Protocol for

Official Title of Study

A Phase 1/2a Study of BMS-986179 Administered Alone and in Combination with Nivolumab (BMS-936558) in Subjects with Advanced Solid Tumors

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Clinical Protocol CA013004

A Phase 1/2a Study of BMS-986179 Administered Alone and in Combination with Nivolumab (BMS-936558) in Subjects with Advanced Solid Tumors

Revised Protocol Number: 08

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

Replace all previous version(s) of the protocol with this revised protocol and please provide a copy of this revised protocol to all study personnel under your supervision, and archive the previous version.

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 08	30-Nov-2018	1) Selection strategy has been modified based on new data on adenosine-axis that is more specific to the pathway being targeted by BMS-986179. 2) Data from completed toxicokinetics study has been added to provide additional safety information. 3) Part 2 expansion cohorts in the tumor-specific indications with high unmet medical need are open. Cardiovascular disease is prevalent in these indications. 4) Cardiovascular exclusion criteria has been modified. Under this modification, some asymptomatic patients with history of cardiovascular disease may be permitted to enroll after mandatory evaluation by specialist that includes functional ischemic test.
Administrative Letter 04	25-Jul-2018	Change in Study Director / Medical Monitor information
Administrative Letter 03	17-Jul-2018	The typographical error was corrected for the dose of rHuPH20 to be 1000 U/mL instead of 2000 U/mL.
Revised Protocol 07	28-Feb-2018	1) Subcutaneous dosing objective has been added to Part 1B of this study to assess a potentially important alternative approach to dosing. 2) Added background for rHuPH20, which enables SC administration of BMS-986179. [redacted]
Revised Protocol 06	20-Oct-2017	1) Changed the tumor types in Part 2, Cohort Expansion to add non-small cell lung cancer (NSCLC), renal cell cancer (RCC), castrate-resistant prostate carcinoma, squamous cell carcinoma of the head and neck, and melanoma, and to delete ovarian cancer, colorectal cancer, and gastric cancer 2) Allowed for monotherapy in Part 2 with BMS-986179 in NSCLC and RCC, with the option for subjects to receive combination therapy with BMS-986179 and nivolumab at disease progression 3) Changed the treatment duration to 2 years, changed follow-up to 3 years after initial dose, and added a Q4W regimen for combination therapy with BMS-986179 and nivolumab [redacted] 5) Added laboratory parameters HbA1c, cardiovascular lipid profile, and PSA to list of assessments in Section 5.3.2 6) Added clinical observations and supporting data throughout Section 1.1 7) Added a replacement criterion to allow subjects without both pre- and on-treatment tumor biopsies, or whose biopsies are uninformative, to be replaced 8) Increased the number of pre-treatment core biopsy specimens from 2 to either 4 (for NSCLC, melanoma, and SCCHN) or 3 (for all other tumor types)

Document	Date of Issue	Summary of Change
		9) Changed the name of the Study Director/Medical Monitor 10) Editorial changes throughout the protocol
Revised Protocol 05	16-Mar-2017	Incorporates Administrative Letters 01 and 02, and Amendments 01, 02, 03, 05 and 07
Amendment 07	16-Mar-2017	1) Included additional exclusion criteria for cardiovascular and cerebrovascular disease in Section 3.1.2 2) Added a new Section 3.4.4 to ensure appropriate assessment and management of cardiovascular risk factors 3) Updated dose delay criteria for subjects with any investigation or symptoms suggestive of possible thrombotic or ischemic events during treatment in Section 4.5.4.1 4) Updated guidelines to permanently discontinue BMS-986179 in subjects with any myocardial infarction or thrombotic/ischemic cerebrovascular event during treatment in Section 4.5.6
Revised Protocol 04	26-Oct-2016	Incorporates Administrative Letters 01 and 02, and Amendments 01, 02, 03 and 05
Amendment 05	26-Oct-2016	1) Included updates made in nivolumab IBv15 in Sections 1.4.4, 3.3.1, and Appendix 1, respectively 2) Added text describing vascular effects in mouse models in literature, and added dose delay in Section 1.5 3) Prohibited use of dipyridamole 2 weeks prior to the first dose and during treatment in Section 3.4.1 4) Removed windows for dosing visits and further clarified minimum treatment interval between 2 doses in Sections 5.1 and 4.5, respectively 5) Revised and clarified requirements for minimum dosing interval, dose delay due to toxicity, medical events or non-medical events, hepatic non-hematologic DLT, and removed tumor assessment procedure when study drugs are permanently discontinued in Section 4.5 6) In Section 5.1, revised Vital Signs requirements during initial treatment and re-treatment in Parts 1B and 2, removed pregnancy test on Days 8 and 22 during retreatment in Q1W, and added windows for tumor assessment during follow-ups 7) Clarified DILI criteria for subjects with abnormal ALT or AST at baseline in Section 6.6 8) Added 1 new reference in Section 12 9) Editorial changes throughout the protocol
Administrative Letter 02	07-Sep-2016	1) Clarified the End of Treatment and Safety Follow-up requirements for subjects who discontinue from study treatment 2) Removed the fasting requirement for glucose testing during screening.
Revised Protocol 03	06-Jun-2016	Incorporates Administrative Letter 01, and Amendments 01, 02 and 03
Amendment 03	06-Jun-2016	1) Clarified rationales for 2 week lead-in and for dose selection in Sections 1.1.3 and 1.1.5.1, respectively 2) Added a 9 day waiting period for doses over 400 mg, and revised waiting periods for each dose level Sections 1.1.7 and 3.1.1, respectively 3) Clarified definition of treatment arm and number of arms in Part 1B in

Document	Date of Issue	Summary of Change
		Sections 3.1.2 and 8.3.1 4) Clarified requirement for dose delay in Part 1A in Section 4.5.4 5) Added language to allow for collection and central review of imaging assessments in Section 5.4 6) Editorial changes throughout the protocol
Revised Protocol 02	31-May-2016	Incorporates Administrative Letter 01, and Amendment 01 and 02
Amendment 02	31-May-2016	1) Revised Target Population in Inclusion Criteria in Section 3.3.1 2) Revised Dose-limiting Toxicities in Section 4.5.1
Administrative Letter 01	26-Apr-2016	Updated the cover page with new Study Director and Medical Monitor
Revised Protocol 01	12-Apr-2016	Incorporates Amendment 01
Amendment 01	12-Apr-2016	1) Added rationale for sentinel subject approach 2) Added additional rationales [redacted] for initiation of PD substudy 3) Revised treatment arms and sample sizes for PD substudy 4) Revised vital sign measurements during infusions 5) Procedure clarifications and typographic changes
Original Protocol	15-Mar-2016	Not applicable

OVERALL RATIONALE FOR REVISED PROTOCOL 08

This amendment includes changes to eligibility which help refine subject selection and establish new requirements for enrollment of subjects with a prior history of cardiovascular risk. The ongoing non-small cell lung cancer, melanoma and squamous cell head and neck cancer cohorts enroll subjects with high tumor mutational burden (TMB), which is a general selection for enriching response to anti-PD-(L)1 therapy. New data focusing on the role of adenosine-axis markers in patients who have progressed on prior anti-PD-(L)1 have become available and supports a more refined selection strategy specific to the pathway being targeted by BMS-986179. Subjects will now be selected based on response to prior anti-PD-(L)1 therapy and not TMB results. Details are provided in Section 1.1.4.1. Furthermore, expansion cohorts in the tumor-specific indications with high unmet medical need are open to subjects with no further treatment options available. Cardiovascular disease is prevalent in these indications. Previous eligibility criteria excluding subjects just based on history of cardiovascular disease (ie, coronary artery disease) may exclude a significant proportion of patients who may not be at a particularly elevated risk of cardiovascular events while receiving BMS-986179. Individual risk evaluation by specialist (ie, cardiologist) that includes functional test such as stress test (and additional structural assessment as needed) may be a better, more reliable approach to identify high-risk subjects to be excluded. Under modified cardiovascular exclusion criteria, some asymptomatic patients with history of cardiovascular disease may be permitted to enroll after mandatory evaluation by specialist that includes functional ischemic test (ie, stress test). Subjects with abnormal findings or high risk findings will be strictly excluded. These measures would also offer better opportunities for close monitoring and risk assessment. In addition this amendment also includes minor corrections and details are provided in the below table.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 08

Section Number & Title	Description of Change	Brief Rationale
Synopsis	Sections updated	Sections in the synopsis have been updated to align with the protocol section changes
Section 1.1.4.1 Overview of Subject Selection Strategy for Part 2 Dose Expansion	Section text has been updated and modified	Selection strategy has been modified based on new data on adenosine-axis that is more specific to the pathway being targeted by BMS-986179. Details are provided in the protocol body.
Section 1.1.4.2 Rationale for Inclusion of Specific Tumor Types	Section text has been updated and modified	Updated to reflect modified selection strategy

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 08		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 1.1.7 Rationale for Subcutaneous Administration	• Additional toxicokinetics information has been added to support the proposed subcutaneous administration in the clinical trials.	Data from completed toxicokinetics study has been added to provide additional safety information.
Section 1.5 Overall Risk/Benefit Assessment	The section has been modified to correct an error and update the study information	Corrected an error (mg/day to Q1W) and provided up to date information.
Section 3.1 Study Design and Duration	• Section for tumor biopsies has been updated to clarify that 4 fresh core biopsy specimens will be collected for all tumor types during screening. • The statement in the last paragraph has been corrected. During response/survival follow-up, treated subjects who do not experience progressive disease prior to treatment discontinuation will be followed for 3 years following the **last** dose of study drug not the first dose of study drug.	Previously 4 fresh core biopsies were required only for tumor types subject to TMB testing. Now this requirement is consistent across all tumor types and will provide more tumor specimens for biomarker evaluation. The word in bold has been corrected from "first" to "last". There is no change to the analysis plan.
Figures 3.1.1-1: Study Design Schematic (Part 1A [Dose Escalation]); Figure 3.1.2-1: Study Design Schematic (Part 1B [PD Substudy] and Part 2 [Expansion] - Q2W and Q3W Schedules; Figure 3.1.2-2: Study Design Schematic (Part 1B [PD Substudy] and Part 2 [Expansion] - Q4W Schedule)	• All the figures were updated for Tumor Assessment during Follow-up to read as: "Every 8 weeks from the last assessment for the first two years and then every 12 weeks in the third year" • Added a footnote to Figure 3.1.2-1 as shown below: "For subcutaneous cohort in PD sub-study Q4W: BMS-986179 would be administered as monotherapy by the subcutaneous route on C1D1, followed by within-patient crossover to the IV on C2D1, then continuing SC on C3D1 and beyond until patients fulfill criteria for treatment discontinuation"	Inconsistency in tumor assessment schedules was noted in the figures and has been corrected. Updated to describe Q4W SC schedule in the figure.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 08		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 3.1.3. Part 2 (Cohort Expansion)	Information about TMB has been removed and section text has been modified	Updated to reflect modified selection strategy
Section 3.3.1 Inclusion Criteria	Criteria 2)c)ii)(2), 2)c)v)(3), 2)c)vi)(3) and 2)j) are not applicable after implementation of this revised protocol 08 and ***"Not applicable as per revised protocol 08"*** has been added in the beginning of each listed criteria.	Updated to reflect modified selection strategy
	Criteria 2)c)ii)(5), 2)c)iii)(3), 2)c)v)(4), 2)c)vi)(5) has been added as a new criteria and it reads as: "Duration of most recent prior therapy (date of the last dose minus date of the first dose) with anti-PD-(L)1 must have exceeded 12 weeks with no evidence of progression (clinical or radiographic) during the first 12 weeks."	Updated to reflect modified selection strategy
	Criteria 2)j) has been modified and it reads as: "Pre-treatment biopsy tissue may have been collected at any time during the screening period prior to the first dose of the study drug, but collection conditions as described below must be met. (1) At least 4 fresh core biopsies must be collected pre-treatment and on-treatment. The biopsies will be taken as outlined in the laboratory manual. The tumor tissue specimen must be a core-needle, excisional or incisional biopsy. Fine-needle biopsies, drainage of pleural effusions with cytospins, or punch biopsies are not considered adequate for biomarker review. Biopsies of bone lesions that do not have a soft tissue component or decalcified bone tumor samples are also not acceptable. In cases where it is difficult to obtain all fresh cores required,	Updated to reflect modified selection strategy (removed prospective TMB selection)

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 08		
Section Number & Title	**Description of Change**	**Brief Rationale**
	additional archival specimens will be accepted."	
	Criteria 3)f) has been modified to remove "Azoospermic males are exempt from contraceptive requirements".	This modification was made since sperm counts are not performed on this study
Section 3.3.2 Exclusion Criteria	Criteria 2)f) has been modified and it reads as: "Subjects with a prior history of deep vein thrombosis within the last 6 months."	As described in Overall Rationale, Part 2 expansion cohorts in the tumor-specific indications with high unmet medical need are open. Cardiovascular disease is prevalent in these indications. Previous eligibility criteria excluding participants just based on history of cardiovascular disease (ie., coronary artery disease) may exclude a significant proportion of participants who may not be at a particularly elevated risk of cardiovascular events while receiving BMS-986179. This study is open to only those subjects with no further therapy options available and limited prognosis. Individual risk evaluation by specialist (ie, cardiologist) that includes functional test such as stress test (and additional structural assessment as needed) may be a better, more reliable approach to identify high-risk subjects to be excluded. Under modified cardiovascular exclusion criteria, some asymptomatic patients with history of cardiovascular disease may be permitted to enroll after mandatory evaluation by specialist that includes functional ischemic test (ie, stress test). Subjects with abnormal findings or high risk findings will be strictly excluded. These measures would also offer better opportunities for close monitoring and risk assessment. Added peripheral artery disease to the list of cardiovascular diseases under the new criteria.
	Criteria 2)k) has been updated as below: • Criteria 2)k)i) and 2)k)ii) are not applicable after implementation of this revised protocol 08 and ***"Not applicable as per revised protocol 08"*** has been added in the beginning of each listed criteria. • Added new criteria as listed below: vii) Acute coronary syndrome (including ST Elevation Myocardial Infarction (STEMI), Non-ST Elevation Myocardial Infarction (NSTEMI), and Unstable Angina (UA)), cerebrovascular disease (stroke/transient ischemic attack) or arterial thrombus within the last 12 months. viii) Surgical or percutaneous revascularization (such as CABG or PCI) within the last 12 months. ix) Subjects with any known history of coronary artery disease, cerebrovascular disease or peripheral arterial disease with symptoms within the last 12 months. x) For subjects with any known history of coronary artery disease, cerebrovascular disease, peripheral arterial disease who have been asymptomatic for 12	

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 08		
Section Number & Title	**Description of Change**	**Brief Rationale**
	months prior to enrollment, evaluation by specialist that includes functional testing (and structural assessment as needed) is required within 12 months prior to study treatment. Subjects with abnormal findings such as functional ischemia (or subjects with high-risk findings) will be excluded.	
Section 3.3.2 Exclusion Criteria; Section 3.4.1 Prohibited and/or Restricted Treatments	Criteria 2)r) has been modified and it reads as below: "Subjects who have received a live/attenuated vaccine within 30 days of first treatment." Additional bullet 5 has been added.	The modification was made to comply with the current BMS standards for studies using nivolumab. This restriction is based on theoretical risk of adverse effects for nivolumab and not on clinical or safety data. The administration of live vaccines is contraindicated in patients receiving BMS-986179 treatment.
Section 3.7 Study Termination	New section added	This section has been added to provide guidelines for study termination.
Section 4.6 Blinding/Unblinding	Text in this section has been added as a clarification about access to IRT treatment codes.	To meet new BMS standards on randomization and blinding
Section 5.1 Flow Chart/Time and Events Schedule; Table 5.1-2: On-treatment Procedural Outline (Part 1A - Q1W Regimen with Monotherapy Lead-in); Table 5.1-3: On-treatment Procedural Outline (Part 1B and Part 2 - Q2W Regimen); Table 5.1-5: On-treatment Procedural Outline (Part 1B and Part 2 - Q4W Regimen)	Notes section under "Vital signs" has been modified to define the window.	The window for vital signs has been added for monitoring purpose.
Section 5.3.2 Laboratory Test Assessments	Clarification text has been added	In the previous version, laboratory tests were required to be performed within 24 hours prior to sequential doses. Provided exceptions for certain laboratory tests with longer turnaround time for this requirement in order to ensure review of the results prior to dosing.
Section 5.4 Efficacy Assessments	Section has been modified to add more clarification of tumor assessments	Added a clarifying statement referring to separate tumor assessment schedules during follow-up period.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 08		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.6 Biomarker Assessments	Clarification text has been added	Added a statement allowing collection of existing biomarker data from the sites if available (microsatellite instability, etc.)
Section 5.7.2.2 Protein Expression and Mutation	Text under this section has been modified and clarification has been added	Provided more details on planned translational analysis
Section 7 Data Monitoring Committee and Other External Committee	Clarification text has been added	The section has been modified to align with BMS standard text.
Section 8.1.3 Sample Size Determination (Part 2); Table 8.1.3-1: Cohort Expansion: Characteristics of the Simon 2-stage Design for Selected NSCLC, RCC, SCCHN, CRPC and Melanoma Cohorts	Table notes "b" and "c" updated	Updated to reflect our modified selection strategy. While we may consider focused enrollment of patients with specific mutations in the future, our priority selection strategy is based on response to prior anti-PD(L)1 therapy.
Appendix 1	Updated	Harmonization with Nivolumab standard program.

SYNOPSIS

Clinical Protocol CA013004

Protocol Title: A Phase 1/2a Study of BMS-986179 Administered Alone and in Combination with Nivolumab (BMS-936558) in Subjects with Advanced Solid Tumors

Investigational Products, Dose and Mode of Administration, Duration of Treatment with Investigational Products: Each subject will be administered an intravenous (IV) infusion or subcutaneous (SC) administration of BMS-986179 alone or in combination with nivolumab per cohort assignment and duration of treatment as indicated in the study design below.

Study Phase: Phase 1/2a

Research Hypothesis: It is anticipated that anti-CD73 antibody (BMS-986179), administered alone and in combination with nivolumab (BMS-936558), will demonstrate adequate safety and tolerability, as well as a favorable risk/benefit profile to support further clinical testing. No prospective hypotheses are being formally evaluated.

Objectives:

Primary Objective:

The primary objective is to assess the safety and tolerability of BMS-986179 administered alone and in combination with nivolumab.

Secondary Objectives:

The secondary objectives are as follows:

- To characterize the pharmacodynamic (PD) activity of BMS-986179 administered alone and in combination with nivolumab
- To assess the preliminary anti-tumor activity of BMS-986179 alone and in combination with nivolumab as measured by objective response rate (ORR), duration of response (DOR), and progression-free survival rate (PFSR)
- To characterize the pharmacokinetics (PK) and immunogenicity of BMS-986179 administered alone and in combination with nivolumab
- To characterize immunogenicity of nivolumab when administered in combination with BMS-986179

Study Design: This is a Phase 1/2a, open-label study of BMS-986179 administered as a single agent and in combination with nivolumab in subjects with advanced solid tumors. The study will be conducted in 3 parts: Part 1A (combination therapy dose escalation with monotherapy lead-in), Part 1B (PD substudy), and Part 2 (cohort

expansion). Duration of treatment is up to approximately 2 years. The entire study is expected to be completed in approximately 4 years.

At the Sponsor's discretion, scans may be submitted to an imaging core lab and may be reviewed by BICR at a later date, or at any time during the study.

Summary of Study Parts:

Part 1A: Various dose levels (150 through 1600 mg), provided in Table 1, may be evaluated for BMS-986179 weekly (Q1W) during monotherapy lead-in followed by combination therapy with nivolumab every 2 weeks (Q2W) and BMS-986179 Q1W. The maximum dose studied may be lower than 1600 mg and will be determined by the human safety data, PK, and PD of the prior dose levels. [redacted]

Part 1B: The PD substudy will provide additional information pertaining to the monotherapy or combination dose and dose regimens of BMS-986179 and nivolumab for further study in Part 2 (cohort expansion) or subsequent studies. The dose schedules studied in Part 1B may include every 2 weeks (Q2W), every 3 weeks (Q3W), and every 4 weeks (Q4W). One or more PD substudy arms (exclusively at North American sites) may explore BMS-986179 subcutaneous administration, according to doses and schedules specified above.

Part 2: The purpose of the cohort expansion study is to gather additional safety, tolerability, and PD information, in addition to preliminary efficacy information, for BMS-986179 administered alone and in combination with nivolumab.

Treatment during the monotherapy lead-in period (Part 1A only) will continue for 2 weeks; treatment during the combination therapy period (Parts 1A and 1B) and the cohort expansion period (Part 2, both monotherapy and combination therapy) will continue for up to 2 years in each study part.

Summary of Study Periods:

Subjects in each study part will complete up to 4 periods in the study: screening, treatment, safety follow-up, and response/survival follow-up.

Screening (within 28 days prior to start of the study drug for Part 1A and Part 1B; up to 42 days for Part 2): Pre-treatment tumor biopsies (at least 4 fresh core biopsies) are required from each subject in addition to the other screening activities.

Treatment (Initial treatment period of 24 weeks with an option for treatment for an additional 80 weeks [a total treatment period of up to approximately 2 years]): Following each treatment cycle, the decision to continue treatment will be based on safety and available tumor assessment findings. Tumor assessments will be performed every 8 weeks from the start of combination treatment for the Q1W, Q2W, and Q4W regimens, and every 9 weeks from the start of combination treatment for the Q3W regimen. Required assessments must be completed before the first dose of the next cycle. Tumor progression or response endpoints will be assessed using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Subjects with a response of stable disease (SD), partial response (PR), or complete response (CR) will continue to the next treatment cycle. Each subject will undergo a single mandatory on-treatment tumor biopsy, the timing of which is dependent on the part of the study in which he/she is enrolled.

- Treatment Beyond Progression may be allowed in select subjects with initial RECIST v1.1-defined progressive disease after discussion and agreement with the Bristol-Myers Squibb (BMS) Medical Monitor that the benefit/risk assessment favors continued administration of study drug (eg, subjects are continuing to experience clinical benefit as assessed by the investigator, tolerating treatment, and meeting other criteria specified in Section 3.5.1). Subjects initially treated with BMS-986179 monotherapy in Part 2 may receive BMS-986179 therapy in combination with nivolumab at disease progression.
- Treatment with Additional Cycles Beyond 24 Weeks: Subjects completing an initial period of 24 weeks of monotherapy or combination treatment with ongoing disease control (CR, PR, or SD), may be eligible for an additional 80 weeks of monotherapy or combination therapy (up to a total of approximately 2 years), on a case-by-case basis, after careful evaluation and discussion with the BMS Medical Monitor to determine whether the risk/benefit ratio supports administration of further study drug.
    - Re-treatment may be allowed in subjects with disease progression during follow-up, within 12 months of the last dose of study drug, on a case-by-case basis, after careful evaluation and discussion with the BMS Medical

Monitor to determine whether the risk/benefit ratio and current study status support administration of further study drug. Re-treatment will be limited to subjects who have already completed treatment before the protocol amendment dated 20-Oct-2017. Subjects meeting criteria for re-treatment will be treated with the originally assigned monotherapy or combination therapy regimen (eg, same dose level and dose schedule administered during the prior treatment period), unless that dose level and schedule were subsequently found to exceed the maximum tolerated dose (MTD), in which case the subject will be treated at the next lower or alternate dose level. Subjects who receive re-treatment may be followed for 3 years from their last dose.

Safety Follow-up (duration of approximately 100 days from the last dose): Subjects will enter safety follow-up and will be evaluated for safety and tolerability, and tumor response (if applicable), for approximately 100 days after the last dose of therapy. Subjects will be required to complete the 3 clinical safety follow-up visits (ie, approximately on Days 30, 60, and 100) regardless of whether they start a new anti-cancer therapy, except those subjects who withdraw consent for study participation.

Response/Survival Follow-up (duration of approximately 3 years from the last dose): Subjects who do not experience progressive disease prior to treatment discontinuation will continue to have radiologic and clinical tumor assessments every 8 weeks (from the last tumor assessment in the treatment period) for the first two years until progression is confirmed, withdrawal of consent, start of a new treatment, lost to follow-up, or death, whichever comes first. Tumor assessment scans will be per standard of care guidelines, at a minimum of every 12 weeks during the third year until progression is confirmed, withdrawal of consent, start of a new treatment, lost to follow-up, or death, whichever comes first. Subject survival status will be assessed by telephone every 12 weeks if there is no scheduled tumor assessment visit.

