Definition, and Definition of Serious Adverse Event (SAE). Modified the following sections: SAEs (text related to pregnancy and drug-induced liver injury); Evaluating AEs and SAEs (updated and rearranged bulleted information); and Reporting of SAEs to Sponsor or Designee (updated and rearranged bulleted information related to pregnancy and paper report forms).	Modifications made to information related to AEs and SAEs to align with the TransCelerate Common Protocol Template, regulatory definition EMA GVP Module VI (EMA/873138/2011) and ICH E2A, and clarify the instructions for reporting pregnancy.
Appendix 10: Management Algorithms for Immuno-oncology Agents	In Hepatic Adverse Event Management algorithm, footnote stating that immuno-oncology therapy may be delayed rather than discontinued if AST/ALT ≤ 8 × ULN or T.bili ≤ 5 × ULN was removed.	Language was modified to align protocol with current study treatment Investigator Brochures and program safety parameters.
Appendix 11: Statistical Methodology	Updated statistical methodology to incorporate changes to study design.	Updated statistical methods to align with updated study design outlined above.

Summary of key changes for Revised Protocol 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
All	Minor formatting and typographical corrections.	Corrections for clarity and consistency within the document were minor, and therefore have not been summarized.

Overall Rationale for the Revised Protocol 02, 14-Feb-2018

The primary reasons for these changes are to expand enrollment in Part 1A to include up to 60 participants, extend the treatment period to 2 calendar years, modify eligibility criteria for participants with advanced PDAC, permit the use of concomitant palliative hormonal therapy, remove the option of re-treatment following progression, [redacted] Additional amendments have been made to align the protocol with respect to these changes.

Summary of key changes of Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-2: On Treatment - Schedule of Activities for the BMS-986218 Monotherapy Escalation (Part 1A), the Safety Evaluation of Combination Doses of BMS-986218 with Nivolumab (Part 1B), the Randomized BMS-986218 Monotherapy Cohort Expansion in Melanoma (Part 2A; BMS-986218 arm only), the BMS-986218 Cohort Expansion Monotherapy (Part 2B), and the BMS-986218 Cohort Expansion - Combination Therapy (Part 2C); Table 2-3: On Treatment - Schedule of Activities for the Randomized BMS-986218 Monotherapy Cohort Expansion in Melanoma (Part 2A), Ipilimumab Monotherapy Only	On-treatment schedule of activities was modified as follows for all study parts: • Added text to column headers for each cycle specifying a visit window of ± 2 days. • Added footnotes detailing that, beyond cycle 3, electrocardiograms (ECGs) must be performed every 3 cycles up to end of treatment (EOT). • Updated CT/MRI tumor imaging assessment from being performed from baseline/screening to first dose.	Clarified the visit window for each on-treatment activity and the frequency and timing of performing EGCs beyond cycle 3. Modified tumor imaging assessments to be performed from first dose.
[redacted]		

Summary of key changes of Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Table 2-1: Screening Schedule of Activities for All Study Parts; Table 2-2: On Treatment - Schedule of Activities for the BMS-986218 Monotherapy Escalation (Part 1A), the Safety Evaluation of Combination Doses of BMS-986218 with Nivolumab (Part 1B), the Randomized BMS-986218 Monotherapy Cohort Expansion in Melanoma (Part 2A; BMS-986218 arm only), the BMS-986218 Cohort Expansion Monotherapy (Part 2B), and the BMS-986218 Cohort Expansion - Combination Therapy (Part 2C); Table 2-3: On Treatment - Schedule of Activities for the Randomized BMS-986218 Monotherapy Cohort Expansion in Melanoma (Part 2A), Ipilimumab Monotherapy Only; Section 5.1.2.4: The Randomized BMS 986218 Monotherapy Cohort Expansion in Melanoma (Part 2A), the BMS-986218 Cohort Expansion Monotherapy (Part 2B), and the BMS-986218 Cohort Expansion Combination Therapy (Part 2C) Cohort Expansions; Section 5.1.2.5: Treatment Beyond Progression; Section 6.1: Inclusion Criteria; Section 8.1: Discontinuation from Study Treatment; Section 8.1.1: Treatment Beyond Progression; Table 10.3.1-1	Added text to refer to Prostate Cancer Working Group 3 (PCWG 3) efficacy assessment criteria for prostate.	Modified efficacy assessment criteria to include PCWG 3 criteria in addition to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria.
Table 2-4: Follow-up Procedural Outline for All Study Parts (CA022001); Section 5.1.3.2: Response Follow-up Period	Text and footnotes related to tumor/response assessments were modified as follows: • Updated language to specify:	Modified tumor/response assessment schedule; clarified submission and review of scans.