Dose Escalation (Part 1A):

Beginning on Day 1 of Cycle 0 (14-day cycle in monotherapy lead-in), subjects in Part 1A will receive their assigned dose of BMS-986179 on a Q1W schedule (Figure 1). Beginning on Day 1 of Cycle 1 (28-day cycle combination therapy) nivolumab at a flat dose of 240 mg Q2W will be added in addition to weekly doses of BMS-986179. The nivolumab dosing regimen will remain the same at each BMS-986179 dose level. Combination treatment will continue for up to 24 weeks until the end of Cycle 6.

The study plan for Part 1A is summarized as follows: Approximately 30 to 60 subjects with advanced solid tumors with biopsy-accessible lesions will be treated in Part 1A. Dose levels to be considered for the next combination cohort (with monotherapy lead-in) will be based on the recommended monotherapy dose from Bayesian Logistic Regression Method (BLRM) and the recommended combination dose from BLRM-Copula; the lower recommended dose from both models will be considered for the next dose escalation. Potential dose levels for Part 1A are provided in Table 1. Once a dose level is selected for a given cohort in the dose-escalation period, approximately 3 subjects will be treated at that specified dose level. Cohort tolerability assessment and subsequent dose recommendation will occur when 2 evaluable subjects within a set have completed [redacted] period. If the [redacted] occurring in the third evaluable subject at a specific dose level does not influence the dose recommendation by BLRM (-Copula), the BLRM (-Copula)-recommended next dose level may proceed without waiting for the third subject to complete the corresponding [redacted] after discussion and agreement between the Sponsor and investigators. While waiting for [redacted] of those 2 or 3 subjects, if additional subjects are available, these subjects could be enrolled to the current dose level. Continuous re-assessment of dose recommendation by BLRM (-Copula) will be carried out at each dose level after each cohort of subjects [redacted]. Additional subjects may be added to a specific dose level according to model recommendations or clinical judgment, or for PD biomarkers. A maximum of 12 subjects will be treated at each dose level. As of 18 August 2017, 56 subjects have been treated under Part 1A. Enrollment in Part 1A is now closed.

[redacted]

No intra-subject dose escalation of BMS-986179 is permitted.

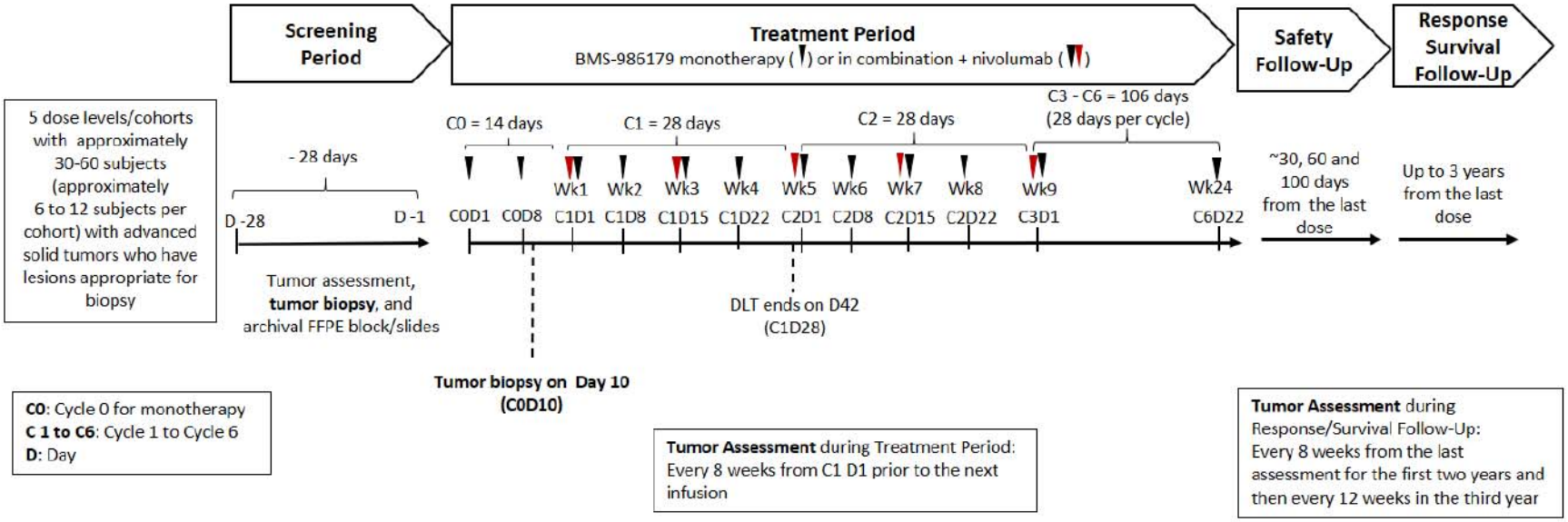
Sentinel Subject: During dose escalation, a staggered dosing (sentinel subject) approach will be used for the first subject in each dose level for both the monotherapy lead-in phase and the combination treatment phase. The first subject will receive Cycle 0 Day 1 (for monotherapy lead-in) or Cycle 1 Day 1 (for combination treatment) dose of the study drug and be observed for 5 days for doses including and below 400 mg (the planned doses of 150 and 300 mg) or 9 days for doses above 400 mg (the planned dose of 600 mg, 1200 mg and 1600 mg) before additional subjects (ie, Subject 2 onward in each cohort) receive study drug.

Table 1: Doses During Part 1A (Dose Escalation)

Dose Level/Cohort	BMS-986179	Nivolumab
1	150 mg	240 mg
2	300 mg[a]	240 mg
3	600 mg[a]	240 mg
4	1200 mg[a]	240 mg
5	1600 mg	240 mg

[a] Dose could be modified based on BLRM-Copula recommendation. Enrollment in Part 1A is now closed.

Figure 1: **Study Design Schematic (Part 1A [Dose Escalation])**



Abbreviation: FFPE = formalin fixed, paraffin embedded.

PD Substudy (Part 1B):

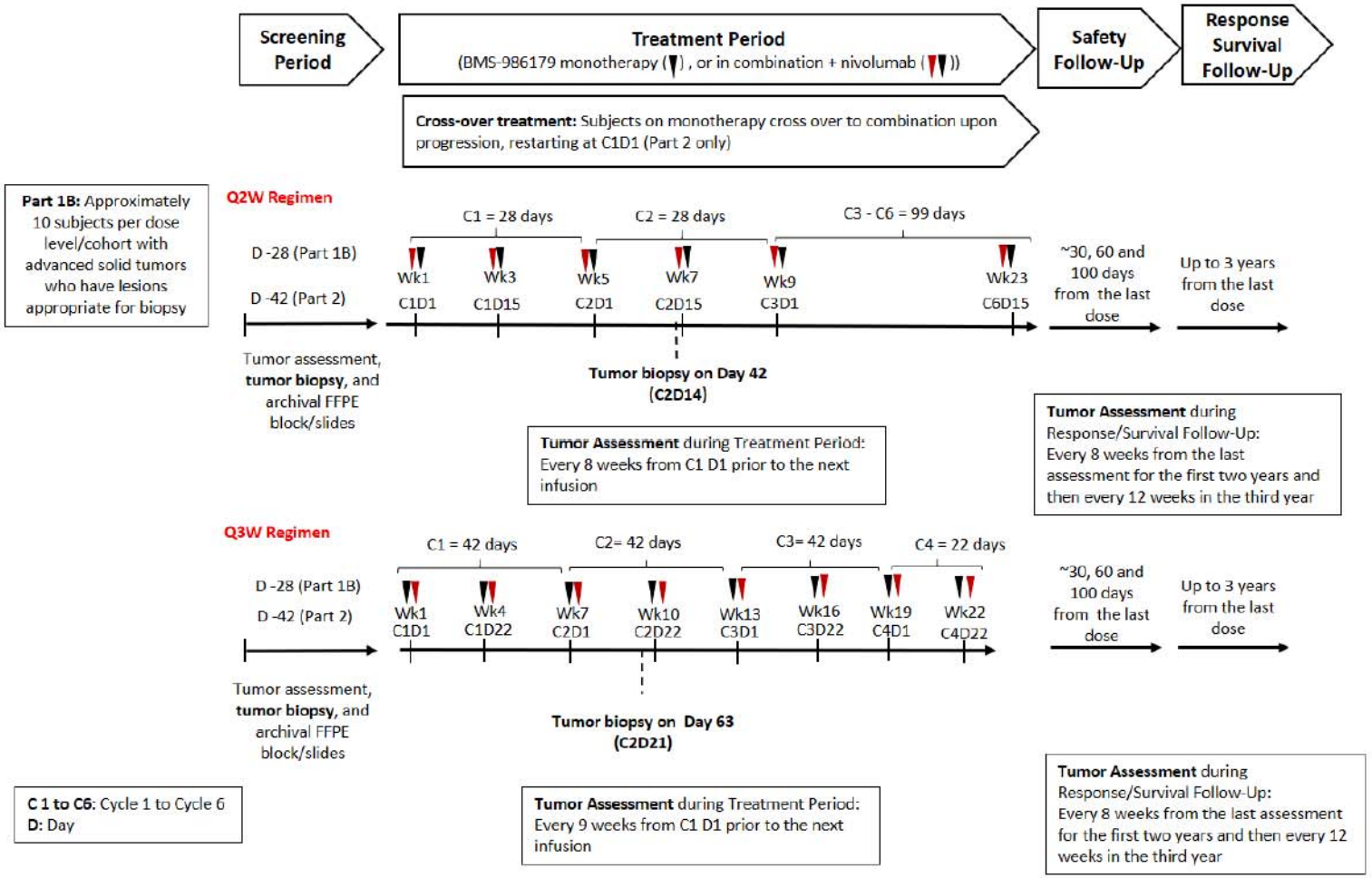
Up to 6 treatment arms will be assessed in Part 1B. These may include Q2W, Q3W and Q4W schedules. Approximately 10 subjects per arm with advanced solid tumors with biopsy-accessible lesions will be enrolled in Part 1B, with the exception of an arm to assess bioavailability for subcutaneous dosing, which will treat approximately 16 subjects. The dose and interval(s) for Part 1B will be determined by the safety, PK, and PD data from Part 1A (Figure 2 and Figure Figure 3). Actual PD and PK data from Part 1A and 1B to date (29-NOV-2017) suggest that effects may be sufficiently durable to permit Q4W dosing of both drugs, a schedule not included in the original protocol design. Therefore, cycles as long as Q4W may be tested in Part 1B, either as monotherapy or in combination with nivolumab. Three dose levels will be explored in Part 1B. The nivolumab dose for combination therapy will be 240 mg for the Q2W regimen and adjusted proportionately to 360 mg for the Q3W regimen or 480 mg for the Q4W regimen, in concordance with the PK/PD modeling of nivolumab.

One or more PD substudy arms (exclusively at North American sites) may explore BMS-986179 subcutaneous administration, according to doses and schedules specified above. For subcutaneous administration, BMS-986179 will be co-administered with recombinant human hyaluronidase PH20 (rHuPH20, 1000 U/mL, Halozyme, Inc.). The bioavailability from already approved subcutaneous cancer therapies such as trastuzumab and rituximab that were co-administered with rHuPH20 was shown to be ~70% as compared to IV formulation. It is anticipated that the PD effects of BMS-986179 by the SC route will be very similar to those seen in intravenous administration, but it is necessary to confirm this prior to utilization of subcutaneous administration in an expansion cohort or future study.

To obtain preliminary data on subcutaneous bioavailability as well as safety over repeated cycles, BMS-986179 would be administered as monotherapy by the subcutaneous route for the first dose, followed by within-patient crossover to the same dose intravenously for the second dose, then continuing subcutaneously for the third dose and beyond until patients fulfill criteria for treatment discontinuation as described in Section 3.5.

Treatment in Part 1B will be for an initial period of up to 24 weeks (ie, to the end of Cycle 6). Additional treatment beyond that time will be as described in Section 3.1.5. If a given subject could potentially enroll in more than 1 open cohort in Part 1B, cohort assignment will be randomized.

Figure 2: **Study Design Schematic (Part 1B [PD Substudy] and Part 2 [Expansion] - Q2W and Q3W Schedules)**

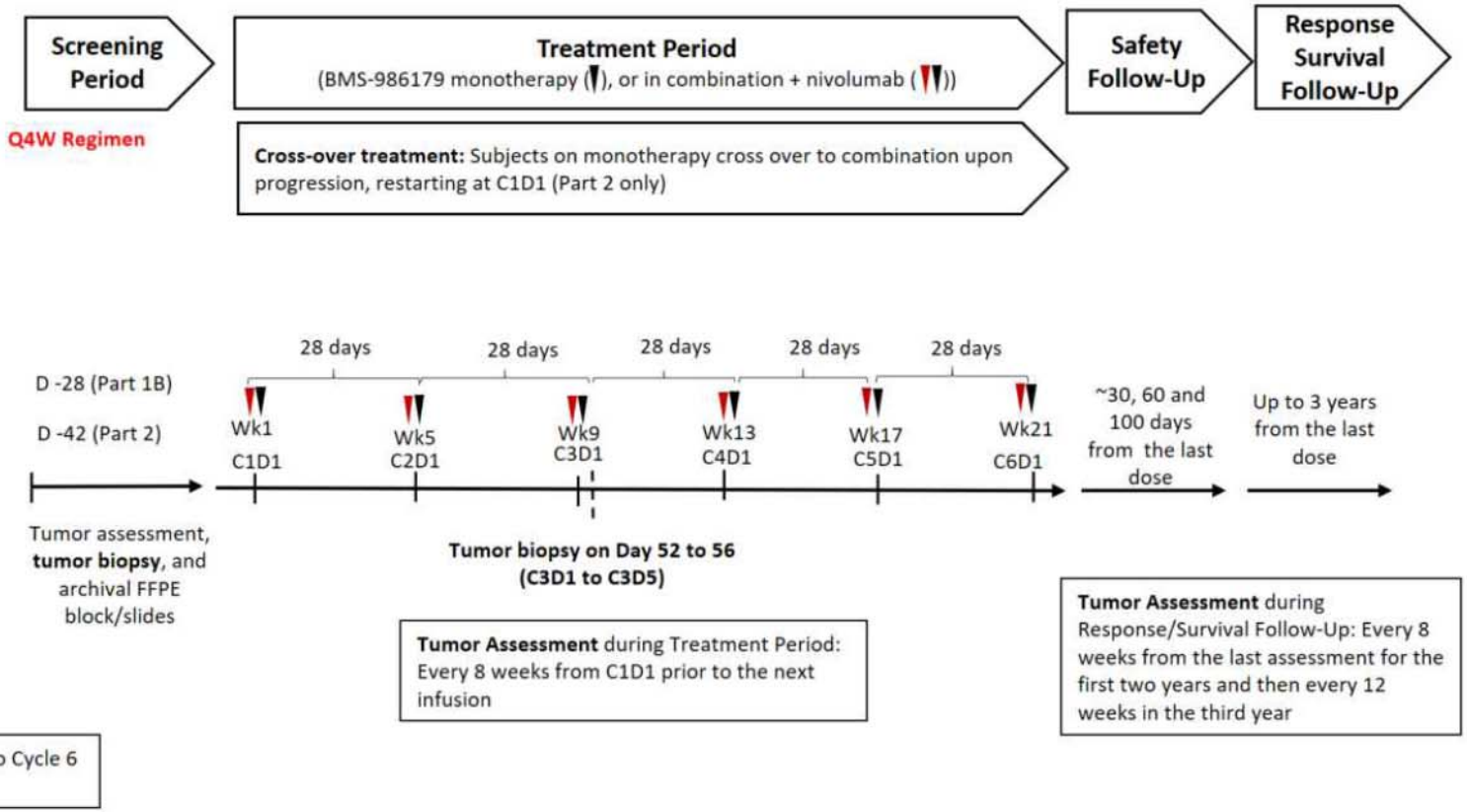


Abbreviation: FFPE = formalin fixed, paraffin embedded.

For subcutaneous cohort in PD sub-study Q2W: BMS-986179 would be administered as monotherapy by the subcutaneous route on C1D1, followed by within-patient crossover to the IV on C1D15, then continuing SC on C2D1 and beyond until patients fulfill criteria for treatment discontinuation.

For subcutaneous cohort in PD sub-study Q3W: BMS-986179 would be administered as monotherapy by the subcutaneous route on C1D1, followed by within-patient crossover to the IV on C1D22, then continuing SC on C2D1 and beyond until patients fulfill criteria for treatment discontinuation.

Figure 3: **Study Design Schematic (Part 1B [PD Substudy] and Part 2 [Expansion] - Q4W Schedule)**



Abbreviation: FFPE = formalin fixed, paraffin embedded.

For subcutaneous cohort in PD sub-study Q4W: BMS-986179 would be administered as monotherapy by the subcutaneous route on C1D1, followed by within-patient crossover to the IV on C2D1, then continuing SC on C3D1 and beyond until patients fulfill criteria for treatment discontinuation.

Cohort Expansion (Part 2):

Approximately 246 subjects with tumors with biopsy-accessible lesions will be enrolled in Part 2: approximately 198 in cohorts of NSCLC, RCC, SCCHN, and melanoma subjects who previously progressed on or after anti-PD-(L)1 therapy and 48 subjects with pancreatic adenocarcinoma and CRPC who progressed on or after any 1L therapy. The dose level and administration schedule of BMS-986179 to be used in Part 2 will be based on a synthesis of all available data, including evaluations of the recommendation from BLRM-Copula and clinical and laboratory safety assessments, PK, PD, and efficacy data, from treated subjects from Parts 1A and 1B. The dose schedules studied in Part 2 may include Q2W, Q3W, and Q4W schedules. Data from Parts 1A and 1B of the protocol identified a recommended phase 2 dose/schedule to evaluate in Part 2 (BMS-986179 600 mg IV Q2W monotherapy or in combination with Nivolumab 480 mg Q4W). With the exception of pancreatic cancer cohort (completed to accrual), this dose has been selected for all ongoing Part 2 cohorts. The study design for Part 2 Q2W and Q3W schedules is presented in Figure 2, and the study design for Part 2 Q4W schedule is presented in Figure 3.

The Simon 2-stage (optimal) design will be used for 2 NSCLC cohorts (one for BMS-986179 monotherapy and the other for BMS-986179 therapy in combination with nivolumab), 2 RCC cohorts (equivalent to those for NSCLC) and single SCCHN, melanoma, and CRPC cohorts that will receive only BMS-986179 in combination with nivolumab. Approximately 15 evaluable subjects in each of the first 6 cohorts and 12 evaluable subjects in the CRPC cohort will be treated during Stage 1 for an initial evaluation of efficacy. NSCLC and RCC subjects initially treated with BMS-986179 monotherapy in Part 2 may receive BMS-986179 therapy in combination with nivolumab at disease progression after specific consultation and agreement with the BMS Medical Monitor. Subjects who receive BMS-986179 in combination with nivolumab after monotherapy disease progression will restart from Cycle 1 Day 1. An additional approximately 18 subjects each of the first 6 above cohorts and 17 for the CRPC cohort may be treated in Stage 2. While this design includes hypothesis testing with decision rules, the decision to proceed to Stage 2 in a cohort will be based on the totality of available data, in consultation with study investigators. The remaining approximately 19 subjects (pancreatic adenocarcinoma) will be treated in single-stage cohort sufficient to evaluate anti-tumor effect sizes that exceed historic ORRs with high confidence.

Because CD73 expression is linked to canonical MAPK signaling, we will explore the safety, PK, PD, and preliminary efficacy of BMS-986179 in subjects whose tumors contain driver mutations in this pathway. Therefore, enrollment may be extended to reach adequate number of BRAF or NRAS mutations in melanoma, and EGFR or KRAS mutations in NSCLC.

Part 2 (Expansion Phase) cohorts will be open to subjects eligible for participation who have completed standard-of-care therapy.

Study Population: Male or female subjects who are at least 18 years old and satisfy eligibility as determined by medical history, physical examination, 12-lead electrocardiogram, and clinical laboratory evaluations will be eligible to participate in the study.

Women of childbearing potential (WOCBP) must not be nursing or pregnant and must be using an acceptable method of contraception. WOCBP must have a negative pregnancy test within 24 hours prior to dosing with study drug.

Study Drug: Investigational products are as listed in Table 2.

Table 2: Study Drugs for CA013004

Medication	Potency	Investigational Product
BMS-986179 injection	35 mg/mL	BMS-986179
BMS-936558-01 (nivolumab) injection	10 mg/mL	Nivolumab
ENHANZE™ Drug Product (rHuPH20)	1 mg/mL	ENHANZE™ Drug Product (rHuPH20)

Study Assessments:

- Safety Outcome Measures: Safety assessments will be based on medical review of adverse event (AE) reports and the results of vital sign measurements, 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 study drug. Both AEs and laboratory tests will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03.
- PK Parameters: PK parameters for BMS-986179 to be assessed include, if feasible, maximum observed serum concentration (Cmax), time of maximum observed serum concentration (Tmax), area under the serum concentration-time curve (AUC) from time zero to the time of the last quantifiable concentration [AUC(0-T)], AUC in 1 dosing interval [AUC(TAU)], apparent terminal half-life (T-HALF), AUC from time zero extrapolated to infinite time [AUC(INF)], effective elimination half-life (T-HALFeff), concentration at the end of the dosing interval (Ctau), trough observed serum concentration at the end of the dosing interval (Ctrough), total body clearance (CLT), volume of distribution at steady state (Vss), accumulation index (AI), apparent volume of distribution of terminal phase (Vz), and degree of fluctuation (DF; to be calculated at steady state). Individual subject PK parameter values will be derived by non-compartmental methods by a validated PK analysis program. [redacted] Actual times will be used for the analyses. Serum samples for BMS-986179 will be collected from all subjects at specified time points. For subjects enrolled in the PD sub-study receiving subcutaneous administration, a non-compartmental or population PK approach will be used to assess the PK data and parameters such as Cmax, AUC(0-T), bioavailability (F) will be assessed as feasible and applicable. [redacted]
- Immunogenicity Measures: Serum samples for BMS-986179 and nivolumab anti-drug antibody (ADA) will be collected from all subjects at specified time points.
- Efficacy Measures: Disease assessment with computed tomography and/or magnetic resonance imaging (MRI), as appropriate, will be performed at baseline and every 8 weeks from the start of combination treatment for the Q1W, Q2W, and Q4W regimens or every 9 weeks for the Q3W regimen from the start of combination treatment during treatment period until disease progression per RECIST v1.1 or until additional disease progression for subjects treated beyond progression (defined as an additional 5mm or greater increase in tumor burden volume from time of initial progression [including all measurable lesions]), discontinuation of treatment or withdrawal from study. Tumor assessments at other time points may be performed if the investigator is concerned about tumor progression. Assessment of tumor response will be reported by the investigator for appropriate populations

of subjects as defined by RECIST v1.1. Within each subject, the same imaging modality should be used for all assessments.

- Biomarker Measures: Biomarker measures of baseline and on-treatment [redacted] serum, and tumor (biopsy) samples will be used to identify PD markers associated with treatment. [redacted]

Statistical Considerations:

Sample Size:

Dose Escalation: As a Phase 1 dose-escalation trial, the sample size at each dose depends on observed toxicity and posterior inference. For BMS-986179 in combination with nivolumab (with BMS-986179 monotherapy lead in), approximately 30 to 60 subjects are expected to be treated during the dose-escalation period. Initially, approximately 3 subjects will be treated at the starting dose levels of BMS-986179 and then in combination with nivolumab. Due to the potential for early discontinuation, additional subjects may be enrolled at the current dose level, before the initially enrolled subjects have completed the [redacted] period, to ensure 3 evaluable subjects at each dose level. Additional subjects will be treated in recommended dose levels per BLRM (-Copula) model during the dose escalation period. [redacted] Additional subjects (up to 12 in total) may be treated at any dose level at or below the estimated MTD/recommended dose for further evaluation of safety and PD/PK parameters as needed.

PD Substudy: Total 6 regimen cohorts will be included in Part 1B with approximately 10 subjects each except for the subcutaneous with approximately 16 subjects. To assess the PD effects of BMS-986179-nivolumab combination, pre- and on-treatment whole blood samples, serum samples, and tumor biopsies will be required. It is of interest to ensure the precision of the estimate of the ratio of on-treatment biomarker assessments to pre-treatment (baseline) levels. Assuming that a biomarker is measured as a continuous variable, a given number of subjects per treatment arm will provide the confidence that the estimate of the ratio of on-treatment to baseline values will be within 20% of the true value, as shown in Table 3.