Summary of key changes of Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
	○ Continuation of tumor assessments following EOT/study treatment discontinuation every 8 weeks (Q8W) until subsequent tumor-directed therapy. ○ Participants who remain free of subsequent therapy will continue to receive tumor assessment scans for the first 48 weeks after discontinuation of study treatment/EOT visit and then Q12W (± 2 weeks) for a total duration of 2 years. • Added that assessment scans will be submitted for blinded independent central review (BICR).	
Table 2-4: Follow-up Procedural Outline for All Study Parts (CA022001); Section 5.1.3.2: Response Follow-up Period; Section 5.1.3.3: Survival Follow-up Period	Added "(± 2 weeks)" next to Q12W follow-up intervals.	Clarified follow-up window permitted for response and survival follow-up schedules.
Table 2-5: Re-treatment Screening Procedural Outline (CA022001); Figure 5.1-2: Study Period and Participant Flow for BMS-986218, Ipilimumab, and Nivolumab; Section 5.1.3.4: Re-treatment During Follow-up Periods; Section 5.4: Scientific Rationale for Study Design; Table 9.5-4: PK and Anti-Drug Antibody Sampling Schedule for BMS-986218 Q4W Monotherapy and Ipilimumab Q3W Monotherapy During Re-treatment; Table 9.5-5: PK and Anti-Drug Antibody Sampling Schedule for BMS-986218 Q4W in Combination with Nivolumab Q4W During Re-treatment; [redacted]	Removed all language related to re-treatment for patients with disease progression during response follow-up.	Modified response follow-up to exclude option for re-treatment for participants with disease progression.
Section 3.3: Benefit/Risk Assessment; Section 5.5.1.1: BMS-986218 Rationale for Starting Dose in Humans; Section 5.5.2.2: Nivolumab; Section 7.5.2: Management Algorithms for Immuno-oncology Agents	Replaced "immune-related adverse events (AEs)" to "immune-mediated AEs."	Modified description of AEs that may reflect activation of the immune system.
Table 4-1: Objectives and Endpoints; Table 10.3.1-1: Efficacy - Statistical Analyses	Added 24- and 48-week analyses for progression-free survival rate (PFSR) by RECIST v1.1.	Modified PFSR study endpoint to include analyses at 24 weeks and

Summary of key changes of Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
		48 weeks, in addition to at 36 weeks.
[redacted]		
Section 5.1: Overall Design	Updated duration of study from approximately 3 years to approximately 5 years.	Modified study duration.
Figure 5.1-1: Study Design Schematic; Section 5.1.2.1: The BMS-986218 Monotherapy Escalation (Part 1A); Section 5.2: Number of Participants; Section 10.1.1: Monotherapy Dose Escalation (Part 1A)	Text related to the number of participants in Part 1A (BMS-986218 monotherapy escalation) was modified as follows: • Planned enrollment for Part 1A was updated from approximately 30 to up to 60 participants. • Rationale for the number of participants to be included in Part 1A was added.	Modified number of participants to be included in Part 1A to fulfill the expected number of participants needed for Bayesian Logistic Regression Model (BLRM) and allow for further evaluation of safety, pharmacokinetic (PK), or pharmacodynamic parameters.
Figure 5.1-1: Study Design Schematic; Section 6.1: Inclusion Criteria	The inclusion criteria for Part 2B (BMS-986218 Cohort Expansion Monotherapy) were modified to remove tumor infiltration requirements for patients with advanced pancreatic ductal adenocarcinoma (PDAC).	Modified the eligibility criteria to include patients with advanced PDAC in Part 2B, regardless of tumor infiltration status.
Figure 5.1-1: Study Design Schematic; Figure 5.1-2: Study Period and Participant Flow for BMS-986218, Ipilimumab, and Nivolumab; Section 5.1.2: Treatment Period; Section 5.1.3.1: Safety Follow-up Period; Section 5.1.3.4: Re-treatment During Follow-up Periods; Section 5.4: Scientific Rationale for Study Design	Text and footnotes related to treatment period were updated to extend the duration of treatment to up to 2 calendar years for all study parts.	Modified treatment period to allow all participants to receive study treatment for a maximum of 2 calendar years.
Section 5.1.2.5: Treatment with Additional Cycles Beyond 36 Weeks	This section was removed.	In accordance with the additional revised protocol 02 modification extending the treatment period to a maximum of 2 calendar years, this section is no longer applicable.
Section 5.1.3.3: Survival Follow-up Period	The survival follow-up period following the first dose of study treatment was updated from 2 years to 4 years.	Modified the survival follow-up period following the first dose of study treatment in accordance