For example, for a biomarker [redacted] with an intra-subject standard deviation of 0.3, if the true ratio of post-baseline to baseline geometric means is 1.2 (increase from baseline is 20%), there is 76% probability that the estimated ratio would be within 0.96 and 1.44 (or a percent change between -4% and 44%) with 6 subjects per treatment arm. If the true increase from baseline is 60%, for a biomarker with the same variability, then there is 76% probability that the estimated percent increase would be between 28% and 92% with 6 subjects per treatment arm.

Table 3: Probability That Estimated Ratio of On-treatment to Pre-treatment (Baseline) Value Is Within 20% of True Value

Intra-subject Standard Deviation (Log-scale)		0.2	0.3	0.4	0.5	0.6	0.7	0.8
Probability	N = 6	92%	75%	61%	52%	44%	38%	34%
	N = 7	94%	79%	65%	55%	47%	41%	36%
	N = 8	95%	82%	68%	58%	50%	44%	39%
	N = 9	97%	84%	71%	61%	53%	46%	41%
	N = 10	97%	86%	74%	63%	55%	48%	43%

Cohort Expansion: BMS-986179 administered either as monotherapy or in combination with nivolumab will be tested in subjects diagnosed with NSCLC or RCC whose disease has progressed during or after prior anti-PD-(L)1 therapy. If both monotherapy and combination therapy cohorts are open, assignments within a particular disease type will be

made in an alternating manner. Subjects diagnosed with SCCHN or melanoma who have progressed on prior anti-PD-(L)1 therapy as their most recent therapy will be enrolled in cohorts to be administered BMS-986179 in combination with nivolumab. Subjects diagnosed with CRPC will also be enrolled in a cohorts to be administered BMS-986179 in combination with nivolumab.

A Simon 2-stage (optimal) design will be used for tumor type cohorts receiving BMS-986179 as monotherapy and in combination with nivolumab in these subjects (see Table 4). The total sample size for each expansion cohort will be calculated to provide a reasonable false positive rate (FPR) and false negative rate (FNR), based on assumptions of true (target) and historic ORR for each indication.

The probability of early stopping is based on the true but unknown probability of response in the cohort being evaluated. The number of subjects receiving treatment at the time of Stage 1 efficacy evaluation is approximate and may exceed the specified minimum number of subjects due to unknown time of response and recruitment.

Additionally, subjects with pancreatic adenocarcinoma will receive BMS-986179 in combination with nivolumab in a single-stage expansion phase design (see Table 5). The total sample size for each expansion cohort will be calculated to provide a reasonable FPR (≤ 10%) and FNR (≤ 13%) based on the assumptions of true (target) ORR and historic ORR for each indication.

Table 4: Cohort Expansion: Characteristics of the Simon 2-stage Design for Selected NSCLC, RCC, SCCHN, CRPC, and Melanoma Cohorts

Expansion Cohort	Treatment Arm	Historic ORR (%)	Target ORR (%)	Stage 1/ Total N	Stage 1/Overall Responses Futility Boundaries[a]	FPR/ (1-FNR) (%)	Probability of Early Stopping (%)
NSCLC Post-PD-(L)1 Therapy[b,c]	Mono	1	15	15/33	1/2	10/90	86
NSCLC Post-PD-(L)1 Therapy[b,c]	Combo	1	15	15/33	1/2	10/90	86
RCC Post-PD-(L)1 Therapy[b]	Mono	1	15	15/33	1/2	10/90	86
RCC Post-PD-(L)1 Therapy[b]	Combo	1	15	15/33	1/2	10/90	86
Melanoma Post-PD-(l)1 Therapy[d]	Combo	1	15	15/33	1/2	10/90	86
SCCHN Post-PD-(L)1 Therapy	Combo	1	15	15/33	1/2	10/90	86
CRPC	Combo	4	20	12/29	1/3	10/90	61

[a] Minimum responder count at end of first and second stage to determine treatment is promising, based on historical and target rates, and FPR and (1-FNR).

[b] Progression following prior anti-PD-(L)1 therapy and expected response rates.

[c] Includes EGFR-mutant and/or KRAS-mutant expressors. Enrollment may be extended to include an adequate number (eg. approximately 10) of subjects with mutant expressions of each type in this cohort.

[d] Includes BRAF- and/or NRAS-mutant expressors. Enrollment may be extended to include an adequate number (eg. approximately 10) of subjects with mutant expressions of each type in this cohort.

Abbreviation: CI = confidence interval; Combo = BMS-986179 in combination with nivolumab; EGFR = epidermal growth factor receptor; FNR = false negative rate; FPR = false positive rate; Mono = BMS-986179 monotherapy until disease progression; NSCLC = non-small cell lung cancer; ORR = objective response rate; PD-(L)1 = either programmed death-1 or programmed death ligand-1; RCC = renal cell carcinoma; CRPC = castrate-resistant prostate carcinoma.

Table 5: Cohort Expansion: Characteristics of the Single-stage Design[a] for Pancreatic Adenocarcinoma

Expansion Cohort	Historic ORR (%)	Target ORR (%)	Total N	FPR/(1-FNR) (%)
Pancreatic adenocarcinoma	8	30	19/4	6/87

[a] All subjects received BMS-986179 therapy in combination with nivolumab.

Abbreviation: FNR = false negative rate; FPR = false positive rate; ORR=objective response rate;

Approximately 227 and 19 subjects will be treated using the Simon 2-stage (optimal) design or a single-stage design, respectively. Should fewer than 10 subjects with each driver-marker expression be enrolled in study cohorts, additional marker-driven enrollment may be permitted. Mutational marker, efficacy, and safety results from these cohorts will inform potential decisions and guide later subject enrollment, planning/operations, and sponsor decision-making.

Endpoints:

Primary Endpoints:

The primary objective of the study is to assess the safety and tolerability of BMS-986179 administered alone and in combination with nivolumab. The assessment of safety will be based on the incidence of AEs, SAEs, AEs leading to discontinuation, and deaths in relation to initial treatment. In addition, clinical laboratory test abnormalities will be examined.

Secondary endpoints:

Pharmacokinetics: PK parameters for BMS-986179 such as Cmax, Tmax, AUC(0-T), AUC(TAU), T-HALF, AUC(INF), T-HALFeff, Ctau, Ctrough, CLT, Vss, AI, Vz, and DF will be assessed for monotherapy or combination therapy, if feasible, from concentration-time data. [redacted]

Pharmacodynamics: PD activities of CD73 inhibition will be measured by CD73 enzyme assays and CD73 immunohistochemistry in pre- and on-treatment tumor biopsies.

Immunogenicity: Incidence of specific ADA to BMS-986179 and nivolumab.

Efficacy: The anti-tumor activity of BMS-986179 as monotherapy and in combination with nivolumab will be measured by ORR, DOR, and PFSR at 24 weeks and will be assessed based on RECIST v1.1 criteria for solid tumors.

Analyses:

Safety Analyses: All recorded AEs will be listed and tabulated by system organ class, preferred term, treatment arm, and dose level and coded according to the most current version of MedDRA. Vital signs, electrocardiograms, Eastern Cooperative Oncology Group performance status, and clinical laboratory test results will be listed. Safety events will be summarized overall and within monotherapy and combined therapy settings as appropriate. Any significant physical examination findings and results of clinical laboratory test will be listed.

PK Analyses: All individual PK parameters for BMS-986179 will be listed for each analytic including any exclusions and reasons for exclusion from summaries. Summary statistics will be tabulated for each PK parameter, if feasible, and wherever applicable, by treatment and dosing regimen. Geometric means and coefficients of variation will be presented for Cmax, Ctrough, Ctau, AUC(0-T), AUC(TAU), AUC(INF), CLT, [redacted] Vz, and Vss after single or multiple dose PK. Medians and ranges will be presented for Tmax. Means and standard deviations will be presented for all other PK parameters, such as T-HALF, T-HALFeff, DF, and AI.

BMS-986179 dose dependency will be assessed in Part 1A. To describe the dependency on dose of BMS-986179, scatter plots of Cmax, AUC(0-T), and AUC(TAU) versus dose may be provided for each day measured. [redacted] BMS-986179 trough concentration

will be tabulated by treatment and study day using summary statistics. These data may also be pooled with other datasets for population PK analysis, which will be presented in a separate report.

Immunogenicity Analyses: A listing of all available immunogenicity data will be provided. The frequency of subjects with a baseline and/or at least 1 positive ADA assessment of BMS-986719 and nivolumab or BMS-986179 will be summarized. [redacted]

Efficacy Analyses: A listing of tumor measurements will be provided by subject and study day in each dose level. Individual subjects' best overall response will be listed based on RECIST v1.1 for solid tumors. To describe the anti-tumor activity of BMS-986179 in monotherapy or in combination with nivolumab, ORR will be calculated. ORR and corresponding 2-sided exact 95% exact CI by the Clopper-Pearson method will be provided by treatment, and/or dose level, and tumor type. Median DOR and corresponding 2-sided 95% CI will be reported by treatment, and/or dose level and tumor type. DOR will be analyzed using the Kaplan-Meier method. In addition, PFSR, the probabilities of a subject remaining progression free and surviving to 24 weeks, will be estimated by the Kaplan-Meier methodology, by treatment, tumor type, prior PD-(L)1 exposure status, and dose level. The corresponding 95% CIs will be derived based on the Greenwood formula. [redacted] Additional details will be provided in the Statistical Analysis Plan.

Biomarker Analyses: Summary statistics for biomarkers and their corresponding changes (or percent changes) from baseline will be tabulated by planned study day and dose in each arm. The time course of biomarker measures will be investigated graphically. If there is indication of a meaningful pattern over time, further analysis (eg, by linear mixed model) may be performed to characterize the relationship. [redacted]

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1 INTRODUCTION AND STUDY RATIONALE

This is a dose-escalation and cohort-expansion study with a pharmacodynamic (PD) substudy of BMS-986179, a high-affinity antibody to the CD73 protein, alone and in combination with nivolumab (anti-programmed death-1 [PD-1]) in humans with advanced solid tumors. This study will evaluate the safety profile, tolerability, pharmacokinetics (PK), PD, and anti-tumor activity of escalating doses of BMS-986179 alone and in combination with nivolumab. In addition, the study is expected to identify the maximum tolerated dose (MTD) and regimen of BMS-986179 alone and in combination with nivolumab to be used in Phase 2b or future studies.

1.1 Study Rationale

Antibody-based therapies that target the immune system are an important strategy to treat cancer.[1] Immunotherapies aim to improve the patient's own anti-tumor immune responses by releasing the suppressive restraints on effector immune cell populations. The most extensively studied immunotherapies in cancer are antibodies that target the negative regulatory receptors, cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4), and PD-1.[2] Inhibition of these negative regulatory receptors, referred to as immune checkpoint blockade, results in the enhanced activation of T-cell responses and potent anti-tumor activity in preclinical models and in cancer patients. Trials with CTLA-4 blockade provided the first clinical evidence of improvement in overall survival (OS) with immune modulatory anti-cancer therapy in subjects with metastatic melanoma.[3,4] Following that, Topalian et al. showed that anti-PD-1 antibody produced objective responses in subjects with non-small cell lung cancer (NSCLC), melanoma, and renal cell cancer (RCC).[5]

Following on the success of CTLA-4 and anti-PD-1 pathway-targeted agents, the field of tumor immunotherapy is rapidly expanding. In addition to blocking co-inhibitory pathways, targeting the immunosuppressive properties of the cancer cells themselves, including the tumor microenvironment, is considered a promising approach, especially with combination of multiple antibody-based immunotherapies. It is possible that combination therapies could potentially lead to greater depth of response and OS, as has been noted with the combination of anti-PD-1 and anti-CTLA-4 in advanced melanoma subjects.[6,7]

1.1.1 Rationale for BMS-986179 Therapy

BMS-986179 is a high-affinity antibody to the CD73 protein that has a dual capacity to efficiently inhibit CD73 enzymatic function and induce downregulation of the glycosylphosphatidylinisotol (GPI)-linked CD73 protein in a variety of tumor cell types. As an enzyme, CD73 (5' ecto-nucleotidase) catalyzes the final step in the adenosine triphosphate (ATP) dephosphorylation pathway, irreversibly converting extracellular adenosine monophosphate (AMP) to adenosine.[8] Adenosine binds to 4 G-protein–coupled receptor subtypes (A1, A2A, A2B, and A3) with variable affinity.[9] The A2A and A2B receptors stimulate G-protein–dependent cyclic AMP accumulation, resulting in signal transduction to target genes. A2B adenosine receptors also activate Jun amino-terminase kinase (JNK) and p38 via phospholipase C-dependent or -independent pathways.[10] While lower levels of adenosine reduce tissue injury in conditions of

cellular stress, high levels of adenosine in the tumor microenvironment suppress immune cell activity, reducing the anti-tumor response.[11,12] Specifically, adenosine disables cytotoxic effector functions of both natural killer (NK) and CD8+ T cells, inhibits the T helper Type 1 CD4+ T-cell response, enhances proliferation of regulatory T cells, and granulocytic myeloid-derived suppressor cells, and induces cytokine release to ultimately enable tumor immune evasion and enhance tumor survival.[13] In addition to its adenosine-mediated activities, CD73 also promotes cellular adhesion, lymphocyte interactions with endothelium, and angiogenesis.[14,15,16] In this capacity, it has been demonstrated to increase metastatic progression of tumor cells. Given the multiple mechanisms by which CD73 can act to promote tumor growth, inhibiting CD73 function represents a potentially powerful mechanism to enhance the anti-tumor response.

CD73 is widely expressed on normal tissues, infiltrating immune cells, stroma, and vasculature. In normal physiological conditions, AMP is present at very low levels. Upon tissue damage, inflammation, or hypoxia, ATP is released. An initial reversible step catalyzed by CD39 generates AMP, which is metabolized in an irreversible step by CD73 to generate adenosine, which blunts the immune response and contributes to the re-establishment of homeostasis.[17,18] Tumors appropriate this pathway through expressing high CD73 levels, which leads to high tumor adenosine.[19] CD73 expression is also elevated in response to activation of canonical mitogen-activated protein kinase (MAPK) signaling, for instance, downstream of B-Raf oncogene (BRAF) mutations or in the presence of activating mutations of epidermal growth factor receptor (EGFR).[20,21] High expression of CD73 has been demonstrated in many different types of cancer, and several studies report an association between high CD73 levels and poor prognosis, increased risk of metastasis,[22] and resistance to chemotherapy.[23,24]

Substantial literature has provided strong mechanistic validation for the importance of CD73 in generating an immunosuppressive tumor environment and for targeting CD73 to enhance anti-tumor activity. CD73 deficiency improved anti-tumor immunity and survival by reducing tumor growth and metastases.[25,26] Pharmacologic targeting of CD73 with small-molecule inhibitors that block the catalytic function of CD73 also inhibited tumor growth and metastasis.[27] Antibody-directed immunotherapies targeting CD73 demonstrated similar anti-tumor properties.[28,29]

Blockade of CD73 activity has the potential to broadly enhance anti-tumor immune responses in combination with other immune-stimulating agents by lowering the activation threshold.

1.1.2 Rationale for BMS-986179 Monotherapy

Recently, preliminary data have been presented showing clinical benefit (including objective response) to monotherapy with a small molecule inhibitor of the A2A adenosine receptor (A2AR) in patients with NSCLC and RCC, including patients who progressed on prior anti-PD-(L)1 (ie, either PD-1 or programmed death ligand-1 [PD-L1]) therapies.[30] These results suggest that monotherapy with adenosine-targeted agents may have potential benefit in some patients and provide a rationale to test CD73 monotherapy in populations enriched by biomarker and/or clinical selection.

At the beginning of the present study, BMS-986179 was not expected to have potent, clinically relevant anti-tumor efficacy as a monotherapy agent, based on preclinical studies.[24,31,32] Mechanistically, it was anticipated that BMS-986179 would augment a response and/or lower the threshold of T-cell activation. Thus, the rationale for including a lead-in period consisting of 2 doses of monotherapy rather than a fully dedicated monotherapy study was based upon an ethical and scientific balance of providing sufficient monotherapy data for safety with a need to provide patients with a potentially active treatment regimen. In addition, pre- and on-treatment biopsies obtained during the monotherapy lead-in period will be used to demonstrate effects of monotherapy BMS-986179 on CD73 enzyme activity and protein expression.

The 2-week duration of the lead-in was determined based on the hypothesis that higher CD73 inhibition would be achieved by administering once weekly (Q1W) doses than by a single dose every 2 weeks (Q2W), at least at the initial dose levels. Additionally, 2 Q1W doses were anticipated to provide a sufficient length of time on therapy to monitor for the development of acute toxicities while maintaining significant CD73 inhibition.

1.1.3 Rationale for Combination Therapy with Nivolumab

Nivolumab (BMS-936558) is a fully human monoclonal antibody that binds PD-1 on activated immune cells and disrupts engagement of the receptor with its ligands, thereby abrogating inhibitory signals and augmenting the host anti-tumor response.

PD-1 is a transmembrane protein primarily expressed on activated T cells, B cells, myeloid cells, and antigen-presenting cells (APCs).[33] Binding of PD-1 to PD-L1 and programmed death ligand-2 (PD-L2) has been shown to down-regulate T-cell activation in both murine and human systems.[34,35,36,37] PD1/PD-L1 interactions may also indirectly modulate the response to tumor antigens through T-cell /APC interactions. Therefore, PD-1 engagement may represent one means by which tumors evade immunosurveillance and clearance. Blockade of the PD-1 pathway by nivolumab has been studied in a variety of preclinical in vitro assays, and anti-tumor activity using a murine analog of nivolumab has been shown in a number of immunocompetent mouse cancer models.[38] Nivolumab was recently approved as first-line treatment for melanoma and second-line treatment for NSCLC (both nonsquamous and squamous histologies) and RCC in the United States (US) and is being evaluated extensively across a wide range of solid tumors and hematological malignancies. In mouse models, the combination of BMS-986179 and nivolumab surrogate antibodies produced better efficacy than nivolumab surrogate alone, suggesting a synergistic effect.

1.1.4 Rationale for Tumor and Subject Selection

The expansion part of this study will enroll subjects with biopsy-accessible lesions having a diagnosis of NSCLC, melanoma, RCC, squamous cell carcinoma of the head and neck (SCCHN), castrate-resistant prostate carcinoma (CRPC), and pancreatic adenocarcinoma.

A combination of nonclinical studies performed by Bristol-Myers Squibb Company (BMS) and primary literature supports the association of increased CD73 expression and/or adenosine with decreased survival in the tumor types selected for the clinical study. In nonclinical assays at BMS,

expression of CD73 and A2AR was assessed in selected primary tumor types by immunohistochemistry (IHC) and messenger ribonucleic acid (mRNA) expression, respectively. Moderate to high CD73 expression was seen in NSCLC, SCCHN, RCC, and pancreatic carcinoma. Expression of A2AR on tumor-infiltrating lymphocytes was high to moderate in all of these tumor types.[32]

Emerging data further link CD73 expression to canonical MAPK signaling; details regarding NSCLC and melanoma are summarized below. Although data do not yet support use of MAPK signaling as a basis for patient selection, sufficient evidence exists to justify exploration of BMS-986179's safety, PK, PD, and preliminary efficacy among subsets of subjects with NSCLC or melanoma with tumors containing driver mutations.

Preliminary data as of 18 August 2017 from this study show that a total of 4 objective responses (1 each in pancreatic carcinoma, SCCHN, CRPC, and RCC) have been observed in the dose-escalation portion (Part 1A) of this study (combination therapy with BMS-986179 and nivolumab).

1.1.4.1 Overview of Subject Selection Strategy for Part 2 Dose Expansion

Despite the success of CTLA-4 and anti-PD-1 pathway-targeted agents, significant numbers of patients either fail to respond or progress after initial response.[39] It is likely that other checkpoints and/or factors in the tumor microenvironment, may contribute to treatment failure.

A recent meta-analysis showed that CD73 was an adverse prognostic factor across a variety of tumor types.[40] Elevated serum adenosine levels in patients with RCC correlated with significantly decreased ORR and shorter progression-free survival following nivolumab therapy.[41] Moreover, breast and colon carcinoma cell lines transformed to overexpress high levels of CD73 were significantly less responsive to PD-1 blockade than isogenic controls; in a mouse model, the effects were reversed by SCH58261, an A2AR inhibitor.[42] Recently, significant elevation of CD73 mRNA expression was seen among patients who were resistant/refractory to anti-PD-(L)1 therapy, versus immuno-oncology-naive patients, in pretreatment biopsy specimens obtained on the CPI-444 Phase 1 study.[43] Furthermore, exposure to anti-PD-(L)1 therapy for greater than 3 months was associated with an increase in tumor A2AR, CD73 and CD39 expression compared to less than 3 months of exposure.[44] This suggests that the adenosine pathway may play a role as a potential mechanism of acquired resistance to anti-PD-(L)1 therapy.

Collectively, these observations support exploration of a patient selection strategy in the NSCLC, melanoma, RCC and SCCHN expansion cohorts where patients have failed prior anti-PD-(L)1 therapy. Patients in the aforementioned cohorts will now be selected for treatment with anti-CD73 by exposure (>3 months) to prior anti-PD-(L)1 therapy. It is hypothesized that relevant adenosine axis genes may be upregulated in this population which may lead to a greater chance of clinical benefit with anti-CD73. This is further supported by recent data showing that in CD73+ tumors at screening, increased expression of T cell activation markers was observed in post-treatment tumor biopsies after treatment with CPI-444.[44]

1.1.4.2 Rationale for Inclusion of Specific Tumor Types

NSCLC

In NSCLC, CD73 is an independent adverse prognostic factor for OS.[45] Adenosine may also have direct growth inhibitory effects on NSCLC tumor cells, in addition to generating an immunosuppressive microenvironment.[46] This suggests that there may be multiple mechanistic rationales for anti-CD73 therapy in this tumor type. Furthermore, recent data suggest that adenosine pathway expression is higher in RCC and NSCLC pre-treatment biopsies. [44]

The subset of patients with EGFR-mutant NSCLC shows less clinical benefit to anti-PD-(L)1 therapy, and CD73 expression is increased in NSCLC tumors or cell lines harboring such mutations.[21] Small-molecule inhibitors of EGFR tyrosine kinase reduce CD73 expression in EGFR-mutant and wild-type NSCLC cell lines in a concentration-dependent manner.[50] In isogenic NSCLC cell lines, knockdown of K-RAS oncogene (KRAS) by RNA interference significantly down-regulated expression of ecto-5′-nucleosidase (NT5E, an alternate name for CD73).[47,48]

Based on these observations, and on the previously noted clinical data for adenosine A2A receptor inhibitor (A2ARi) monotherapy, BMS-986179 will be evaluated in subjects with NSCLC who previously progressed on prior anti-PD-(L)1 as their most recent therapy. Targeted enrollment of patients with mutations in EGFR or KRAS may be considered in order to better understand safety, PK, PD, and potential efficacy in these subgroups.

Melanoma

In melanoma, unmethylated CpG islands in the promoter of the NT5E (also known as CD73) gene correlated with increased risk of relapse and a greater propensity for metastasis to lymph nodes, viscera, and brain.[49,50] Mutational activation of MAPK signaling is extremely common in melanoma cells; this drives CD73 expression and is associated with a more invasive, mesenchymal phenotype.[51] Downregulating MAPK signaling with small-molecule inhibitors of BRAF or MAPK/ERK (extracellular signal-regulated kinase) kinase (MEK) significantly reduced CD73 expression.[63] Treatment of mice bearing BRAF-mutant melanoma with inhibitors of either BRAF or adenosine signaling (A2AR) reduced tumor size and numbers of metastases; significantly greater effects were seen when inhibitors were given in combination.[63] Together, these results show that CD73 expression is highly dependent on MAPK signaling. Response of BRAF-mutant melanoma to A2ARi monotherapy in vivo suggests that therapeutically targeting adenosine signaling in MAPKdriven- tumors is reasonable to explore.

Targeted enrollment of patients with mutations in BRAF or neuroblastoma RAS oncogene (NRAS) may be conducted in order to better understand safety, PK, PD, and potential efficacy in these subgroups.

SCCHN

Anti-PD-(L)1 therapy is approved as standard of care therapy for second-line, platinum-refractory SCCHN in the US, with monotherapy yielding objective responses in 13% to 18% of patients.

Among patients with SCCHN, CD73 IHC correlated with tumor size and stage and inversely correlated with disease-free survival and OS on multivariate analysis.[52] Furthermore, SCCHN was among tumor types in which objective response was seen in Part 1A of the current study.

Given these considerations, BMS-986179 will be evaluated in combination with nivolumab in subjects with SCCHN who have failed prior anti-PD-(L)1 therapy.

RCC

In RCC, CD73 is associated with shorter median OS (multivariate analysis).[53] As noted above, patients with RCC who failed prior anti-PD-(L)1 therapy showed clinical benefit, including objective response, to monotherapy with A2ARi monotherapy. It is also noteworthy that many patients with sporadic and familial RCC have mutations or other alterations affecting the von Hippel-Lindau (VHL) gene, leading to abnormal hypoxia-inducible factor (HIF)-1 and HIF-2 signaling, a hypoxic phenotype.[54,55] CD73 expression is upregulated by hypoxia.[56,57] As previously noted, RCC is among the tumor types that have relatively high CD73 expression, possibly related to this underlying hypoxic phenotype. Finally, partial response of a subject with RCC to the combination of BMS-986179 with nivolumab in Part 1A of the current study supports further evaluation of the therapy in this disease type.

Considering these observations, as well as data for A2ARi monotherapy noted above, BMS-986179 will be evaluated in 2 parallel cohorts of subjects with RCC who have failed prior anti-PD-(L)1 therapy: monotherapy and in combination with nivolumab. Subjects who initially receive BMS-986179 monotherapy may receive nivolumab in combination therapy if they progress on monotherapy.

CRPC

In prostate carcinoma, CD73 independently predicted worse survival on multivariate analysis; effects correlated with decreased immune surveillance by CD8 T cells, potentially related to adenosine effects on nuclear factor kappa B signaling mediated via alpha 2B adrenergic receptors.[58] Prostate carcinoma was among disease types that demonstrated objective response in Part 1A of the current study.

Immunotherapies are an area of active investigation in CRPC.[59] However, while some activity has been observed with anti-PD-(L)1 therapies, these are not yet proven effective or approved for this indication. Therefore, BMS-986179 will be evaluated in combination with nivolumab in subjects with CRPC without selection on the basis of prior anti-PD-(L)1 therapy.

Pancreatic Adenocarcinoma

In pancreatic cancer, CD39 expression has been shown to be increased in pancreatic tumors and to correlate with survival.[60,61] Pancreatic carcinoma was among disease types that demonstrated objective response in Part 1A of the current study.

Anti-PD-(L)1 therapies are not yet proven effective or approved for this indication. Pancreatic carcinoma is not among tumor types classically considered to be immunoresponsive; thus,

observation of an objective response justifies further evaluation to determine whether a potential efficacy signal is present. Therefore, BMS-986179 will be evaluated in combination with nivolumab in subjects with pancreatic adenocarcinoma, without selection for prior anti-PD-(L)1 status.

1.1.5 Rationale for Dose and Schedule

1.1.5.1 BMS-986179

The first-in-human dose of BMS-986179 selected for Part 1A of this study (150 mg) is based on all available nonclinical data.[62] The proposed starting dose is far below (~10x) the maximum recommended starting dose (25 mg/kg or 1600 mg) based on the no-observed-adverse-effect-level (NOAEL) from the 1-month weekly-dose toxicity study in monkeys.[84] It is also lower (approximately 2.7-fold lower) than the projected human efficacious dose (400 mg), which should facilitate demonstration of a dose-related PK/PD relationship.[63] Thus, the first-in-human starting dose of BMS-986179 appropriately balances regard for patient safety with the potential of exposing patients with advanced cancer to non-pharmacologically active doses.

The human PK of BMS-986179 was predicted using the PK data generated in cynomolgus monkeys. In lieu of significant nonlinear PK in monkeys [redacted], both saturable and non-saturable pathways were used to describe the clearance of BMS-986179. The saturable portion of the clearance (likely due to target-mediated drug disposition) was assumed to be the same between monkeys and humans, because of comparable binding affinity of BMS-986179 to CD73 and CD73 target load between the two species. The non-saturable portion of the clearance was allometrically scaled from monkeys to humans using a power exponent of 0.85.[32]

The human efficacious dose of BMS-986179 is projected to achieve the steady-state serum trough concentration [redacted] that is predicted to produce approximately ~95% CD73 inhibition in the tumor. At this level of CD73 inhibition, a significant improvement in anti-tumor efficacy was observed in the MC38 mouse tumor model when combining an anti-CD73 mouse surrogate monoclonal antibody (19C8) with an anti-mouse PD-1 monoclonal antibody (mIgG1). By assuming comparable tumor drug distribution between mice and humans, the projected human efficacious dose of BMS-986179 is 5 mg/kg intravenous (IV) given Q1W. Given that the observed in vivo efficacy in MC38 tumor model was not dose-dependent and the results were variable, partial efficacy may be expected at lower doses in humans. Additionally, a non-linear PK is also expected but has not yet been characterized in humans.

A flat IV-administered dose of 150 mg has been selected as the first-in-human starting dose of BMS-986179. The expected, and in fact actual, dose increments for evaluation in this protocol are as follows: 150, 300, 600, 1200, and 1600 mg flat doses. Subsequent dose levels after the initial 150 mg dose level may be modified based on the Bayesian Logistic Regression Method (BLRM)-Copula recommendation, but will not exceed a doubling of the previously tested dose. Moreover, the top dose of 1600 mg is selected based on the product specification of the clinical batch of BMS-986179. Based upon the NOAEL of BMS-986179 IV-administered dose in monkeys, which was determined to be 150 mg/kg, or a human equivalent dose of 25 mg/kg, or 2000 mg for 80 kg

person,[32] the entire human dose range administered is within the toxicity limitations above. Based on preliminary results from Part 1A of this study, in which subjects received combination therapy with IV-administered BMS-986179 and nivolumab, this initial assumption appears to have been justified.

In summary, the synergistic effect of combination therapy of BMS-986179 surrogate and nivolumab surrogates was demonstrated with high CD73 activity inhibition (~95%) in tumor tissue in MC38 tumor models. A minimum human efficacious dose of the IV formulation was projected to be about 400 mg for an adult of 80 kg for a dose schedule of IV Q1W. After a preliminary analysis of the PK/PD in Part 1A, IV-administered and SC-administered doses below the MTD will be used to evaluate alternative dose schedules (potentially Q2W, every 3 weeks [Q3W], and every 4 weeks [Q4W] in Part 1B [PD substudy]).

1.1.5.2 Nivolumab

Nivolumab at a dose of 3 mg/kg has been approved to be used as monotherapy in patients with melanoma and NSCLC.[64]

Nivolumab monotherapy has been extensively studied in a number of tumor types, including melanoma, NSCLC, RCC, and CRC, with body-weight–normalized dosing (mg/kg). Population PK analyses showed that the PK of nivolumab is linear, with doseproportional exposures over a dose range of 0.1 to 10 mg/kg, and is similar across tumor types. In addition, the -exposureresponse- relationships of nivolumab safety and efficacy are also well understood in patients with melanoma and NSCLC.

[redacted]

Nivolumab has been shown to be safe and well tolerated up to a dose level of 10 mg/kg, and the relationship between nivolumab exposure produced by 3 mg/kg and efficacy has been found to be relatively flat.[65] In the current study, the standard flat dose of nivolumab 240 mg Q2W (identical to a dose of 3 mg/kg for subjects weighing 80 kg) and the proportionately adjusted dose of 360 mg Q3W or 480 mg every 4 weeks (Q4W) may be administered with BMS-986179, in concordance with the PK/PD modeling of nivolumab.

The safety and efficacy of a flat dose of nivolumab 480 mg Q4W is also expected to be similar to that of nivolumab 3 mg/kg Q2W. The regimen of nivolumab 480 mg Q4W, either as the starting therapy or as maintenance treatment following nivolumab 240 mg Q2W, is currently being evaluated in multiple clinical studies. As of November 2016, approximately 50 subjects in the nivolumab clinical development programs have received at least 1 dose of nivolumab 480 mg Q4W. There have been no reports of any symptoms that may potentially be linked to infusion reactions on the day of infusion or on the following day. There have been no new safety signals identified during routine clinical and pharmacovigilance monitoring of these studies. Clinical evaluation of this dose regimen is ongoing; as such, a summary of safety, PK, and immunogenicity data is not currently available. The nivolumab 480 mg Q4W dose was selected based on clinical data and modeling and simulation approaches using population pharmacokinetics (PPK) and exposure-response analyses of data from studies in multiple tumor types (melanoma [MEL], NSCLC, and RCC). Using the PPK model, the overall distributions of nivolumab Cavgss are comparable after treatment with either nivolumab 3 mg/kg Q2W or 480 mg Q4W. Although nivolumab Cmaxss is predicted to be higher following 480 mg Q4W, these exposures are predicted to be within the exposure ranges observed at doses up to 10 mg/kg Q2W used in the nivolumab clinical program and are not considered to put subjects at increased risk. The exposures predicted following administration of nivolumab 480 mg Q4W are on the flat part of the exposure-response curves for previously investigated tumors, MEL, and NSCLC, and are not predicted to affect efficacy. Based on these data, nivolumab 480 mg Q4W is expected to have efficacy and safety profiles similar to those of nivolumab 3 mg/kg Q2W.

The risk/benefit profile for nivolumab has primarily been investigated using a 60-minute infusion. Long infusion times place a burden on patients and treatment centers. Establishing that these agents can be safely administered using shorter infusion times will diminish some of this burden. Previous clinical studies of nivolumab have used 60-minute infusion duration. Nivolumab has been administered safely at doses ranging up to 10 mg/kg at this treatment duration. Overall, infusion reactions including high-grade hypersensitivity reactions have been uncommon across multiple clinical studies, and all have been managed by following the safety algorithms. An infusion duration of 30 minutes for 3 mg/kg nivolumab (30% of the dose provided at 10 mg/kg) is not expected to present any safety concerns compared with the prior experience at 10 mg/kg nivolumab dose infused over the 60-minute duration.

1.1.5.3 Rationale for ≥ 24-week Duration

Published and ongoing nivolumab clinical studies (monotherapy and combination) in melanoma[66,67,68] suggest that most patients who will respond to anti-PD-1 treatment will do so

within the first 6 months of treatment. In previously untreated patients with melanoma without BRAF mutation,[69] treatment with nivolumab alone was associated with a rapid median time to response (2.1 months) and durable responses (the median duration of response [DOR] was not reached, but the duration of follow-up was short). Similarly, the majority of all responses were observed at the time of the first scan at 12 weeks in treatment-naive patients with melanoma following combination therapy with nivolumab and ipilimumab.[66,67,68] Accordingly, treatment in this study was initially limited to 6 months, with the option to continue therapy on an individual case-by-case basis.

As of 18 August 2017, 6 subjects received ≥ 24 weeks of on-study treatment and tolerated treatment well. In contrast to previous experience with nivolumab monotherapy, many responses seen to date occurred relatively late (range 22 to 26 weeks), including 1 partial response (PR) in a subject with RCC treated beyond progression. These results suggest that prolonged treatment with BMS-986179 is safe and that treatment beyond 24 weeks is reasonable in patients who are tolerating treatment and showing clinical benefit by that time. Recent results for nivolumab monotherapy also support longer treatment durations. For example, data from the CheckMate 153 trial show superior progression-free survival, and a trend toward improved OS, for patients treated with nivolumab until progression versus those who discontinued therapy after 1 year.[70] Based on these considerations, the initial treatment period of 24 weeks will be followed by the option of treatment for an additional 80 weeks, for a total treatment period of up to a total of approximately 2 years (see Section 3.1.5).

1.1.5.4 Rationale for Treatment Beyond Progression

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

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.

This phenomenon was observed in the Phase 2 study of nivolumab, CA209003[71,72], in patients with solid tumors. Two hypotheses explain this phenomenon. First, enhanced inflammation within tumors could lead to an increase in tumor size, which would appear as enlarged index lesions and as newly visible small non-index lesions. Over time, both the malignant and inflammatory portions of the mass may then decrease, leading to overt signs of clinical improvement. Alternatively, in some individuals, the kinetics of tumor growth may initially outpace anti-tumor immune activity. With sufficient time, the anti-tumor activity will dominate and become clinically apparent. Therefore, it is important to avoid premature discontinuation of the study drug(s) that might induce a non-conventional response pattern in some patients.

The decision to continue treatment beyond investigator-assessed progression should be discussed with the BMS Medical Monitor and the patient, and documented in the study records. The

assessment of clinical benefit should take into account whether the subject is clinically deteriorating and unlikely to receive further benefit from continued treatment.

As of 18 August 2017, 1 subject with RCC who was treated past progression subsequently demonstrated PR.

1.1.6 Rationale for PD Substudy

A PD substudy (Part 1B) will be conducted to characterize the effects of alternate dosing regimens and formulations on duration of enzymatic inhibition, downregulation of CD73 protein, and extent of T-cell infiltration. In this part of the study, BMS-986179 will be given at less frequent intervals, the exact intervals for which will be determined by the human safety, PK, and PD data generated in Part 1A. A mandatory criteria for the start of Part 1B will be the demonstration that the intratumoral CD73 enzyme activity is inhibited by > 50% at a single dose level of IV-administered BMS-986179 in Part 1A. The data generated in this part of the study will be compared to that from the Q1W schedule to determine the optimal dose and schedule for expansion.

1.1.7 Rationale for Subcutaneous Administration

In addition, the PD substudy may obtain preliminary data on the potential bioavailability of subcutaneously administered BMS-986179, in comparison to intravenous dose(s) and schedule(s) shown to be safe in Part 1A and Part 1B. For subcutaneous administration, BMS-986179 will be administered with recombinant human hyaluronidase PH20 (rHuPH20, 1000 U/mL, Halozyme, Inc.).

Public data presented to the FDA ODAC[73] to support coadministration of rituximab and rHuPH20, summarizing data from randomized PK bridging trials in patients with Follicular Lymphoma, CLL, or DLBCL (SparkThera, SABRINA, SAWYER, MabEase, PrefMab) show: (1) comparable Ctrough and overall exposure; (2) comparable safety, aside from administration site reactions; and (3) comparable efficacy (ORR, CRR, PFS, EFS, and OS in various studies) for subcutaneous versus intravenous routes. Injection site reactions (discomfort, erythema) were increased following subcutaneous administration, occurring in 1.9 - 25.9% of subjects; these were generally mild and did not limit therapy. Importantly, patient preference and patient-reported outcomes were evaluated in a randomized crossover trial (PrefMab) of 743 previously-untreated patients with DLBCL or FL receiving R-CHOP, R-CVP, or R-Bendamustine to subcutaneous versus intravenous administration. Over 80% of patients preferred subcutaneous administration, due to reduced time for administration and greater comfort.

Subcutaneous administration of BMS-986179 is expected to be feasible because: (1) biopsies obtained to date (12-DEC-2017) show approximately 100% target engagement and significant inhibition of CD73 enzyme activity at all IV-administered dose levels, in both tumor and adjacent normal tissue; [redacted] (3) quantification of soluble free and drug-bound CD73 shows peripheral saturation; and, (4) despite these findings, no adverse cutaneous effects have been seen. Recombinant human hyaluronidase PH20 (rHuPH20, 1000 U/mL; Halozyme, Inc) is expected to facilitate use of the subcutaneous route of administration for BMS-986179, with or without nivolumab, analogous to

several rHuPH20-enabled subcutaneous biologic therapies already approved in the US, EU, and other countries (for example, with trastuzumab, rituxumab, and immune globin (IG)).

A single-dose subcutaneous toxicokinetics and local tolerance study in cynomolgus monkeys has been completed. BMS-986179 was well-tolerated when administered to cynomolgus monkeys as a single subcutaneous dose at 150 mg/kg containing 2000 U/mL rHuPH20 with no clinical observations (including feeding behavior), no effects on survival, and no BMS-986179-related histopathologic findings observed in any of the skin biopsies. Additional details are provided in section 4.3.6 in BMS-986179 Investigator's Brochure (IB).[32] This further supports subcutaneous administration in the proposed clinical trial. Potential risks will be further mitigated through a sentinel subject dosing strategy. [redacted]

While no adenosine antagonists have been administered subcutaneously, it is noteworthy that cutaneous toxicity has not been reported in early trials of a drug with closely-related mechanism of action (CPI-444, an A2AR inhibitor) and has not been seen to date in the present trial with BMS-986179, despite evidence of target saturation both in tumor and in peripheral tissues (see section 3.1.2 for additional details). However, adenosine antagonists (selective A2AR inhibitor CGS 21680, and the repurposed antiviral compound Tenofovir) have been administered topically as potential therapeutics for inflammatory skin diseases in nonclinical models.[74,75] Moreover, global genetic knockout of the ectonucleases CD39 and/or CD73 has been investigated in nonclinical models of dermal fibrosis.[76] Although these experiments were not explicitly designed to assess safety, no adverse effects on skin were reported.

Taken together, these observations suggest that subcutaneous administration of BMS-986179, at a dose previously shown to be safe intravenously, should reasonably be anticipated to be feasible and tolerable.

1.1.8 Rationale for Sentinel Subject Approach

BMS-986179 is a human monoclonal antibody that binds to and antagonizes the activity of CD73. In vitro, BMS-986179 blocks cellular CD73 activity and induces its internalization. These functions are expected to reduce the capacity of tumor cells and suppressive immune subsets to produce adenosine, thus indirectly relieving immune suppression in the tumor microenvironment. BMS-986179 does not induce immune cell activation as monotherapy nor does it act directly on effector cells. Based on this mechanism of action, an anti-CD73 mAb should not induce toxicity due to T cell activation by itself or exacerbate such toxicity in combination with anti-PD-1 therapy.[77,78,83,84] Preclinical studies in rodents and cynomolgus monkeys did not indicate acute or repeat dose safety concerns, even at high doses. However, to mitigate the risk of unexpected acute toxicity when dosed in humans, a staggered dosing (sentinel subject) approach will be used at all dose levels in this study. To mitigate the risk of unexpected acute toxicity upon first human exposure at each dose level, the initial subjects in the 150 and 300 mg dose levels will be observed for 5 days before additional subjects in each cohort are treated with study drug. This time frame is based upon a projected human half-life < 5 days at lower dose levels, where there is an expectation

of target-mediated drug disposition (TMDD). At doses higher than 400 mg, including the planned 600 mg dose level, there is an expectation that half-life will increase once TMDD has been saturated. Consequently, the initial subject for this dose will be observed for 9 days before additional subjects in that cohort are treated. These waiting periods will also apply at the initiation of combination dosing after the 2 week monotherapy lead-in segment. For subcutaneous administration, in order to mitigate the risk of potential local toxicity, the initial subject in each cohort will be observed for 5 days before additional subjects in the cohort are treated with study drug.

1.1.9 Rationale for Use of Blood and Tumor Tissue in Biomarker Studies

Biomarkers are increasingly playing a key role in the development of cancer therapeutics. By tracking treatment-induced changes in molecular markers measured in tissue and body fluids, the activity of experimental agents may be assessed and the details of their mechanisms of action may be elucidated. Such PD measures may be instrumental also for identifying appropriate doses and treatment schedules and may provide supporting information for future regimens.

Blood and tumor tissue samples will be collected in this study at baseline and on treatment to identify molecular markers associated with clinical activity and mechanism of action of BMS-986179 monotherapy or in combination with nivolumab. This information will used to identify appropriate doses and treatment schedules of BMS-986179 alone and in combination with nivolumab. Additionally, examination of biomarkers in samples obtained prior to treatment may provide information that allows identification of patients with specific characteristics that will respond best to these agents.

Specific questions that will be addressed by biomarker analysis include the following:

Does treatment with BMS-986179, alone or in combination with nivolumab, modulate:

- CD73 enzyme activity and/or CD73 protein expression

[redacted]

[redacted]

PD changes between baseline and on-treatment measures will also be monitored and evaluated for associations with PK data and adverse events (AEs). Baseline measures will be assessed for their predictive value in an effort to identify candidate markers for future studies (with comparator arms) where their ability to predict AEs associated with anti-CD73 monotherapy or combination therapy with nivolumab treatment may be appropriately evaluated.

1.1.10 Rationale for Enrolling Additional Subjects for PD in Dose Escalation Cohorts

A critical aspect of Part 1 of this study is the demonstration of deep and durable inhibition of CD73 enzyme activity. This will require pre- and on-treatment fresh core tumor biopsies for all subjects to be assessed using fresh frozen tissue for CD73 enzyme measurements. It is anticipated that some of these samples will not be useful for assessment due to technical reasons, such as inadequate tumor content in the biopsy or inadequate enzyme activity levels. Moreover, both pre- and on-treatment biopsy samples will have to be analyzable in order to show the effects of treatment. Therefore, the dose escalation cohorts (Part 1A) and sub-study cohorts (Part 1B) may include additional subjects beyond those needed to assess the PD, PK, and safety of BMS-986179.

1.2 Research Hypothesis

It is anticipated that anti–CD73 antibody (BMS-986179), administered alone and in combination with nivolumab (BMS-936558), will demonstrate adequate safety and tolerability, as well as a favorable risk/benefit profile, to support further clinical testing. No prospective hypotheses are being formally evaluated.

1.3 Objectives

1.3.1 Primary Objective

The primary objective is to assess the safety and tolerability of BMS-986179 administered alone and in combination with nivolumab.

1.3.2 Secondary Objectives

The secondary objectives are as follows:

- To characterize the PD activity of BMS-986179 administered alone and in combination with nivolumab
- To assess the preliminary anti-tumor activity of BMS-986179 alone and in combination with nivolumab as measured by ORR, DOR, and progression-free survival rate (PFSR)
- To characterize the PK and immunogenicity of BMS-986179 administered alone and in combination with nivolumab
- To characterize the immunogenicity of nivolumab when administered in combination with BMS-986179

1.4 Product Development Background

1.4.1 Pharmacology

BMS-986179

BMS-986179 is a monoclonal antibody that has been engineered to be a hybrid between human immunoglobulin G (IgG) 2 and human IgG 1 isotypes. The IgG2 isotype, through the hinge of the molecule, enhances the internalization and therefore functional activity of the antibody in reducing cellular CD73 activity levels. The modified IgG1 Fc portion of the antibody is inert for effector function (ADCC, complement binding, phagocytosis activity) to avoid potential toxicity to normal tissues expressing CD73. The antibody is predicted to have a low immunogenicity risk based on preliminary findings with in vitro immunogenicity assessments.

Biacore surface plasmon resonance data demonstrate that BMS-986179 binds with high affinity to the extracellular domain of human CD73 or a fragment corresponding to the N-terminal domain. Binding to the full-length human CD73 extracellular domain (ECD) protein has higher affinity than to the N-terminal domain due to avidity since the full-length human CD73 ECD is a dimer. Binding to full-length cynomolgus monkey CD73 ECD is also comparable to human CD73; human and cynomolgus monkey CD73 differ at only 2 of 574 amino acids and neither of the divergent residues is located at the BMS-986179 binding site. No cross-reactivity was observed for BMS-986179 toward mouse CD73 or rat CD73. Surface plasmon resonance studies also demonstrate that BMS-986179 has significantly reduced or undetectable binding affinity for several human Fcγ-receptors, while maintaining FcRn binding that is comparable to other IgG1 or IgG2 antibodies. These qualities ensure the lack of effector function to avoid potential toxicity to normal tissues expressing CD73, while retaining the advantage to PK provided by FcRn binding. Additional details are provided in BMS-986179 Investigator's Brochure (IB).[32]

Nivolumab

Nivolumab is a fully human, IgG4 (kappa) isotype monoclonal antibody that binds to PD-1 with nanomolar affinity (KD, 3.06 nM) and a high degree of specificity. Nivolumab blocks binding of PD-1 to its ligands PD-L1 and PD-L2. Nonclinical in vitro testing of nivolumab demonstrated that binding to PD-1 results in enhanced T-cell proliferation and release of interferon gamma (IFNγ) in vitro in mixed lymphocyte reaction and cytomegalovirus assays. Additional details are provided in the current version of the nivolumab IB.[38]

Recombinant Human Hyaluronidase PH20 (rHuPH20)

rHuPH20 is a highly recombinant human protein that increases the dispersion and absorption of co-administered therapeutics by locally and transiently depolymerizing interstitial hyaluronan in the subcutaneous space thereby decreasing viscosity of subcutaneous (SC) extracellular matrix (ECM).[80,81]This facilitates administration of higher volumes via the subcutaneous route and also the potential for more antibody reaching the systemic circulation as compared to SC administration without rHuPH20. The half-life of rHuPH20 in skin is < 30 minutes and hyaluronan in the SC space is restored via normal biological processess within 24 - 48 hours. Thus rHuPH20 offers an advantage of increasing the dispersion and absorption of co-injected drugs across a broad range of molecular weights. rHuPH20 has been shown to facilitate SC administration of several immunoglobulin-based biologic therapies and has been approved in for use with these agents in the US, EU, and other countries (for example, with trastuzumab, rituxumab, and immune globin (IG)).[81] Additional details are provided in the current version of the rHuPH20 IB.[82]

1.4.2 Toxicity

BMS-986179

The nonclinical safety of BMS-986179 was evaluated in in vitro human tissue cross-reactivity study and cytokine release and lymphocyte activation assays and in vivo IV toxicity studies up to 1 month in cynomolgus monkeys. The cynomolgus monkey was selected as the toxicology species because BMS-986179 binds to cynomolgus monkey CD73, is pharmacologically active in monkeys, and does not bind rodent CD73. BMS-986179 did not induce cytokine release or increase the expression of activation markers on human T, B, or NK cells, indicating that BMS-986179 does not induce nonspecific T- or NK-cellular activation or cytokine release (up to 10 µg/well).[83] In the pivotal 1-month IV toxicity study in monkeys (0, 15, 50, or 150 mg/kg, Q1W, 5 slow bolus doses), BMS-986179 was clinically well tolerated with no adverse effects at any dose.[84] The high dose of 150 mg/kg (mean sex-combined area under the serum concentration-time curve [AUC] from time zero to 168 hours of the last measurable concentration [AUC(0-168h)] of 661,000 µg•h/mL) was considered the NOAEL. No irritation or local tolerance issues were observed at the injection sites following repeated IV administration of BMS-986179 as a slow bolus injection (approximately 2 to 4 mL/minute for 3 to 5 minutes) at ≤ 150 mg/kg in cynomolgus monkeys. There were no BMS-986179–related cardiovascular, respiratory, ophthalmologic, or neurological effects at ≤ 150 mg/kg (mean maximum observed serum concentration [Cmax] 7,220 µg/mL). In a Good Laboratory Practice-compliant tissue cross-reactivity study in normal

human tissues, fluoresceinated BMS-986179 (BMS-986179-FITC)-stained multiple cell types throughout the human tissue panel were examined, including epithelium, mesothelium, endothelium, spindloid cells, mononuclear leukocytes, hematopoietic precursor cells, smooth muscle cells, neural elements, placental decidual cells, and testicular interstitial cells, as well as extracellular elements in select tissues.[85] Most cellular staining was present in both the cytoplasm and plasma membrane. As CD73 is found on the cell surface in a broad variety of cell types, the widespread immunoreactivity of BMS-986179-FITC was anticipated.