Summary of key changes of Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
		with the additional revised protocol 02 update extending the treatment period to a maximum of 2 calendar years.
Section 5.4.5: Rationale for Two Years Fixed Duration of Treatment with Checkpoint Blockade	This section has replaced Section 5.4.5: Rationale for Treatment Duration in the previous amendment of this protocol.	Modified the rationale provided for treatment duration to reflect the additional revised protocol 02 update extending the treatment period to a maximum of 2 calendar years.
Section 6.2: Exclusion Criteria	The exclusion criteria were modified to: • Remove the list of permitted prior anticancer treatments within the 2) Prohibited Treatments subsection. • Add reference to new Appendix 8 (Country Specific Requirements) for HIV testing within the 3) Medical History and Concurrent Diseases subsection. • Removed text around prisoners or involuntarily incarcerated participants being permitted to continue as a participant" within the 5) Other Exclusion Criteria subsection	Clarified which therapies are prohibited within the eligibility criteria and country-specific requirements for HIV testing. Change to text for prisoners/involuntarily incarcerated participants was made because the statement referring to "continue as participant" was not applicable to the eligibility criteria.
Section 7.4: Method of Treatment Assignment	Text added describing scenarios in which participant replacement is not permitted after study discontinuation in Part 1B and Part 2A.	Clarified when participant replacement is not permitted.
Section 7.5.1: Dose-limiting Toxicities	Added scenarios in which participants withdrawn from the study during the dose limiting toxicity (DLT) period may be considered DLT-evaluable.	Clarified which participants may be considered DLT-evaluable.
Section 7.8.1: Prohibited and/or Restricted Treatments; Section 7.8.3: Permitted Therapy	Added permitted use of palliative hormonal therapy.	Modified permitted therapy to include palliative hormonal therapy when indicated.
Section 8.1: Discontinuation from Study Treatment	Modified text in this section to: • Remove bullet regarding separate discontinuation criteria for nivolumab and BMS-986218. • Add a note to bullet describing discontinuation for participants who become imprisoned or involuntarily	Clarified that participants receiving combination therapy must discontinue both therapies if they meet discontinuation criteria and that there may be specific circumstances that permit study treatment continuation.

Summary of key changes of Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
	incarcerated to clarify scenarios in which continuation is permitted.	
Section 8.1.1.1: Discontinuation Due to Further Progression (Confirmed Progression)	Added scenarios in which participants who have progressed should continue to receive treatment and monitoring or should discontinue the study.	Clarified when participants should remain on the trial or permanently discontinue the study following progression.
Section 9.2.1: Time Period and Frequency for Collecting AE and SAE Information	Added further direction on when information on AEs and serious AEs (SAEs) must be collected.	Clarified the time period for collecting AE and SAE information.
Section 9.2.2: Method of Detecting AEs and SAEs	Added text related to avoiding bias when collecting AEs and SAEs.	Clarified expectation for collecting AEs/SAEs and inquiry guidance based on program/protocol.
Section 9.3.1: Imaging Assessment for the Study	Added language describing the timing and frequency of tumor assessments for participants at the time of EOT or study treatment discontinuation and participants who are allowed to be treated beyond initial disease progression.	Clarified tumor assessment schedules for participants at EOT or study treatment discontinuation and participants treated beyond progression.
Section 9.5: Pharmacokinetic and Immunogenicity Assessments; Table 9.5-2: Pharmacokinetic and Anti-Drug Antibody Sampling Schedule for BMS-986218 Q4W Monotherapy in Dose Escalation and Dose Expansion and Ipilimumab Q3W Monotherapy in Dose Expansion (Parts 1A, 2A, and 2B); Table 9.5-3: Pharmacokinetic and Anti-Drug Antibody Sampling Schedule for BMS-986218 Q4W in Combination with Nivolumab Q4W in Dose Escalation and Dose Expansion (Parts 1B and 2C)	Modified PK assessment text and tables to: • Update sample collection types and frequency between C5D1 and EOT. • Remove collection of dose delay samples.	Modified PK assessments to collect predose BMS-986218 and nivolumab blood samples every fourth cycle after C5 until EOT and exclude collection of dose delay samples.
[redacted]		

Summary of key changes of Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 10.3: Statistical Analyses	Added statement that a description of the participant population will be included in the statistical output reported, including subgroup of age, gender, and race.	Statement added to meet compliance requirements.
Appendix 2: Study Governance Considerations	Added bullet to clarify that the study will also be conducted in accordance with ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines Good Clinical Practice.	Modified text to align with statement in the ICF and TransCelerate Common Protocol Template.
Appendix 8: Country Specific Requirements	Added new appendix for country specific requirements related to HIV testing.	Appendix added to support country specific requirements for HIV testing within the 3) Medical History and Concurrent Diseases subsection.
Appendix 12: Prostate Cancer Working Group 3 (PCWG 3) Guidelines (with Modified Response Evaluation Criteria in Solid Tumors (RECIST) Criteria for Soft Tissue Lesion Assessment)	Added new appendix for PCWG 3.	Appendix added to support inclusion of PCWG 3 criteria for efficacy assessments.

Summary of key changes of Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
All	Minor formatting and typographical corrections.	Made corrections for clarity and consistency within the document.