Overall, the nonclinical toxicology assessment of BMS-986179 has demonstrated an acceptable safety profile, supporting clinical use in oncology patients. Additional details are provided in the BMS-986179 IB.[32]

Nivolumab

Please see the nivolumab IB for current data.[38]

Recombinant Human Hyaluronidase PH20 (rHuPH20)

Please see the rHuPH20 IB for current data.[82]

1.4.3 Preclinical Metabolism and Pharmacokinetics

BMS-986179

BMS-986179 demonstrated evident nonlinear PK following single IV dosing in cynomolgus monkeys, likely due to target-mediated drug disposition. At doses from 5 to 40 mg/kg, systemic total body clearance (CLT) decreased from [redacted]. Volume of distribution at steady state (Vss) was similar among the different dose levels, ranging from [redacted], suggesting that BMS-986179 mainly resides in the extravascular space. Given the different CLTs values with similar Vss, apparent terminal half-life (T-HALF) increased from [redacted] over the dose range from 5 to 40 mg/kg. No metabolism studies have been conducted with BMS-986179.

Nivolumab

Please see the nivolumab IB for current data.[38]

Recombinant Human Hyaluronidase PH20 (rHuPH20)

Please see the rHuPH20 IB for current data.[82]

1.4.4 Clinical Pharmacology and Safety

BMS-986179

The current study is a first-in-human study. Before the current study, there was no previous clinical experience with BMS-986179. See Section 1.4.4.1 for preliminary clinical pharmacology and Section 1.5 for nonclinical safety and clinical data obtained to date in the present study.

Nivolumab

The multiple-dose PK of nivolumab given Q2W in patients with multiple tumor types was determined from the CA209003 study as well as population PK analyses using data from 909 subjects across nivolumab studies. Multiple-dose PK of nivolumab following Q2W dosing was linear with dose-proportional increase in Cmax and AUC in 1 dosing interval (AUC[TAU]) in the studied range of 0.1 to 20 mg/kg. The geometric mean steady state clearance was 8.2 mL/h, which is consistent with those of full human IgG antibodies. Additional details are provided in the current version of the nivolumab IB.[38]

1.4.4.1 Pharmacokinetics of BMS-986179

Preliminary human PK data suggest that BMS-986179 demonstrates non-linear PK at doses from 150 to 600 mg and dose-proportional PK from 1200 to 1600 mg. Therefore, the half-life of BMS-986179 is expected to increase as dose increases from 150 to 600 mg and become stable at 1200 to 1600 mg. The summary statistics of non-compartmental PK analysis for these preliminary data are provided in the BMS-986179 IB.[32]

1.5 Overall Risk/Benefit Assessment

Before the current study, there was no prior human experience with BMS-986179; therefore, clinical benefit had not been assessed in subjects with advanced cancer. Preclinically, the evaluation of risk was initially based on information from nonclinical studies in monkeys with BMS-986179. Overall, there were no adverse findings observed in the nonclinical toxicology studies that identify specific safety concerns for using BMS-986179 as a single agent (see Section 1.4.2). Within the literature, there have been animal studies describing vascular effects (e.g. roles in leukocyte adhesion to vascular endothelium and in coronary vascular tone), in mice.[86] To date, one first-in-human, Phase 1 study with an anti-CD73 therapeutic antibody (MEDI9447,

MedImmune LLC) and 1 first-in-human Phase 1 study with an adenosine 2A receptor inhibitor (PBF-509, Palobiofarma SL) are recruiting patients. There are no published safety data available on either of these entities. However, preliminary data for a different A2AR inhibitor, CPI-444 (Corvus) show minimal adverse effects and potential clinical benefit in immunotherapy-naive and -experienced patients with NSCLC and RCC.[30]

As of 21 September 2017, a total of 85 subjects have been treated with BMS-986179 in the current study (doses ranging from 150 to 1600 mg Q1W alone and in combination with nivolumab). During dose-escalation, all dose levels were tolerable and MTD was not reached. Two subjects experienced myocardial infarction (1 at 150 mg and 1 at 600 mg dose levels; both Grade 3, with full recovery). Both subjects had multiple risk factors for coronary artery disease. These events were considered related to BMS-986179, since adenosine may contribute to protection of hypoxic myocardium. More stringent eligibility criteria and cardiac risk factor monitoring were instituted in Protocol Amendment 07 (21 March 2017), and no further cardiac ischemic events were observed as dose escalation was completed through the 1,600 mg cohort.

The study has further progressed and currently Part 2 expansion cohorts in the tumor-specific indications with high unmet medical need are open to subjects who have been considered for all other potentially efficacious therapies. As of 20 November 2018, a total of 129 subjects have been treated with BMS-986179 with no further cardiac ischemic events. In addition, objective response and/or prolonged stable disease have been observed in some subjects. Collectively, these observations suggest a favorable risk/benefit profile for BMS-986179.

Continuous safety assessments will be utilized by the investigators and the Sponsor to determine whether additional dose cohorts, additional safety measures, dose delays, or termination of the study is required at any time. In addition, AEs and serious adverse events (SAEs) will be reviewed on an ongoing basis by the BMS Medical Monitor and Global Pharmacovigilance and Epidemiology representatives to monitor for any safety signals or trends.

In preclinical studies, BMS-986179 alone did not provide significant anti-tumor efficacy as a monotherapy agent; however, it did show significant anti-tumor effects when combined with anti-PD-1. Treatment with BMS-986179 is therefore expected to broaden and deepen the responses seen with nivolumab and potentially other immune-modulating anti-cancer agents. In addition, the responses seen for monotherapy with CPI-444 suggest that BMS-986179 alone has potential activity in certain contexts.

1.5.1 Risk/Benefit for Combination with Nivolumab

Nivolumab has demonstrated clinical activity and a manageable safety profile in subjects with advanced NSCLC, RCC, melanoma, and lymphomas, as well as other tumors.[38] The overall safety experience, when used either as a monotherapy or in combination with another therapeutic, is based on experience in approximately 167,400 study subjects treated as of 03-Jul-2017 (the cut-off).[38]

There is no pattern in the incidence, severity, or causality of AEs to nivolumab dose level. The most common AEs include fatigue, rash, pruritus, diarrhea, nausea, and musculoskeletal pain. Side

effects of nivolumab therapy may include those associated with immune-mediated activation, such as pneumonitis, colitis, hepatitis, and hypophysitis. Most of these events, with the exception of the endocrine effects, resolved with immune-modulating medication and/or with holding nivolumab for brief periods.[64] To mitigate risk from immune-mediated SAEs, subject management algorithms for nivolumab-related AEs from prior collective nivolumab experience have been included (Appendix 1). As with any combination treatment, there is potential for overlapping toxicities between BMS-986179 and nivolumab. Finally, preliminary data from recent trials suggest that it may be possible to restore response to anti-PD-(L)1 therapy by administering nivolumab in combination with other immunomodulators (such as anti-LAG3). Together, these observations are consistent with a favorable risk-benefit profile for nivolumab combination therapy.

1.5.2 Summary

Despite innovations in cancer treatment, alternative therapies are needed for subjects with advanced cancer that has progressed or not responded to existing treatments. The emerging role of combination immune-modulating therapies in producing deep and durable responses in a variety of tumor types suggests that, once a pharmacologically-active dose range is reached, there may be a potential benefit of CD73 inhibition with BMS-986179 for subjects when used alone or in combination with nivolumab. This supports the evaluation of BMS-986179 alone or in combination with nivolumab in subjects with advanced cancer who have few treatment options.

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the US Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

All potential serious breaches must be reported to BMS immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

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

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

2.2 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, subject recruitment materials

(eg, advertisements), and any other written information to be provided to subjects. The investigator or BMS should also provide the IRB/IEC with a copy of the IB or product labeling information to be provided to subjects and any updates.

The investigator or BMS 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.

2.3 Informed Consent

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

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

BMS will provide the investigator with an appropriate (ie, Global or Local) sample informed consent form(s) [ICF] that will include all elements required by ICH, GCP, and applicable regulatory requirements. The sample ICF will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

- Provide a copy of the consent form(s) and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be nontechnical and easily understood.
- Allow time necessary for the subject or the subject's legally acceptable representative to inquire about the details of the study.
- Obtain an informed consent signed and personally dated by the subject or the subject'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 ICF(s) and any other information to be provided to the subjects prior to the beginning of the study and after any revisions are completed for new information.
- If informed consent is initially given by the subject's legally acceptable representative or legal guardian and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject.
- Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

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

The consent form(s) must also include a statement that BMS and regulatory authorities have direct access to subject records.

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

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

This is a Phase 1/2a, open-label study of BMS-986179 administered as a single agent and in combination with nivolumab in subjects with advanced solid tumors. The study will be conducted in 3 parts: Part 1A (combination therapy dose escalation with monotherapy lead-in; see Section 3.1.1), Part 1B (PD substudy; see Section 3.1.2), and Part 2 (cohort expansion; see Section 3.1.3). Subjects in each study part will complete up to 4 periods in the study: Screening (within 28 days prior to start of the study drug for Part 1A and Part 1B; up to 42 days for Part 2), treatment (approximately 6 months with an option for treatment for an additional 80 weeks), safety follow-up (approximately 100 days from the last dose), and response/survival follow-up (approximately 3 years from the last dose).

During screening, pre-treatment tumor biopsies (at least 4 fresh core biopsy specimens) are required from each subject in addition to the other screening activities.

During the treatment period, the decision to continue the treatment will be based on safety and available tumor assessment findings. Tumor assessments will be performed every 8 weeks from the start of treatment for the Q1W, Q2W, and Q4W regimens and every 9 weeks from the start of treatment for the Q3W regimen (see Table 5.1-2, Table 5.1-3, Table 5.1-4, and Table 5.1-5). Assessments must be completed before the subsequent dose. Tumor progression or response endpoints will be assessed using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (Appendix 2). In addition, each subject will undergo a single mandatory on-treatment tumor biopsy, the timing of which is dependent on the part of the study in which he/she is enrolled (see Table 5.6-1 through Table 5.6-5).

Subjects will generally be allowed to continue study drug until the first occurrence of one of the following: 1) completion of the maximum number of cycles, 2) progressive disease, 3) clinical deterioration suggesting that no further benefit from treatment is likely, 4) intolerability to therapy, or 5) the subject meets criteria for discontinuation of study drug as outlined in Section 3.5. Subjects with confirmed complete response (CR) will be given the option to discontinue study drug on a case-by-case basis after specific consultation and agreement between the investigator and BMS Medical Monitor in settings where benefit/risk justify discontinuation of study drug.

Subjects may continue study drug and imaging assessments after the first occurrence of progressive disease on a case-by-case basis after specific consultation and agreement among the investigator, BMS Medical Monitor and the subject in settings where benefit/risk may justify continuation of therapy. (Section 3.1.4)

During safety follow-up, treated subjects will be evaluated for safety and tolerability, and tumor response (if applicable), for approximately 100 day after the last dose of therapy (see Table 5.1-

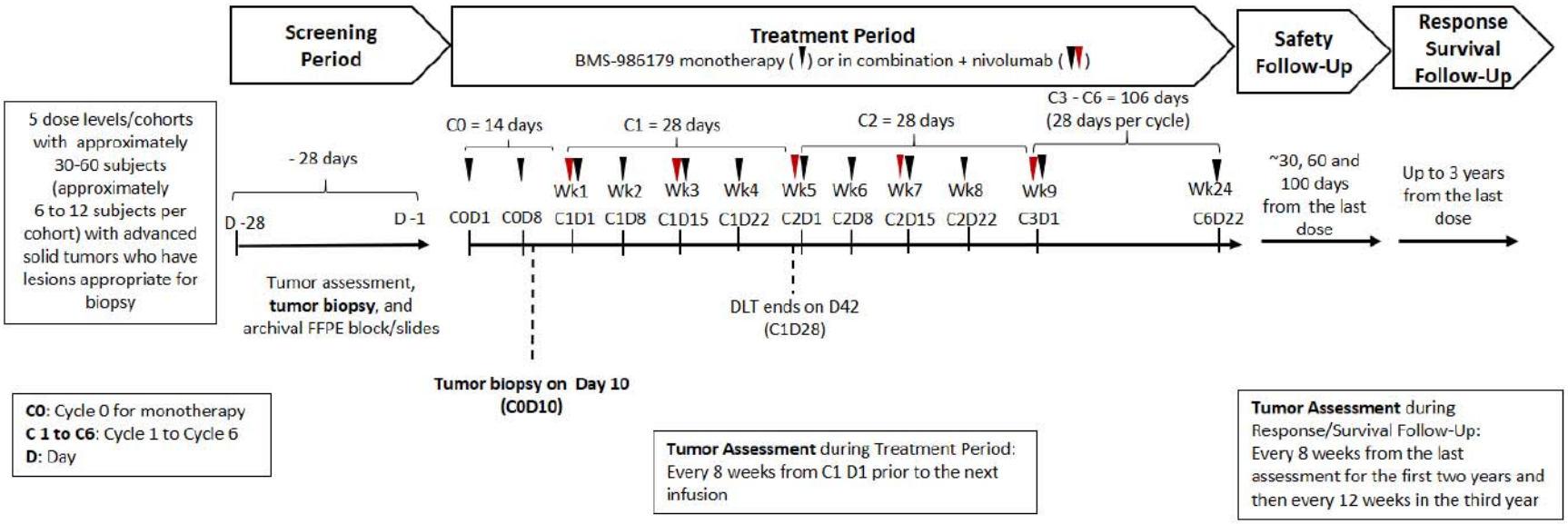
10). All subjects will be required to complete the 3 clinical safety follow-up visits, on approximately Days 30, 60, and 100, regardless of whether they start a new anti-cancer therapy, except those subjects who withdraw consent for study participation (see Section 3.6.1).

During response/survival follow-up, treated subjects who do not experience progressive disease prior to treatment discontinuation will be followed for 3 years following the last dose of study drug (see Table 5.1-10) and will continue to have radiologic and clinical tumor assessments every 8 weeks (from the last tumor assessment in the treatment period) for the first two years until progression is confirmed, withdrawal of consent, start of a new treatment, lost to follow-up, or death, whichever comes first. Tumor assessment scans will be per standard of care guidelines or at a minimum of every 12 weeks during the third year until progression is confirmed, withdrawal of consent, start of a new treatment, lost to follow-up, or death, whichever comes first. Subject survival status will be assessed by telephone every 12 weeks if there is no scheduled tumor assessment visit.

3.1.1 Part 1A (Dose Escalation)

The study design schematic for Part 1A is presented in Figure 3.1.1-1.

Figure 3.1.1-1: Study Design Schematic (Part 1A [Dose Escalation])



Abbreviation: FFPE = formalin fixed, paraffin embedded.

Beginning on Day 1 of Cycle 0 (14-day cycle in monotherapy lead-in), subjects in Part 1A will receive their assigned dose of BMS-986179 (see Table 3.1.1-1) on a Q1W schedule. Beginning on Day 1 of Cycle 1 (28-day cycle combination therapy) nivolumab at a dose of 240 mg Q2W will be added in addition to weekly doses of BMS-986179. The nivolumab dosing regimen will remain the same at each BMS-986179 dose level. Combination treatment will continue for up to 24 weeks until the end of Cycle 6.

The dose-escalation period of the study will determine the MTD/recommended Phase 2 dose of BMS-986179 alone and in combination with nivolumab based on DLTs using a BLRM model (for BMS-986179 monotherapy lead-in) and a BLRM-Copula model (for BMS-986179 in combination with nivolumab) with an escalation with overdose control principle, to ensure that safety is not compromised during dose escalation (see Appendix 4).

The initial dose level of BMS-986179 planned for this study is 150 mg. Dose levels to be considered for the next combination cohort (with monotherapy lead-in) will be based on the recommended monotherapy dose from BLRM and the recommended combination dose from BLRM-Copula; the lower recommended dose from both models will be considered for the next dose escalation. Potential dose levels for Part 1A are provided in Table 3.1.1-1. Final dose selection for the next cohort/dose level will be made in conjunction with all available PK, PD, and safety data from all treated subjects and will be made after discussion and agreement between investigators and the BMS Medical Monitor. Also, intermediate or lower doses, or less frequent dosing of BMS-986179, may be investigated if none of the planned doses/schedules are found to be tolerated as monotherapy for the lead-in period or in combination with nivolumab.

[redacted]

The study plan for Part 1A is summarized as follows: approximately 30 to 60 subjects with advanced solid tumors with biopsy-accessible lesions will be treated in Part 1A. Once a dose level is selected for a given cohort in the dose-escalation period, approximately 3 subjects will be treated at that specified dose level, following the sentinel subject approach described below and in Section 1.1.8. Cohort tolerability assessment and subsequent dose recommendation will occur when 2 evaluable subjects within a set have completed the [redacted] period. If the potential [redacted] occurring in the third evaluable subject at a specific dose level does not influence the dose recommendation by BLRM (-Copula), the BLRM (-Copula)-recommended next dose level may proceed without waiting for the third subject to complete the corresponding [redacted] after discussion and agreement between the Sponsor and investigators. While waiting for the [redacted] of those 2 or 3 subjects, if additional subjects are available, these subjects could be enrolled to the current dose level. Continuous re-assessment of dose recommendation by

BLRM (-Copula) will be carried out at each dose level after each cohort of subjects [redacted]. Additional subjects may be added to a specific dose level according to model recommendations or clinical judgment, or for PD biomarkers. A maximum of 12 subjects will be treated at each dose level. As of 24 October 2017, 59 subjects have been treated under Part 1A. Enrollment in Part 1A is now closed.

[redacted]

During dose escalation, a staggered dosing (sentinel subject) approach will be used for the first subject in each dose level for both the monotherapy lead-in phase and the combination treatment phase (see Section 1.1.8). The first subject will receive Cycle 0 Day 1 (for monotherapy lead-in) or Cycle 1 Day 1 (for combination treatment) dose of the study drug and be observed for 5 days (for the planned 150 and 300 mg dose levels and any other doses up to and including 400 mg) or 9 days (for any doses between 400 mg and the planned 1600 mg dose level) before additional subjects (ie, Subject 2 onward in each cohort) receive study drug.

No intra-subject dose escalation of BMS-986179 is permitted.

Table 3.1.1-1: Doses During Part 1A (Dose Escalation)

Dose Level/Cohort	BMS-986179	Nivolumab
1	150 mg	240 mg
2	300 mg[a]	240 mg
3	600 mg[a]	240 mg
4	1200 mg[a]	240 mg
5	1600 mg	240 mg

[a] Dose could be modified based on BLRM-Copula recommendation. Enrollment in Part 1A is now closed.

3.1.2 Part 1B (PD Substudy)

The purpose of the PD substudy (Part 1B) is to provide additional information pertaining to the monotherapy or combination dose, schedule and BMS-986179 formulation for further study in Part 2 (cohort expansion) or subsequent studies. Up to 6 treatment arms will be assessed in Part 1B; each treatment arm is defined by a dose level, a dose schedule, and a formulation. Approximately 10 subjects per arm will be treated in Part 1B, with the exception of an arm to assess bioavailability for subcutaneous dosing, which will treat approximately 16 subjects. Dose level(s) explored and interval(s) for Part 1B will be determined by the safety, PK, and PD data from Part 1A (see Figure

3.1.2-1 and Figure 3.1.2-2:). A mandatory criteria for the start of Part 1B will be the demonstration that the intratumoral CD73 enzyme activity is inhibited by > 50% at a single dose level in Part 1A.

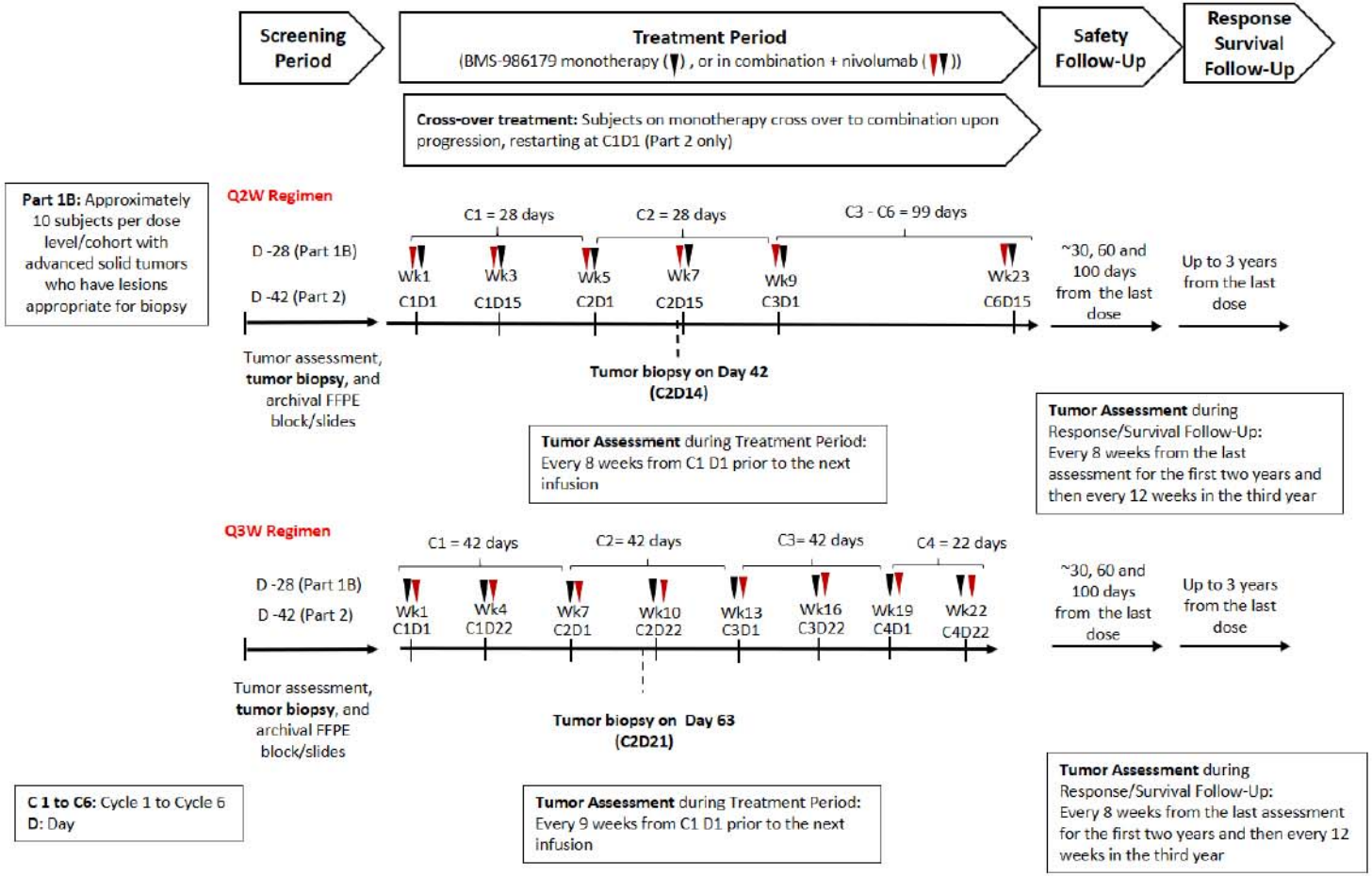
Based on nonclinical modeling, a Q2W or Q3W schedule was predicted to yield durable enzyme inhibition and immune cell effects in combination with nivolumab on the same dosing schedule. Actual PD and PK data from Part 1A and 1B to date (29-NOV-2017) suggest that effects may be sufficiently durable to permit Q4W dosing of both drugs, a schedule not included in the original protocol design. Therefore, cycles as long as Q4W may be tested in Part 1B, either as monotherapy or in combination with nivolumab. The nivolumab dose for combination therapy will be 240 mg for the Q2W arm and adjusted proportionately to 360 mg for the Q3W arm or 480 mg for the Q4W arm in concordance with the PK/PD modeling of nivolumab.

One or more PD substudy arms (exclusively at North American sites) may explore BMS-986179 subcutaneous administration, according to doses and schedules specified above. For subcutaneous administration, BMS-986179 will be co-administered with recombinant human hyaluronidase (rHuPH20, 1000 U/mL, Halozyme, Inc.). The bioavailability from already approved subcutaneous cancer therapies such as trastuzumab and rituximab that were co-administered with rHuPH20 was shown to be ~70% as compared to IV formulation. It is anticipated that the PD effects of BMS-986179 by the SC route will be very similar to those seen in intravenous administration, but it is necessary to confirm this prior to utilization of subcutaneous administration in an expansion cohort or future study.

To obtain preliminary data on SC bioavailability as well as safety over repeated cycles, BMS-986179 would be administered as monotherapy by the subcutaneous route for the first dose, followed by within-patient crossover to the same dose intravenously for the second dose, then continuing subcutaneously for the third dose and beyond until patients fulfill criteria for treatment discontinuation (section 3.5).

Treatment in Part 1B will be for an initial period of up to 24 weeks (ie, to the end of Cycle 6). Additional treatment beyond that time will be as described in Section 3.1.5. If a given subject could potentially enroll in more than 1 open cohort in Part 1B, cohort assignment will be randomized (see Section 4.4).

Figure 3.1.2-1: Study Design Schematic (Part 1B [PD Substudy] and Part 2 [Expansion] - Q2W and Q3W Schedules

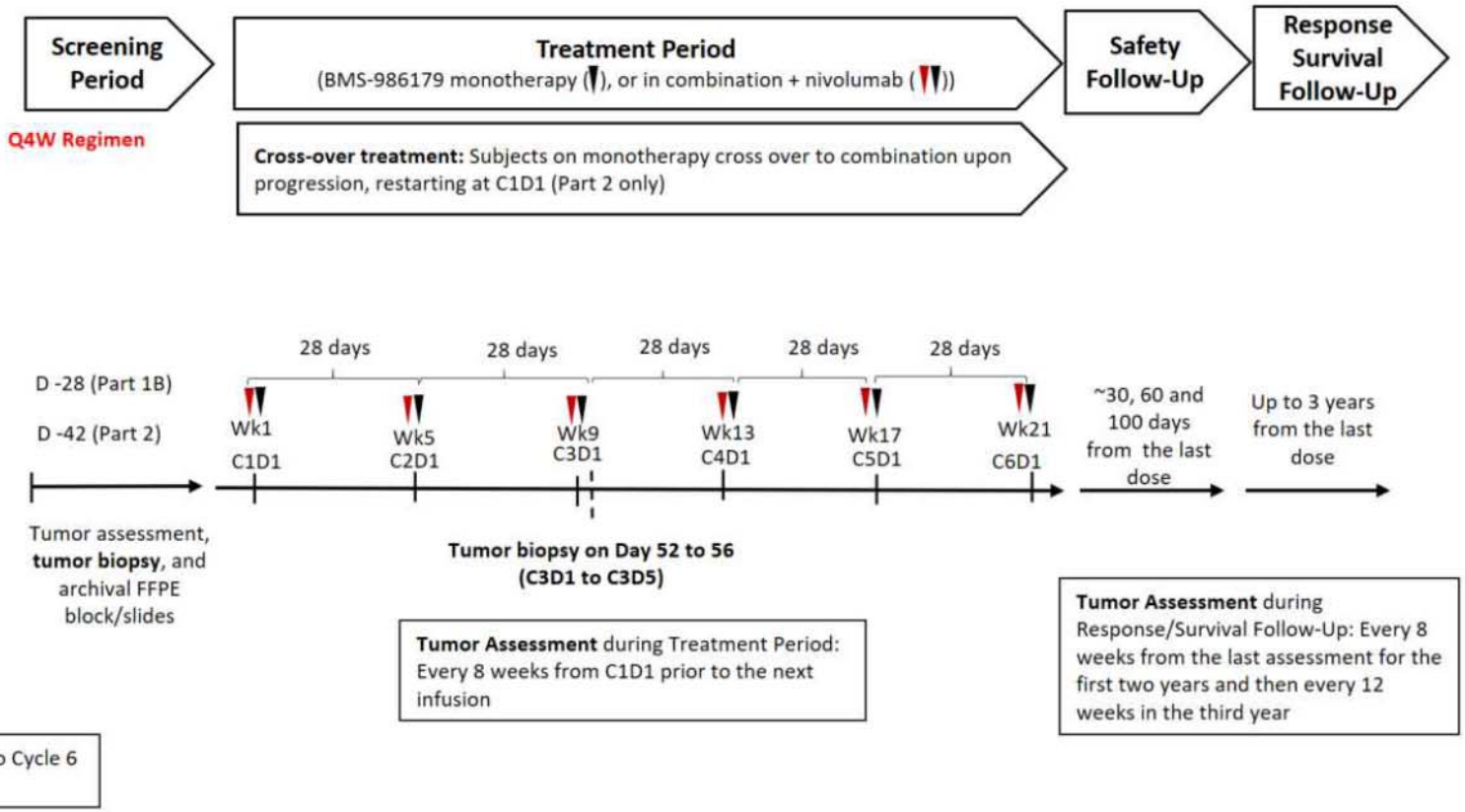


Abbreviation: FFPE = formalin fixed, paraffin embedded.

For subcutaneous cohort in PD sub-study Q2W: BMS-986179 would be administered as monotherapy by the subcutaneous route on C1D1, followed by within-patient crossover to the IV on C1D15, then continuing SC on C2D1 and beyond until patients fulfill criteria for treatment discontinuation.

For subcutaneous cohort in PD sub-study Q3W: BMS-986179 would be administered as monotherapy by the subcutaneous route on C1D1, followed by within-patient crossover to the IV on C1D22, then continuing SC on C2D1 and beyond until patients fulfill criteria for treatment discontinuation.

Figure 3.1.2-2: Study Design Schematic (Part 1B [PD Substudy] and Part 2 [Expansion] - Q4W Schedule)



Abbreviation: FFPE = formalin fixed, paraffin embedded.

For subcutaneous cohort in PD sub-study Q4W: BMS-986179 would be administered as monotherapy by the subcutaneous route on C1D1, followed by within-patient crossover to the IV on C2D1, then continuing SC on C3D1 and beyond until patients fulfill criteria for treatment discontinuation.

3.1.3 Part 2 (Cohort Expansion)

The purpose of the cohort expansion is to gather additional safety, tolerability, and PD information, in addition to preliminary efficacy information, for BMS-986179 administered alone (NSCLC and RCC only) and in combination with nivolumab (all expansion cohorts). Subject selection criteria for expansion cohorts are summarized in Table 3.1.3-1. Please refer to Section 3.3 and Section 8.1.3 for additional details.

Table 3.1.3-1: Expansion Cohorts for Part 2

Expansion Cohort	Treatment Arm[a]	Patient Segment Inclusion Description	Prior Therapy Patient Status	Simon 2-stage Evaluation[b]
NSCLC	Mono[c]	2L+ [redacted]	Progressed on prior anti-PD-(L)1 therapy as most recent therapy (monotherapy or part of a combination) Duration of most recent prior anti-PD-(L)1 therapy must be > 12 weeks with no evidence of progression during the first 12 weeks	Yes
NSCLC	PD-1 combo	2L+ [redacted]		Yes
RCC	Mono[c]	2L+		Yes
RCC	PD-1 combo	2L+		Yes
Melanoma	PD-1 combo	2L+ [redacted]		Yes
SCCHN	PD-1 combo	2L+		Yes
CRPC	PD-1 combo	2L+	PD-(L)1 naive or experienced	Yes
Pancreatic adenocarcinoma	PD-1 combo	2L+	PD-(L)1 naive or experienced	No

[a] BMS-986179 monotherapy or in combination with nivolumab (PD-1).

[b] Cohort included for Simon criteria evaluation of futility (Stage 1) and efficacy (Stage 2).

[c] Subjects who initially receive BMS-986179 monotherapy may receive nivolumab in combination therapy if they progress on monotherapy.

[redacted]

Abbreviation: 2L+ = 2nd line or later therapy

Approximately 246 subjects with tumors with biopsy-accessible lesions will be enrolled in Part 2: approximately 198 in cohorts of NSCLC, RCC, SCCHN, and melanoma subjects who previously progressed on or after anti-PD-(L)1 therapy and 48 subjects with pancreatic adenocarcinoma and CRPC who progressed on or after any 1L therapy.

The dose level and administration schedule of BMS-986179 to be used in Part 2 will be based on a synthesis of all available data, including evaluations of the recommendation from BLRM-Copula and clinical and laboratory safety assessments, PK, PD, and efficacy data from treated subjects from Parts 1A and 1B. Data from Parts 1A and 1B of the protocol identified a recommended phase 2 dose/schedule to evaluate in Part 2 (BMS-986179 600 mg IV Q2W monotherapy or in

combination with Nivolumab 480 mg Q4W). With the exception of pancreatic cancer cohort (completed to accrual), this dose has been selected for all ongoing Part 2 cohorts. The study design for Part 2 is presented in Figure 3.1.2-1 (Q2W and Q3W schedules) and Figure 3.1.2-2: (Q4W schedule).

As shown in Table 3.1.3-1, the Simon 2-stage (optimal) design will be used for 2 NSCLC cohorts (one for BMS-986179 monotherapy and the other for BMS-986179 therapy in combination with nivolumab), 2 RCC cohorts (equivalent to those for NSCLC) and single SCCHN, melanoma, and CRPC cohorts that will receive only BMS-986179 in combination with nivolumab. Approximately 15 evaluable subjects in each of the first 6 cohorts and 12 evaluable subjects in the CRPC cohort will be treated during Stage 1 for an initial evaluation of efficacy. NSCLC and RCC subjects initially treated with BMS-986179 monotherapy in Part 2 may receive BMS-986179 therapy in combination with nivolumab at disease progression after specific consultation and agreement with the BMS Medical Monitor. Subjects who receive BMS-986179 in combination with nivolumab after monotherapy disease progression will restart from Cycle 1 Day 1.

Because CD73 expression is linked to canonical MAPK signaling, we will explore the safety, PK, PD, and preliminary efficacy of BMS-986179 in subjects whose tumors contain driver mutations in this pathway. Therefore, enrollment may be extended to reach adequate number of BRAF or NRAS mutations in melanoma, and EGFR or KRAS mutations in NSCLC.

At the completion of Stage 1, a decision based on the totality of available data will be made to (1) proceed to Stage 2, (2) enroll additional biomarker-enriched Stage 1 cohorts in one or more of the specified disease types, (3) both of the above, or (4) declare that the investigational therapy does not merit further investigation in that particular cohort.

[redacted]

Approximately 18 subjects each of the first 6 above cohorts and 17 for the CRPC cohort may be treated in Stage 2. The remaining approximately 19 subjects (pancreatic adenocarcinoma) will be treated in single-stage cohorts sufficient to evaluate anti-tumor effect sizes that exceed historic ORRs with high confidence. See Section 8.1.3 for details.

Part 2 (Expansion Phase) cohorts will be open to subjects eligible for participation who have completed standard-of-care- therapy. Dosing in Part 2 will follow 1 of 3 schedules for all cohorts, Q2W and Q3W as shown in Figure 3.1.2-1 or Q4W as shown in Figure 3.1.2-2:.

3.1.4 Treatment Beyond Progression

As described in Section 1.1.5.4, accumulating evidence indicates a minority of subjects with solid tumors treated with immunotherapy may derive clinical benefit despite initial evidence of progressive disease. Subjects will be permitted to continue on treatment beyond initial

RECIST v1.1 (see Appendix 2) defined progressive disease, as long as they meet the following criteria:

- Investigator-assessed clinical benefit and not having rapid disease progression
- Continue to meet all other study protocol eligibility criteria
- Tolerance of study drug
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, central nervous system [CNS] metastases)
- Agreement to continue therapy among the investigator, BMS Medical Monitor and the participant

See Table 3.1.3-1 for expansion cohorts that may be considered for combination therapy post-progression on monotherapy. The assessment of clinical benefit should take into account whether the subject is clinically deteriorating and unlikely to receive further benefit from continued treatment. All decisions to continue treatment beyond initial progression must be discussed with the BMS Medical Monitor, and an assessment of the benefit/risk of continuing with study drug must be documented in the study records. Subjects will be re-consented to explain the rationale for this ongoing treatment.

Subjects should continue to receive monitoring according to the on-treatment assessments in Section 5.1. Radiographic assessment by computed tomography (CT; preferred) or magnetic resonance imaging (MRI) described in Section 5 is required when subjects continue post-progression treatment. For subjects who discontinue post-progression treatment with study drug (see Section 3.5.1), no additional radiographic assessments will be required.

3.1.5 Treatment with Additional Cycles Beyond 24 Weeks

All subjects will be treated for an initial period of 24 weeks of monotherapy or combination therapy unless criteria for study drug discontinuation are met earlier (Section 3.5). All subjects completing approximately 24 weeks of treatment with ongoing disease control (CR, PR, or stable disease [SD]) (see Appendix 2) may be eligible for up to an additional 80 weeks of monotherapy or combination therapy, on a case-by-case basis, after careful evaluation and discussion with the BMS Medical Monitor to determine whether the risk/benefit ratio supports administration of further study drug. Treated subjects will enter the safety follow-up period upon completion of the last dose, after which subjects will enter the response/survival follow-up period, with a duration of up to 3 years from the initial treatment.

3.1.6 Re-treatment During Follow-up

Re-treatment will be limited to subjects who completed treatment before the protocol amendment dated 20-Oct-2017. Re-treatment may be allowed in subjects who complete at least 24 weeks of monotherapy or combination therapy and enter follow-up with ongoing disease control (CR, PR, or SD), upon subsequent disease progression within 12 months of the last dose of the study drug, on a case-by-case basis, after careful evaluation and discussion with the BMS Medical Monitor to determine whether the risk/benefit ratio supports administration of further study drug. Subjects

will be treated with the originally assigned monotherapy or combination therapy regimen (eg, same dose level and dose schedule administered during the prior treatment period), unless that dose level and schedule were subsequently found to exceed the MTD, in which case the subject will be treated at the next lower or alternate dose level (Table 3.1.1-1). Subjects entering this period will follow the schedules outlined in Section 5.1. Samples for PK will be collected less frequently (at predose of each treatment cycle). Subjects who receive re-treatment may be followed for 3 years from their last dose. On the day the biopsy sample is collected, the samples for biomarkers should be collected according to Table 5.6-6 through Table 5.6-9, if applicable. The duration of re-treatment will be up to approximately 24 weeks. Per discretion of the Medical Monitor, the subject may receive an additional 24 weeks of re-treatment (for a total of 48 weeks of re-treatment).

3.1.7 Subject Replacement

Subjects enrolled in Part 1A who withdraw from the study during the [redacted] period for reasons other than a [redacted] may be replaced within the same dose level.

Subjects enrolled in Part 1B who have a dose delay of > 12 days within the first 42 days of the study for the Q2W regimen or > 19 days within the first 63 days of the study for the Q3W and Q4W regimens may be replaced within the same dose level. Subjects who do not have both pre- and on-treatment tumor biopsy, or whose biopsies are uninformative (due to insufficient tumor or other technical issues), may be replaced.

Subjects enrolled in Part 2 who are not able to provide the on-treatment biopsy may be replaced. If replaced, successor subjects will be assigned to the same dose level and schedule.

3.1.8 End of Study Definition

The start of the study is defined as the first visit for the first participant screened.

The end of study is defined as the last visit or scheduled procedure shown in the Schedule of Activities (Section 5.1) for the last participant. Study completion is defined as the final date on which data for the primary endpoint were or are expected to be collected if they are not the same.

3.2 Post-study Access to Therapy

At the end of the study, BMS will not continue to provide BMS-supplied study drug to subjects/investigators unless BMS chooses to extend the study. The investigator should ensure that the subject receives appropriate standard of care to treat the condition under study.

3.3 Study Population

For entry into the study, the following criteria MUST be met prior to dosing on Day 1. No exceptions will be granted.

3.3.1 Inclusion Criteria

1) Signed Written Informed Consent

a) Subjects must sign the ICF prior to the performance of any studyrelated- procedures that are not considered part of standard of care.

2) Target Population

a) Subjects must be at least 18 years old and have histologic or cytologic confirmation of a malignancy that is advanced (metastatic and/or unresectable) with measureable disease per RECIST v1.1 (see Appendix 2) and have at least 1 lesion that is biopsy-accessible.

b) **Part 1A (Dose Escalation) and Part 1B (PD Substudy):**

i) Subjects must have received, and then progressed or been intolerant to, at least 1 standard treatment regimen in the advanced or metastatic setting, if such a therapy exists, and have been considered for all other potentially efficacious therapies prior to enrollment. Subjects who are ineligible for standard therapy (due to medical factors such as co-morbid illness, age, etc) will be allowed to enroll provided their ineligibility is documented in medical records.

ii) All solid tumor histologies will be permitted, with the following exceptions:

- Subjects with primary CNS tumors or with CNS metastases as the only site of active disease are not eligible.
- For Part 1B (PD Substudy) only: the BMS medical monitor may limit enrollment in treatment arms by tumor type/histology and types/numbers of prior therapies, as necessary to obtain focused PK/PD data in select populations.

c) **Part 2 (Cohort Expansion)**:

The following tumor types will be permitted:

i) For pancreatic adenocarcinoma:

(1) Subjects must have received and progressed/been intolerant of (or not be a candidate for) at least 1 prior standard therapy, and have been considered for all other potentially efficacious therapies.

ii) For NSCLC:

(1) Subjects must have received and progressed/been intolerant of at least 1 prior standard systemic therapies for metastatic and/or unresectable disease and have been considered for all other potentially efficacious therapies.

(2) ***"Not applicable as per revised protocol 08"*** Subjects must have TMB above the minimum threshold in blood or tumor tissue. Minimum thresholds for TMB are described in Table 3.1.3-2.

(3) Subjects must have progressed on prior anti-PD-(L)1 therapy as their most recent therapy (monotherapy or part of combination).

(4) Subjects must have known EGFR and KRAS mutation status.

(5) Duration of most recent prior therapy (date of the last dose minus date of the first dose) with anti-PD-(L)1 must have exceeded 12 weeks with no evidence of progression (clinical or radiographic) during the first 12 weeks.

iii) For RCC:

(1) Subjects must have received and progressed/been intolerant of at least 1 prior standard systemic therapy for metastatic and/or unresectable disease and have been considered for all other potentially efficacious therapies.

(2) Subjects must have progressed on prior anti-PD-(L)1 therapy as their most recent therapy (monotherapy or part of combination).

(3) Duration of most recent prior therapy (date of the last dose minus date of the first dose) with anti-PD-(L)1 must have exceeded 12 weeks with no evidence of progression (clinical or radiographic) during the first 12 weeks.

iv) For CRPC:

(1) Subjects must have received and progressed/been intolerant of (or not be a candidate for) at least 1 prior standard systemic therapy and have been considered for all other potentially efficacious therapies in the hormone-refractory setting.

v) For SCCHN:

(1) Subjects must have received and progressed/been intolerant of at least 1 prior standard systemic therapy for metastatic and/or unresectable disease and have been considered for all other potentially efficacious therapies.

(2) Subjects must have progressed on prior anti-PD-(L)1 therapy as their most recent therapy (monotherapy or part of combination).

(3) ***"Not applicable as per revised protocol 08"*** Subjects must have TMB above the minimum threshold in blood or tumor tissue. Minimum thresholds for TMB are described in Table 3.1.3-2.

(4) Duration of most recent prior therapy (date of the last dose minus date of the first dose) with anti-PD-(L)1 must have exceeded 12 weeks with no evidence of progression (clinical or radiographic) during the first 12 weeks.

vi) For melanoma:

(1) Subjects must have received and progressed/been intolerant of at least 1 prior standard systemic therapy for metastatic and/or unresectable disease and have been considered for all other potentially efficacious therapies.

(2) Subjects must have progressed on prior anti-PD-(L)1 therapy as their most recent therapy (monotherapy or part of combination).

(3) ***"Not applicable as per revised protocol 08"*** Subjects must have TMB above the minimum threshold in blood or tumor tissue. Minimum thresholds for TMB are described in Table 3.1.3-2.

(4) Subjects must have known BRAF and NRAS mutation status.

(5) Duration of most recent prior therapy (date of the last dose minus date of the first dose) with anti-PD-(L)1 must have exceeded 12 weeks with no evidence of progression (clinical or radiographic) during the first 12 weeks.

d) Subjects must have an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 1.

e) Subjects must have at least one lesion with measureable disease as defined by RECIST v1.1. Subjects with lesions in a previously irradiated field as the sole site of measurable disease will be permitted to enroll provided that the lesion(s) have demonstrated clear progression and can be measured accurately.

f) Subjects who have had prior exposure to therapy with any agent specifically targeting checkpoint pathway inhibition (such as anti-PD-1, anti-PD-L1, anti-PD-L2, anti-LAG-3, and anti-CTLA-4 antibody) are permitted after a washout period of any time greater than 4 weeks from the last treatment.

   Note: (i) Subjects who experienced prior Grade 1 to 2 checkpoint therapy-related immune-mediated AEs must have confirmed recovery from these events at the time of study entry, **other than endocrinopathies treated with supplementation**, as documented by resolution of all related clinical symptoms, abnormal findings on physical examination, and/or associated laboratory abnormalities. Where applicable, these subjects must also have completed steroid tapers for treatment of these AEs by a minimum of 14 days prior to commencing treatment with study drug.

   (ii) Eligibility of subjects with prior ≥ Grade 3 checkpoint therapy-related immune AEs will be considered on a case-by-case basis after discussion with the BMS Medical Monitor (eg, asymptomatic isolated Grade 3 lipase elevations without clinical or radiological features of pancreatitis will be permitted to enroll).

g) Subjects with prior therapy with any agent specifically targeting T-cell co-stimulation pathways such as anti-glucocorticoid induced tumor necrosis factor receptor, anti-CD137, or anti-OX40 antibody, with exceptions listed below, are permitted after a washout period of any time greater than 4 weeks from the last treatment.

h) Prior palliative radiotherapy must have been completed at least 2 weeks prior to first dose of the study drug. Subjects with symptomatic tumor lesions at baseline that may require palliative radiotherapy within 4 weeks of first dose of study drug are strongly encouraged to receive palliative radiotherapy prior to treatment.

i) Subjects must consent to a pre-treatment tumor biopsy. Subjects must also consent to the acquisition of existing formalin-fixed paraffin-embedded tumor tissue (**if available**), either a block or 15 to 20 unstained slides, for performance of correlative studies. Study personnel must ensure that the tissue block or slides samples are located and shipped to central laboratory as soon as possible after signing the consent. Subjects who either do not consent to a pre-treatment tumor biopsy or do not have accessible lesions are not eligible. (However, subjects whose pre-treatment biopsy yields inadequate tissue quantity or quality will not be ineligible on this basis alone.) All subjects will also be required to undergo a mandatory on-treatment biopsy at acceptable clinical risk as judged by the investigator.

j) Pre-treatment biopsy tissue may have been collected at any time during the screening period prior to the first dose of the study drug, but collection conditions as described below must be met.

- **At least 4 fresh core biopsy specimens will be collected pre-treatment and on-treatment. The biopsies will be taken as outlined in the laboratory manual. The tumor tissue specimen must be a core-needle, excisional or incisional biopsy. Fine-needle biopsies, drainage of pleural effusions with cytospins, or punch biopsies are not considered adequate for biomarker review. Biopsies of bone lesions that do not have a soft tissue component or decalcified bone tumor samples are also not acceptable. In cases where it is difficult to obtain all fresh cores required, additional archival specimens will be accepted.**

k) Subjects must have adequate organ function as defined by the following:

i) White blood cell count ≥ 2000/μL (stable off any growth factor within 2 weeks of the first study drug administration)

ii) Neutrophils ≥ 1500/μL (stable off any growth factor within 2 weeks of the first study drug administration)

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

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

v) Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 × the upper limit of normal (ULN)

vi) Total bilirubin ≤ 1.5 × ULN (except subjects with Gilbert's Syndrome who must have normal direct bilirubin)

vii) Albumin > 2 g/dL (20 g/L)

viii) International normalized ratio < 1.5 × ULN, activated partial thromboplastin time < 1.5 × ULN

ix) Clinically normal thyroid function or have controlled hypothyroidism on appropriate thyroid supplementation

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

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

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

l) Ability to comply with treatment, PK, immunogenicity, biomarker, and PD sample collection, and required study follow-up.

m) Subject re-enrollment: This study permits the re-enrollment of a subject who has discontinued the study as a pre-treatment failure (ie, subject has not been treated). If re-enrolled, the subject must be re-consented.

3) Age and Reproductive Status

a) Subjects must be males and females ages ≥ 18 years at the time of informed consent.

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

c) Women must not be breastfeeding.

d) WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drugs plus at least 5 half-lives of BMS-986179 plus 30 days (for subjects who discontinue during the monotherapy lead-in) or at least 5 months after the last dose of nivolumab (for subjects who discontinue during combination therapy).

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drugs plus at least 5 half-lives of BMS-986179 plus 90 days (for subjects who discontinue during the monotherapy lead-in) at least 7 months after the last dose of nivolumab (for subjects who discontinue during combination therapy).

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

Investigators shall counsel WOCBP and male subjects who are sexually active with 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 that have a failure rate of < 1% when used consistently and correctly.

At a minimum, subjects must agree to use 1 highly effective method of contraception as listed in Appendix 5.

3.3.2 Exclusion Criteria

1) Target Disease Exceptions

a) Subjects with known CNS metastases, untreated CNS metastases, or with the CNS as the only site of disease are excluded. However, subjects with controlled brain metastases 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), off of steroids for at least 2 weeks, and no new or progressive neurological signs and symptoms.

b) Subjects with carcinomatous meningitis are excluded.

c) For pancreatic adenocarcinoma:

i) Subjects with clinically relevant ascites at baseline (defined as requiring paracentesis) or with moderate radiographic ascites are excluded. Only a minimal amount of radiographic ascites is allowed.

2) Medical History and Concurrent Diseases

a) Subjects with a prior malignancy, different from the one used for enrollment in this study, diagnosed less than 2 years ago are excluded (except non-melanoma skin cancers; in situ cancers such as the following: bladder, colon, cervical/dysplasia, melanoma, or breast; and localized prostate cancer that was adequately treated). Subjects with second malignancies diagnosed more than 2 years ago who have received therapy with curative intent with no evidence of disease during the interval and who are considered by the investigator to present a low risk for recurrence will be eligible.

b) Subjects with other active malignancy requiring concurrent intervention are excluded.

c) Subjects with prior organ allograft are excluded.

d) Subjects who have received prior anti-cancer treatments are permitted (ie, chemotherapy, radiotherapy, hormonal, or immunotherapy)

   i) For cytotoxic agents, at least 4 weeks must have elapsed from last dose of prior anti-cancer therapy and the initiation of study therapy.

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

e) Subjects who have received prior therapy with an anti-CD73 antibody, an anti-CD39 antibody, or an adenosine 2A receptor inhibitor are excluded.

f) Subjects with a prior history of deep vein thrombosis within the last 6 months.

g) Subjects with active, known or suspected autoimmune disease, with the following exceptions, are excluded. Subjects with vitiligo, Type 1 diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, subjects with euthyroid with a history of Grave's disease (subjects with suspected autoimmune thyroid disorders must be negative for thyroglobulin and thyroid peroxidase antibodies and thyroid-stimulating immunoglobulin prior to the first dose of the study drug), psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

h) Subjects with interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity are excluded.

i) Subjects with chronic obstructive pulmonary disease requiring recurrent steroids bursts or chronic steroids at doses greater than 10 mg/day of prednisone or the equivalent are excluded.

j) Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration except for adrenal replacement steroid doses > 10 mg daily prednisone equivalent in the absence of active autoimmune disease are excluded. **Note**: Treatment with a short course of steroids (< 5 days) up to 7 days prior to initiating study drug is permitted.

k) Subjects with uncontrolled or significant cardiovascular disease including, but not limited to any of the following, are excluded:

   i) ***"Not applicable as per revised protocol 08"*** Myocardial infarction or stroke/transient ischemic attack at any time

   ii) ***"Not applicable as per revised protocol 08"*** Any known history of coronary artery disease, cerebrovascular disease, or any procedures for the treatment of these conditions, as well as any uncontrolled angina at any time.

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

   iv) QT interval corrected for heart rate using Fridericia's formula (QTcF) prolongation > 480 msec

   v) History of other clinically significant heart disease (eg, cardiomyopathy, congestive heart failure with New York Heart Association [NYHA] functional Classification III to IV, pericarditis, significant pericardial effusion, or myocarditis)

   vi) Requirement for daily supplemental oxygen therapy

   vii) Acute coronary syndrome (including ST Elevation Myocardial Infarction (STEMI), Non-ST Elevation Myocardial Infarction (NSTEMI), and Unstable Angina (UA)), cerebrovascular disease (stroke/transient ischemic attack) or arterial thrombus within the last 12 months.

   viii) Surgical or percutaneous revascularization (such as CABG or PCI) within the last 12 months.

   ix) Subjects with any known history of coronary artery disease, cerebrovascular disease or peripheral arterial disease with symptoms within the last 12 months.

   x) For subjects with any known history of coronary artery disease, cerebrovascular disease, peripheral arterial disease who have been asymptomatic for 12 months prior to enrollment, evaluation by specialist that includes functional testing (and structural assessment as needed) is required within 12 months prior to study treatment. Subjects with abnormal findings such as functional ischemia (or subjects with high-risk findings) will be excluded.

l) Subjects with active hepatitis as evidenced by the following are excluded:

   i) Positive test for hepatitis B surface antigen

   ii) Positive test for hepatitis C antibody and/or qualitative viral load (by polymerase chain reaction [PCR])

   Note: *Subjects with positive hepatitis C antibody and negative quantitative hepatitis C by PCR are eligible. History of resolved hepatitis A virus infection is not an exclusion criterion.*

m) Subjects with evidence of active bacterial, viral, or fungal infections ≤ 7 days prior to initiation of study drug therapy are excluded.

n) Subjects with a known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS) are excluded.

o) Subjects with evidence or history of active or latent tuberculosis infection including purified protein derivative recently converted to positive, chest x-ray with evidence of infectious infiltrate, or recent unexplained changes in fever/chill patterns are excluded.

p) Subjects who have undergone any major surgery within 4 weeks of study drug administration are excluded. Subjects must have recovered from the effects of major surgery or significant traumatic injury at least 14 days before the first dose of the study drug.

q) All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have resolved to Grade 1 (National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] Version 4.03) or baseline before administration of the study drug. Subjects with toxicities attributed to prior anti-cancer therapy that are not expected to resolve and result in long-lasting sequelae, such as chronic neuropathy after platinum based therapy, are permitted to enroll.

r) Subjects who have received a live/attenuated vaccine within 30 days of first treatment. The use of inactivated seasonal influenza vaccines, eg, Fluzone®, will be permitted on study without restriction.

s) Subjects who have received packed red blood cells or received a platelet transfusion within 2 weeks prior to the first dose of the study drug as specified in Section 3.3.1 2)k)ii) and 2)k)iii) are excluded.

t) Subjects with a known or underlying medical condition that, in the opinion of the investigator or Sponsor, could make the administration of study drug hazardous to the subjects, or could adversely affect the ability of the subject to comply with or tolerate the study, are excluded.

3) Allergies and Adverse Drug Reaction

a) Subjects with a history of allergy to nivolumab are excluded.

b) Subjects with a history of any significant drug allergy (such as anaphylaxis) to prior anti-cancer immune modulating therapies (eg, checkpoint inhibitors, T-cell co-stimulatory antibodies) are excluded.

4) Other Exclusion Criteria

a) Subjects who are prisoners or are involuntarily incarcerated are excluded. (Note: Under certain specific circumstances, a person who has been imprisoned may be included or permitted to continue as a subject. Strict conditions apply and BMS approval is required.)

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

c) Subjects who are unable to comply with restrictions and prohibited activities/treatments as listed in Section 3.4 are excluded.

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

3.3.3 Women of Childbearing Potential

Women of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a documented serum follicle-stimulating hormone (FSH) level > 40 mIU/mL to confirm menopause.

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

- 1 week minimum for vaginal hormonal products (eg, 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.

3.4 Concomitant Treatments

3.4.1 Prohibited and/or Restricted Treatments

Prohibited and/or restricted medications taken prior to study drug administration in the study are described below. Medications taken within 4 weeks prior to initial and re-treatment study drug administration must be recorded on the Case Report Form (CRF). Any concomitant therapies during initial and re-treatment periods must be recorded on the CRF. Any concomitant therapies during the initial and re-treatment safety follow-up periods must be recorded on the CRF.

The following medications are prohibited during the study:

- Immunosuppressive agents (except as stated in Section 3.4.3)
- Any anti-cancer therapies (investigational or approved) not specified as study drugs for this study, except for continued androgen deprivation therapy in men with CRPC
- Use of dipyridamole or ticagrelor within 2 weeks prior to the first dose of the study drug or while receiving study drugs
- Use of any medicinal herbal preparations within 2 weeks prior to the first dose of the study drug unless prescribed by a treating physician
- 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.

3.4.2 Other Restrictions and Precautions

It is the local imaging facility's responsibility to determine, based on subject attributes (eg, allergy history, diabetic history, and renal status), the appropriate imaging modality and contrast regimen for each subject. Imaging contraindications and contrast risks should be considered in this assessment. Subjects with renal insufficiency should be assessed as to whether or not they should receive contrast and if so, what type and dose of contrast is appropriate. MRI contrast should not be given to subjects with severe renal insufficiency (eg, estimated glomerular filtration rate < 30 mL/min/1.73 m^2) because of increased risk of nephrogenic systemic fibrosis in this subject population. In these subjects, alternative imaging tests, or MRI without gadolinium should be considered. In addition, subjects are excluded from MRI if they have tattoos, metallic implants, pacemakers, etc.

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

3.4.3 Permitted Therapy

- Subjects are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption).
- Treatment with a short course of systemic steroids up to 7 days prior to initiating study drug is permitted.
- A brief course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.
- Immunosuppressive agents and the use of systemic corticosteroids and other medications are permitted in the context of treating adverse events after discussion with the BMS Medical Monitor.

3.4.4 Management of Cardiovascular Risk Factors

All subjects must have an assessment of cardiovascular risk factors; those with known cardiovascular risk factors such as hypertension, dyslipidemia, etc. must have management of these risk factors according to local guidelines, including but not limited to the use of aspirin for primary prophylaxis; other pharmacologic interventions targeting vascular risk factors such as the use medications targeting dyslipidemia and anti-hypertensives; and other measures such as smoking cessation.

3.4.5 Palliative/Local Therapy

- Palliative and supportive care for disease-related symptoms may be offered to all subjects on the trial after the [redacted] period.
- Limited radiation therapy or surgery to control isolated lesions is permitted for subjects who have investigator-assessed clinical benefit following consultation with the BMS Medical Monitor.
- Subjects should not receive study treatment during radiation as the potential for overlapping toxicities with radiotherapy and BMS-986179 or combination of BMS-986179 and nivolumab

currently is not known. Anecdotal data suggest that radiotherapy administered to subjects 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, then BMS-986179 alone or BMS-986179 in combination with nivolumab should be withheld for at least 1 week before, during, and 1 week after radiation. Subjects 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 therapy.

- Bisphosphonates and RANKL directed-therapies for bone metastases are permitted.

3.5 Discontinuation of Subjects Following Any Treatment with Study Drug

Subjects MUST discontinue investigational product (and non-investigational product at the discretion of the investigator) for any of the following reasons:

- Subject's request to stop study treatment and/or participation in the study
- 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 subject
- 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
- Inability to comply with protocol
- Discretion of the investigator
- Any dosing delay lasting > 6 weeks will be cause for permanent discontinuation. Extensions to the period of dose delays may be granted for individual subjects on a case-by-case basis after specific consultation and agreement between the investigator and BMS Medical Monitor in settings where benefit/risk may justify continued study drug (eg, subject deriving clinical benefit who requires prolonged steroid taper for management of immune-related AEs or experiences delays for management of a non-drug-related AE). Tumor assessments should continue as per protocol even if dosing is delayed.
- Pregnancy

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

All subjects who discontinue investigational product should comply with protocol-specified follow-up procedures as outlined in Section 5.1. The only exception to this requirement is when a subject 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 the study drug is discontinued prior to the subject's completion of the study, the reason for the discontinuation must be documented in the subject's medical records and entered on the appropriate CRF page.

3.5.1 Discontinuation due to Further Progression

Subjects should discontinue study drug upon evidence of further progression, defined as an additional 5mm or greater increase in tumor burden volume from time of initial progression (including all measurable lesions).

The tumor burden volume from the 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 as follows:

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

3.5.2 Stopping Rules during Cohort Expansions

Continuous evaluation of toxicity events in the cohort expansion will be performed throughout enrollment in the expansion cohorts. If, at any time, the aggregate rate of treatment-related toxicities meeting DLT criteria exceed 33% across all subjects treated in cohort expansions, the findings will be discussed and further enrollment may be interrupted. Depending on the nature and grade of the toxicity and after assessing the risk/benefit ratio, a new dose for all cohorts may be initiated at a previously tested lower dose level, at a dose level intermediated to previously tested lower dose levels, or an alternate less frequent treatment regimen. Enrollment of a given cohort may also be interrupted in response to futility based on the Simon 2-stage design.

All safety signals throughout the conduct of the study will be reviewed by the BMS-986179 Medical Surveillance Team (MST). If unexpected safety findings are identified between scheduled MST meetings, an ad hoc meeting will be convened as appropriate.

3.6 Post-study Drug Follow-up

[redacted] Post-study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue the study drug must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with Section 5.1 until death or the conclusion of the study.

3.6.1 Withdrawal of Consent

Subjects who request to discontinue the study drug 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 subject specifically withdraws consent for any further contact with him/her or persons previously authorized by the subject to provide this information. Subjects 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 drug 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 subject 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.

3.6.2 Lost to Follow-up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of 3 documented phone calls, faxes, texts, or emails as well as lack of response by subject to one registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the 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 subject's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining subject'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 subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

3.7 Study Termination

The use of a 2-stage design allows for possible early termination of enrollment into an expansion cohort based on anti-tumor activity evaluation of Stage I patients. While there is no formal stopping rule based on efficacy, a futility signal based on Sponsor's assessment may also lead to cohort termination.

BMS continuously evaluates the benefit/risk of the program and may choose to hold further recruitment in a particular cohort or at a particular site, or terminate the development of BMS-986179 for reasons including, but not limited to safety and efficacy.

4 STUDY DRUG

Product description and storage information is described in Table 4-1.

Table 4-1: Study Drugs for CA013004

Product Description Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Packaging/Appearance	Storage Conditions (per label)
BMS-986179 injection	35 mg/mL	IP	Open	Vial	2 to 8°C. Do not freeze. Protect from light.
BMS-936558 (nivolumab) injection[a]	10 mg/mL	IP	Open	Vial	2 to 8°C. Do not freeze. Protect from light.
ENHANZE ™ Drug Product (rHuPH20)[b]	1 mg/mL	IP	Open	Vial and various packaging configurations	Refer to the label on container or manufacturer instructions

Abbreviation: IMP = investigational medicinal product; IP = investigational product.

[a] Nivolumab will be provided in single 100 mg vials.

[b] ENHANZE ™ Drug Product (rHuPH20) is a formulation of rHuPH20 for experimental use referred to as rHuPH20 in the protocol.

4.1 Investigational Product

An investigational product, 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.

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

The investigational products for this study are BMS-986179, nivolumab, and ENHANZE™ Drug Product (rHuPH20).

4.2 Non-investigational Product

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

Non-investigational products are not applicable for this study.

4.3 Storage and Dispensing

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

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

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

4.4 Method of Assigning Subject Identification

This is an open-label study. All subjects must be assigned a subject number upon providing signed written informed consent. During the screening visit, the investigative site will call into the enrollment option of the Interactive Voice Response System (IVRS) or equivalent system designated by BMS for assignment of a 5-digit subject number that will be unique across all sites. Enrolled subjects, including those not dosed, will be assigned sequential subject numbers starting with 00001, (eg, 00001, 00002, 00003… 00010). The site number and subject number will form a distinct patient identification number for each subject (eg, 0002 00001). Those enrolled subjects meeting inclusion and exclusion criteria will be eligible to be dosed. Once it is determined that the subject meets the eligibility criteria following the screening visit, the investigative site will call the IVRS (or equivalent system) to assign the subject into the open-dose panel prior to dosing. If more

than 1 cohort in Part 1B is open for enrollment simultaneously, eligible subjects will be randomized in a 1:1:1:1 ratio according to a computer-generated randomization scheme prepared by a Randomization Coordinator within the Drug Supply Management Department of BMS Research and Development. If both monotherapy and combination therapy cohorts are open, assignments within a particular disease type will be made in an alternating manner.

During dose escalation (Part 1A), subjects who are not evaluable for [redacted] determination may be replaced. During the PD substudy (Part 1B), subjects who do not have both pre- and ontreatment- tumor biopsy as planned, or whose biopsies are uninformative (due to insufficient tumor or other technical issues), may be replaced. Replacement subjects will receive the same treatment but will be assigned a new subject number.

Specific instructions for using IVRS will be provided to the investigational sites in a separate document.

4.5 Selection and Timing of Dose for Each Subject

Each subject will be assigned to a specific flat dose of BMS-986179 as listed described in Section 3.1 and Section 4.4.

Nivolumab will be administered at the standard flat dose of 240 mg for the Q2W regimen and adjusted proportionately to be 360 mg for the Q3W regimen or 480 mg for the Q4W regimen, in concordance with the PK/PD modeling of nivolumab. There are no premedications recommended for nivolumab on the first cycle. If an acute infusion reaction is noted, the subjects should be managed according to Section 4.5.7. Nivolumab will be administered via a 30-minute IV infusion. BMS-986179 will be administered via IV infusion with a duration dependent upon dose (ie, 1-hour infusion for doses 150 to 800 mg and 2-hour infusion for doses > 800 mg). For treatment visits where both BMS-986179 and nivolumab are administered, nivolumab will be administered first followed by BMS-986179 a minimum of 30 minutes after completion of the nivolumab infusion. Further details regarding preparation and administration will be provided separately in site/pharmacy manual or the training materials.

4.5.1 Dose-limiting Toxicities

Dose-limiting Toxicities:

A. Hepatic Non-hematologic DLT

Any one of the following events for which an alternative cause cannot be identified will be considered a hepatic DLT:

- Any ≥ Grade 3 elevation of AST, ALT, or total bilirubin
- Grade 2 AST or ALT with symptomatic liver inflammation (eg, right upper quadrant tenderness, jaundice, pruritus)
- Combination of AST or ALT and total bilirubin meeting criteria for potential DILI* (see Section 6.6):
  - Aminotransferase (ALT or AST) elevation > 3 × ULN if liver chemistries are normal at baseline; if liver chemistries are abnormal at baseline, then >2 × baseline values or any value > 8 × ULN should be used as cutoffs

AND

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

AND

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

*Note that this special category of DLT uses ULN rather than Common Terminology Criteria grade for definition.

B. Non-hepatic Non-hematologic DLT

Any of the following events for which an alternative cause cannot be identified will be considered a non-hepatic non-hematologic DLT:

- Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks OR requires systemic treatment
- Any non-hepatic, non-hematologic Grade ≥ 3 AE for which no alternative cause can be identified, with the exception of the following
  - ≥ Grade 3 electrolyte abnormality that lasts < 72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical intervention
  - ≥ Grade 3 increase in amylase or lipase that is not associated with symptoms or clinical manifestations of pancreatitis
  - Grade 3 nausea or vomiting that lasts < 48 hours, and resolves to ≤ Grade 1 either spontaneously or with conventional medical intervention
  - ≥ Grade 3 fever that lasts < 72 hours, and is not associated with hemodynamic compromise (including hypotension, or clinical or laboratory evidence of end organ perfusion impairment)
- Grade 3 drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation

C. Dermatologic DLT

- Grade 3 rash if no improvement (ie, resolution to ≤ Grade 1) after a 1- to 2-week infusion delay. Subjects who have not experienced a Grade 3 drug-related skin AE may continue treatment in the presence of Grade 2 skin toxicity.
- Grade 4 rash of any duration

D. Hematologic DLT

- Grade 4 neutropenia ≥ 5 days in duration
- Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding or any requirement for platelet transfusion
- ≥ Grade 3 febrile neutropenia for 48 hours
- ≥ Grade 3 hemolysis (ie, requiring transfusion or medical intervention such as steroids)

- Grade 4 anemia not explained by underlying disease
- ≥ Grade 3 other hematologic DLTs per CTCAE v4.03 (eg, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, etc)

4.5.2 Management Algorithms for Immuno-oncology Agents

Immuno-oncology agents are associated with AEs that can differ in severity and duration from AEs caused by other therapeutic classes. Nivolumab and BMS-986179 are considered immuno-oncology agents in this protocol. Early recognition and management of AEs associated with immuno-oncology agents may mitigate severe toxicity. Management algorithms that have been developed from extensive experience with nivolumab to assist investigators in assessing and managing the following groups of AEs:

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

The clinical nature of AEs noted with BMS-986179 will determine the role of the above algorithms for use in toxicities related to its use in this study.

The algorithms recommended for utilization in this protocol are included in Appendix 1.

4.5.3 Guidelines for Dose Modification

Intra-subject dose escalation of BMS-986179 or nivolumab is not permitted in this study in order to allow better evaluation of extended safety and efficacy at individual dose levels and schedules.

4.5.4 Dose Delays

Dose delays of BMS-986179 and nivolumab are permitted as outlined below. During dose delays, both study drugs should be delayed to maintain a synchronous schedule. Regardless of the reason for dose delay, the minimum number of days between the delayed dose and the next scheduled dose of BMS-986179 must be maintained as specified in Section 4.5.

4.5.4.1 Delays Due to Drug-Related Toxicity and Other Medical Events

Subjects who experience a DLT must have study drug held. All related Grade 2 hepatic, pulmonary, renal, gastrointestinal, and neurological AEs should be evaluated and managed per the toxicity management algorithms (Appendix 1), including implementation of dose delays. In addition, study drug may also be held for any AE, laboratory abnormality, or concurrent illness that, in the judgement of the investigator, warrants delay even if not related to any study drug. If conditions that require permanent discontinuation of both study drugs (see Section 3.5 and Section 4.5.6) are not met, subjects will be permitted to resume therapy based on the criteria specified in Section 4.5.5 after discussion with the Medical Monitor. .

In addition, any subject with investigations (EKG, troponin, etc.) or symptoms suggestive of possible vascular thrombotic or ischemic events, including new or changed symptoms, should have dosing delayed until a full workup is complete and the event is discussed with the BMS medical monitor or designee. Furthermore, subjects who develop arterial or venous thrombosis or embolism while on study, regardless of relation to study drug, must have all study drugs held until a discussion with the BMS medical monitor or designee regarding the risks and benefits of continuing study treatment has occurred (see Section 4.5.5). Any subject experiencing a myocardial infarction or thrombotic or ischemic stroke must have BMS-986179 discontinued.

Adjustment to the on-treatment study events due to dose delays are as follows:

In Part 1A, if there is a delay in dosing of BMS-986179 for 1 to 5 days, the dosing schedule and procedures of subsequent doses should be adjusted to follow the new dosing schedule except for imaging assessments, which should follow the original schedule. For dose delays greater than 5 days, the visit and dose will be considered skipped and the BMS Medical Monitor will be consulted before subsequent treatment. During Cycle 0 (monotherapy lead-in), the on-treatment biopsy should be obtained 2 ± 1 day after the second dose of BMS-986179, regardless of dose delay. Skipping the Day 1 visit within a Cycle is not allowed.

In Parts 1B and 2, depending on the dosing schedule (see Section 3.1), if there is a delay in dosing of combination dose (same day dose of BMS-986179 and nivolumab) of more than 12 days on the Q2W schedule or more than 19 days on the Q3W and Q4W schedules, the visit and dose will be considered skipped and the BMS Medical Monitor will be consulted before subsequent treatment. The on-treatment biopsy on the Q2W schedule must be performed after 3 doses and must be 11 ± 2 days from the third dose. On-treatment biopsy on the Q3W schedule must be performed after 3 doses and must be 18 ± 2 days from the third dose. The schedule of imaging assessments should be maintained relative to the first dose (C1D1) of combination therapy, regardless of dosing delays. Skipping the Day 1 visit within a Cycle is not allowed.

If a dose delay of greater than 12 or 19 days (depending on dosing schedule, as explained above) occurs prior to obtaining the on-treatment biopsy, the subject will continue on therapy, but an additional subject may be added to that dose cohort in order to obtain a pre- and ontreatment- biopsy per the original visit schedule. No additional subjects will be added for biopsy purposes if dose delay > 12 or 19 days occurs after the on-treatment biopsy is obtained.

4.5.4.2 Delays for Non-Medical Events

All dose delays for non-medical events (administrative, vacation, etc) require approval of the Study Director and should be minimized to the greatest extent possible.

For the Q1W dosing schedule, a delay of greater than 5 days for any reason will result in the dose and visit being skipped. Furthermore, cumulative dose delays of greater than 6 days will not be permitted within any four week period.

For the Q2W schedule, dose delays greater than 12 days will be considered skipped, and for the Q3W and Q4W schedules, dose delays of 19 days will be considered skipped. The BMS Medical Monitor must be consulted before subsequent treatment after a skipped dose.

For all dosing schedules, the schedule of imaging assessments should be maintained relative to the first dose (C1D1) of combination therapy, regardless of dosing delays. Skipping the Day 1 visit within a Cycle is not allowed.

4.5.5 Criteria to Resume Treatment

Subjects experiencing AEs not meeting criteria for permanent discontinuation as outlined in Section 3.5 may resume treatment with study drug under the following criteria:

- Subjects may resume treatment with study drug when the drug-related AE(s) resolve to Grade ≤ 1 or baseline value with the following exceptions:
  - Subjects may resume treatment in the presence of Grade 2 fatigue
  - Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
  - Subjects with Grade 2 uveitis or eye pain or blurred vision not meeting DLT criteria (Section 4.5.1) must resolve to baseline prior to resuming study drug
  - Drug-related pulmonary toxicity, diarrhea, or colitis, must have resolved to baseline (by clinical criteria) before treatment is resumed
  - Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment
- Subjects with a Grade 4 drug-related amylase and/or lipase increase that is not associated with symptoms or clinical manifestations of pancreatitis can be restarted on therapy once the levels have recovered to Grade 3 or less and after consultation with the BMS Medical Monitor.

The consideration to re-initiate study drug under these exceptions will be made on a case-bycase- basis after considering the overall benefit-risk profile and in consultation between the investigator and the study Sponsor

If the criteria to resume treatment are met, the subject should restart treatment at the next scheduled time point per protocol.

For subjects with new arterial or venous thrombosis on study who have study drug held (see Section 4.5.4), the decision to resume study therapy will be made after a discussion of the risks and benefits of continuing study therapy has occurred between the treating physician and the BMS Medical Monitor or designee, taking into account severity of the thrombotic event, relation to study drug, risk of re-thrombosis, and the overall clinical situation.

Any adverse event with clinical risk will be assessed on a case-by-case basis with the investigator and the BMS Medical Monitor to determine the risks and benefits of continuing on therapy following resolution versus discontinuing therapy permanently.

4.5.6 Guidelines for Permanent Discontinuation

Subjects will be required to permanently discontinue all study drugs for the following adverse events:

- Any drug related AE occurring at any time that meets DLT criteria as outlined in Section 4.5.1 will require permanent discontinuation with the following **exceptions**:
  a) Grade 3 diarrhea, nausea, vomiting, or abdominal pain that returns to grade 1 or baseline within 3 days with medical intervention;
  b) Grade 3 pruritus or rash that returns to grade 1 or baseline within 7 days or baseline with medical intervention;
  c) Grade 4 electrolyte abnormalities < 72 hours in duration;
  d) Grade 4 neutropenia ≤ 7 days in duration;
  e) Grade 4 increase in amylase or lipase that is not associated with clinical or radiographic evidence of pancreatitis;
  f) Grade 4 lymphopenia < 7 days in duration.
- Any dosing delay lasting > 6 weeks will be cause for permanent discontinuation. Extensions to this period may be granted for individual subjects on a case-by-case basis after specific consultation and agreement between the investigator and the BMS Medical Monitor in settings where benefit/risk may justify continued study therapy (eg, subject deriving clinical benefit who requires prolonged steroid taper for management of non-DLT immune-related AEs, or experiences delays for management of an AE).

In addition, any myocardial infarction or thrombotic or ischemic cerebrovascular accident regardless of causality will require discontinuation of BMS-986179.

In most cases of discontinuation, all study drugs will be discontinued. In rare instances, subjects who received BMS-986179 in combination with nivolumab may be considered for continuation of nivolumab alone on a case-by-case basis and in consultation with the BMS Medical Monitor. Continuation of nivolumab monotherapy is only appropriate when prior treatment-related toxicities were most likely attributable to BMS-986179, when the likelihood of sustained clinical benefit is high, and when the risk due to ongoing nivolumab treatment is low.

4.5.7 Treatment of Drug-related Infusion Reactions

Since BMS-986179 and nivolumab contain only human immunoglobulin protein sequences, they are unlikely to be immunogenic and to induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the BMS Medical Monitor and reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE v4.03 guidelines.

Treatment recommendations 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 subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg at least 30 minutes before additional study drug administrations.

For Grade 2 symptoms: Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids); prophylactic medications indicated for ≤ 24 hours.

- Stop the infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); monitor subject until resolution of symptoms.
- Bronchodilator or corticosteroid therapy may also be administered as appropriate.
- The infusion may be restarted 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 subject closely.
- The amount of study drug infused must be recorded on CRF.
- If symptoms recur, then no further BMS-986179 or nivolumab, as the case may be, will be administered at that visit.
- The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional nivolumab administrations. If necessary, corticosteroids (up to 25 mg of SoluCortef® [hydrocortisone sodium succinate] or equivalent) may be used.

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).

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

Immediately discontinue study drug infusion. Begin an IV infusion of normal saline, and treat the subject as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. The subject should be monitored until the investigator is comfortable that the symptoms will not recur. The study drug will be permanently discontinued. Investigators

should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside, and monitor the subject until recovery from 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, corticosteroids).

4.6 Blinding/Unblinding

This is an open-label study. Data emerging from this exploratory study may be necessary to inform timely decisions for adjusting procedures in subsequent portions of the study, including early termination of the study, requiring access to IRT treatment codes. Additionally, treatment assignments may facilitate optimization of the bioanalytical analysis of samples.

Designated ***members of the study team, as well as the Bioanalytical and/or clinical pharmacology groups*** of the Sponsor can access IRT treatment codes prior to the formal locking of the study database ***for these purposes***. This access to the treatment codes will not impact the data integrity of the study.

4.7 Treatment Compliance

Study drug will be administered in the clinical facility by trained medical personnel. Treatment compliance will be monitored by drug accountability, as well as by recording BMS-986179 and nivolumab administration in subjects' source documents and CRF.

4.8 Destruction of Study Drug

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

Any unused study drugs can only be destroyed after being inspected and reconciled by the responsible BMS study monitor unless study drug containers must be immediately destroyed as required for safety or to meet local regulations (eg, cytotoxics or biologics).

On-site destruction is allowed provided the following minimal standards are met:

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

If conditions for destruction cannot be met, the responsible BMS study monitor will make arrangements for return of study drug.

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

4.9 Return of Study Drug

If the study drug will not be destroyed upon completion or termination of the study, all unused and/or partially used study drug that was supplied by BMS must be returned to BMS. The return of study drug will be arranged by the responsible study monitor.

4.10 Retained Samples for Bioavailability

Not applicable.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Study assessments and procedures are presented in Table 5.1-1 (screening procedural outline), Table 5.1-2 (ontreatment- procedural outline for the Part 1A Q1W regimen with monotherapy lead-in), Table 5.1-3 (ontreatment- procedural outline for the Part 1B/Part 2 Q2W regimen), Table 5.1-4 (ontreatment- procedural outline for the Part 1B/Part 2 Q3W regimen), Table 5.1-5 (on-treatment procedural outline for the Part 1B/Part 2 Q4W regimen), Table 5.1-6 (re-treatment Day 0 procedural outline), Table 5.1-7 (re-treatment procedural outline for the Part 1A Q1W regimen), Table 5.1-8 (re-treatment procedural outline for the Part 1B/Part 2 Q2W regimen), Table 5.1-9 (re-treatment procedural outline for the Part 1B/Part 2 Q3W regimen), and Table 5.1-10 (safety and response/survival follow-up).

Table 5.1-1: Screening Procedural Outline (CA013004)

Procedure	Screening Period (Day -28 to -1 for Part 1A and Part 1B) (Day -42 to -1 for Part 2)	Notes
Eligibility Assessments		
Informed Consent	X	A subject is considered enrolled only when a protocol-specific informed consent is signed. Obtain subject number from IVRS (or equivalent system).
Inclusion/Exclusion Criteria	X	
Medical History	X	Includes any toxicities or allergy related to previous treatments.
Prior Systemic Therapies	X	
Archived Tumor Tissue Sample	X	If available, 1 paraffin block or 15 to 20 formalin-fixed, paraffin-embedded unstained slides should be located and shipped to a central laboratory as soon as possible after signing the consent.
Fresh Pre-treatment Tumor Biopsy	X	A minimum of 4 fresh core biopsy specimens will be collected (from a single biopsy procedure) in all subjects, pre-treatment and on treatment, as described in Section 5.7.2. The biopsies will be taken as outlined in the laboratory manual.
Safety Assessments		
Physical Examination	X	If the screening physical examination is performed within 48 hours prior to dosing on Day 1 of Cycle 0 or Cycle 1, then a single exam may count as both the screening and pre-dose evaluation.
ECOG Performance Status	X	See Appendix 3.
Physical Measurements	X	Includes height and weight.

Table 5.1-1: Screening Procedural Outline (CA013004)

Procedure	Screening Period (Day -28 to -1 for Part 1A and Part 1B) (Day -42 to -1 for Part 2)	Notes
Vital Signs	X	Includes body temperature, respiratory rate, blood pressure, and heart rate. Blood pressure, respiratory rate, and heart rate should be measured after the subject has been resting quietly for at least 5 minutes.
Oxygen Saturation	X	
Electrocardiogram	X	12-lead electrocardiograms should be recorded after the subject has been supine for at least 5 minutes.
Laboratory Tests		C1D1(C0D1 for Part 1A) laboratory tests are not required if the screening laboratory test is performed **within 48 hours** prior to dosing, with the exception of pregnancy testing, which must be done within 24 hours prior to dosing. Subsequent on-treatment laboratory tests may be performed **within 24 hours** prior to dosing. See Section 5.3.2 for further details.
Chemistry (Excluding Liver Function Tests)	X	Includes cardiovascular lipid profile. Details are in Section 5.3.2.
Complete Blood Count with Differential and Platelets	X	Details are in Section 5.3.2.
Liver Function Test and Coagulation Assessments	X	Includes AST, ALT, total bilirubin, direct bilirubin, alkaline phosphatase, GGT, international normalized ratio, prothrombin time, and activated partial thromboplastin time.
Urinalysis	X	Details are in Section 5.3.2.
Thyroid Function Tests	X	Thyroid-stimulating hormone with free triiodothyronine (T3) and free thyroxine (T4), or equivalent.

Table 5.1-1: Screening Procedural Outline (CA013004)

Procedure	Screening Period (Day -28 to -1 for Part 1A and Part 1B) (Day -42 to -1 for Part 2)	Notes
Mutational Status	X (or at any time during the study)	For subjects with NSCLC: document EGFR and KRAS mutation status. For subjects with melanoma: document BRAF and NRAS mutation status. Other historical mutation status may be reported for all cancer types.
Serology Tests	X	Details are in Section 5.3.2.
Pregnancy Test	X	For WOCBP only, if the screening pregnancy test is performed within 24 hours of dosing on Day 1 of Cycle 0 (for Part 1A) or Cycle 1 (for Part 1B or Part 2), then a single test may count as both the screening and pre-dose evaluation.
Follicle-stimulating Hormone	X	Women only, if needed to document post-menopausal status (Section 3.3.3).
Tumor Marker Assessments	X	For subjects with pancreatic adenocarcinoma: Cancer antigen 19-9 (CA19-9). For subjects with CRPC: Prostate-specific antigen (PSA).
Adverse Event Reporting and Concomitant Medication Assessments		
Concomitant Medications	X	Medications taken within 4 weeks prior to initial and re-treatment study drug administration must be recorded in the CRF.
Clinical Complaints	X	Collected during the 2 weeks prior to initial study drug administration.
Monitor for Serious Adverse Events	X	All SAEs must be collected from the date of subject's written consent until 100 days after discontinuation of dosing.

Table 5.1-1: Screening Procedural Outline (CA013004)

Procedure	Screening Period (Day -28 to -1 for Part 1A and Part 1B) (Day -42 to -1 for Part 2)	Notes
Efficacy Assessments		
Tumor Assessments	X	CT with contrast of the chest, contrast enhanced CT/MRI of abdomen, pelvis, and all other known/suspected sites of disease will be performed within 28 days prior to date of first dose.
Brain Imaging	X	MRI of the brain with and without contrast is required for participants with known or suspected brain metastases. CT of the brain (with and without contrast) can be performed if MRI is contraindicated.
Bone Scan	X	As clinically indicated per local standards.

Table 5.1-2: On-treatment Procedural Outline (Part 1A - Q1W Regimen with Monotherapy Lead-in)

Procedure	Cycle 0 (14 days)		Cycle 1 (C1) (28 days)				Cycle 2 (C2) Onward (28 days each)[a]					
	D1	D8[b]	D1	D8	D15	D22	D1	D8	D15	D22	EOT [c]	Notes
IVRS (or Equivalent System) Assignment												
IVRS (or Equivalent System) Assignment	X											Once subject eligibility has been confirmed, IVRS (or equivalent system) assignment can be performed
Safety Assessments												
Complete Physical Examination (PE)	X		X				X					Predose. See note in Table 5.1-1.
Symptom-Directed PE		X		X	X	X		X	X	X	X	
Weight Measurement	X		X				X				X	
ECOG Performance Status	X		X				X					Predose. See Appendix 3.
Vital Signs (VS)	X	X	X	X	X	X	X	X	X	X	X	Vital signs (body temperature, seated blood pressure, heart rate, and respiratory rate) will be obtained before the first infusion, every 15 minutes (+/- 5 minutes) during the infusions, during the interval between the 2 infusions if applicable, at the end of the last infusion, 30 minutes (+/- 5 minutes) and 60 minutes (+/- 5 minutes) post the last infusion. Please note that for the first two combination treatments in Cycle 1 (i.e. C1D1 and C1D15 in Part 1A), VS should also be taken every 30 minutes for 2 hours after completion of the BMS-986179 infusion.
Oxygen Saturation	X	X	X	X	X	X	X	X	X	X	X	
Electrocardiogram	X		X				X					See note in Table 5.1-1.

Table 5.1-2: On-treatment Procedural Outline (Part 1A - Q1W Regimen with Monotherapy Lead-in)

Procedure	Cycle 0 (14 days)		Cycle 1 (C1) (28 days)				Cycle 2 (C2) Onward (28 days each)[a]					
	D1	D8[b]	D1	D8	D15	D22	D1	D8	D15	D22	EOT [c]	Notes
Laboratory Tests												C0D1 laboratory tests are not required if the screening laboratory test is performed **within 48 hours** prior to dosing, with the exception of pregnancy testing, which must be done within 24 hours prior to dosing. Subsequent on-treatment laboratory tests may be performed **within 24 hours** prior to dosing. See Section 5.3.2 for further details.
Chemistry (Excluding Liver Function Tests)	X	X	X	X	X	X	X	X	X	X	X	Predose.
Complete Blood Count with Differential and Platelets	X	X	X	X	X	X	X	X	X	X	X	Predose.
Liver Function Test Assessments	X	X	X	X	X	X	X	X	X	X	X	Predose.
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	Predose.
Thyroid Function Tests			X				X				X	Predose every other cycle during combination treatment (ie, Cycle 1, 3, 5, etc). See note in Table 5.1-1.
Pregnancy Test (WOCBP)	X		X		X		X		X		X	Per Section 6.4.
Tumor Marker Assessments	X		X				X				X	Predose on Day 1 of each cycle; see Section 5.3.2 and Table 5.1-1. For subjects with pancreatic adenocarcinoma: Cancer antigen 19-9 (CA19-9) only if elevated as baseline. For subjects with CRPC: PSA predose on Day 1 of each cycle.

Table 5.1-2: On-treatment Procedural Outline (Part 1A - Q1W Regimen with Monotherapy Lead-in)

Procedure	Cycle 0 (14 days)		Cycle 1 (C1) (28 days)				Cycle 2 (C2) Onward (28 days each)[a]					
	D1	D8[b]	D1	D8	D15	D22	D1	D8	D15	D22	EOT [c]	Notes
Adverse Event Reporting and Concomitant Medication Assessments												
Concomitant Medication Assessments	X	X	X	X	X	X	X	X	X	X	X	Review prior to each dosing.
Monitor for Non-serious Adverse Events	X	X	X	X	X	X	X	X	X	X	X	Non-serious AEs will be collected starting with the first dose of the study drug and through 100 days after discontinuation of dosing.
Monitor for Serious Adverse Events	X	X	X	X	X	X	X	X	X	X	X	See note in Table 5.1-1.
Sample Collection												
Pharmacokinetic Assessments	See Section 5.5.1 and Table 5.5.1-1.											Performed in all subjects.
Immunogenicity Assessments	See Section 5.5.1 and Table 5.5.1-1.											Performed in all subjects.
Biomarker Assessments												
Tumor Biopsy	Day 10 (Cycle 0 Day 10)											See Section 5.6.
[redacted]												
PD Biomarkers	See Section 5.7 and Table 5.6-1.											See Section 5.7.

Table 5.1-2: On-treatment Procedural Outline (Part 1A - Q1W Regimen with Monotherapy Lead-in)

Procedure	Cycle 0 (14 days)		Cycle 1 (C1) (28 days)				Cycle 2 (C2) Onward (28 days each)[a]					
	D1	D8[b]	D1	D8	D15	D22	D1	D8	D15	D22	EOT [c]	Notes
Efficacy Assessments												
Tumor/Response Assessment			See note.									See note in Table 5.1-1. Assessments must be completed every 8 weeks (± 7 days) starting from date of first dose, before the subsequent dose, namely within 7 days of dosing on Day 22 in Cycles 2, 4, 6, etc until participant discontinues treatment. Results must be reviewed prior to the dosing
Brain Imaging			See note.									As clinically indicated. Participants with a history of brain metastasis or symptoms should have surveillance MRI per standard of care (approximately every 12 weeks), or sooner if clinically indicated.
Bone Scan			See note.									As clinically indicated per local standards. Same as tumor/response assessment above.
Study Drug Administration												The start and stop time of the study drug infusion must be documented. See Section 4.5.7 for treatment of infusion reaction.
BMS-986179 (Q1W)	X	X	X	X	X	X	X	X	X	X		
Nivolumab (Q2W)			X		X		X		X			

[a] Cycle 6 will be 22 days duration only if treatment ends at Cycle 6. If additional cycles after Cycle 6 are approved, Cycle 6 should be 28 days long. The first additional cycle should follow Cycle 2 procedures.

[b] Subjects who discontinue prior to Cycle 0 Day 8 must complete their Day 8 assessments at the end of treatment (EOT) visit.

[c] End of treatment (EOT) procedures should be performed when it is determined that the subject will no longer be treated with study drug. However, if the decision to discontinue study treatment is made more than 21 days after the last administered treatment, the EOT procedures are no longer required; all Safety Follow-up visits should be completed as detailed in Table 5.1-10.

Table 5.1-3: On-treatment Procedural Outline (Part 1B and Part 2 - Q2W Regimen)

Procedure	Cycle 1 (C1) (28 days)		Cycle 2 (C2) Onward (28 days each)[a]			
	D1	D15	D1	D15	EOT[b]	Notes
IVRS (or Equivalent System) Assignment						
IVRS (or Equivalent System) Assignment	X					Once subject eligibility has been confirmed, IVRS (or equivalent system) assignment can be performed within 3 days prior to the first study drug administration. (Discuss with the Sponsor if institutional policies and procedures require additional lead-time.)
Safety Assessments						
Complete Physical Examination (PE)	X		X			Predose. See note in Table 5.1-1.
Symptom-Directed PE		X		X	X	
Weight Measurement	X		X		X	
ECOG Performance Status	X		X			Predose. See Appendix 3.
Vital Signs	X	X	X	X	X	Vital signs (body temperature, seated blood pressure, heart rate, and respiratory rate) will be obtained before the first infusion, every 15 minutes (+/- 5 minutes) during the infusions, during the interval between the 2 infusions, at the end of the last infusion, 30 minutes (+/- 5 minutes) and 60 minutes (+/- 5 minutes) post the last infusion.
Oxygen Saturation	X	X	X	X	X	
Electrocardiogram	X		X			See note in Table 5.1-1.

Table 5.1-3: On-treatment Procedural Outline (Part 1B and Part 2 - Q2W Regimen)

Procedure	Cycle 1 (C1) (28 days)		Cycle 2 (C2) Onward (28 days each)[a]			
	D1	D15	D1	D15	EOT[b]	Notes
Laboratory Tests						C1D1 laboratory tests are not required if the screening laboratory test is performed **within 48 hours** prior to dosing, with the exception of pregnancy testing, which must be performed within 24 hours prior to dosing. Subsequent on-treatment laboratory tests may be performed **within 24 hours** prior to dosing. See Section 5.3.2 for further details.
Chemistry (Excluding Liver Function Tests)	X	X	X	X	X	Predose.
Complete Blood Count with Differential and Platelets	X	X	X	X	X	Predose.
Liver Function Test Assessments	X	X	X	X	X	Predose.
Urinalysis	X	X	X	X	X	Predose.
Thyroid Function Tests	X		X		X	Predose on Day 1 of every other cycle. See note in Table 5.1-1.
Pregnancy Test (WOCBP)	X	X	X	X	X	Per Section 6.4.
Tumor Marker Assessments	X		X		X	Predose on Day 1 of each cycle; see Section 5.3.2. For subjects with CRPC: PSA predose on Day 1 of each cycle. See note in Table 5.1-1 and Table 5.1-2.
Adverse Event Reporting and Concomitant Medication Assessments						
Concomitant Medication Assessments	X	X	X	X	X	Review prior to each dosing.

Table 5.1-3: On-treatment Procedural Outline (Part 1B and Part 2 - Q2W Regimen)

Procedure	Cycle 1 (C1) (28 days)		Cycle 2 (C2) Onward (28 days each)[a]			
	D1	D15	D1	D15	EOT[b]	Notes
Monitor for Non-serious Adverse Events	X	X	X	X	X	Non-serious AEs will be collected starting with the first dose of the study drug and through 100 days after discontinuation of dosing.
Monitor for Serious Adverse Events	X	X	X	X	X	See note in Table 5.1-1.
Sample Collection						
Pharmacokinetic Assessments	See Section 5.5.1, Table 5.5.1-2 (Part 1B), Table 5.5.1-5 (Part 2), Table 5.5.1-8 (Part 1B and Part 2 for BMS-986179 monotherapy) [redacted].					Performed in all subjects.
Immunogenicity Assessments	See Section 5.5.1, Table 5.5.1-2 (Part 1B), Table 5.5.1-5 (Part 2), Table 5.5.1-8 (Part 1B and Part 2 for BMS-986179 monotherapy) [redacted].					Performed in all subjects.
Biomarker Assessments						
Tumor Biopsy	Day 42 (Cycle 2 Day 14 before next dose)					See Section 5.6.
[redacted]						
PD Biomarkers	See Section 5.7, Table 5.6-2 (Part 1B), and Table 5.6-4 (Part 2).					See Section 5.7.
Efficacy Assessments						
Tumor/Response Assessment	See note.					See note in Table 5.1-1 and Table 5.1-2.
Brain Imaging	See note.					As clinically indicated. Same as tumor/response assessment above.
Bone Scan	See note.					As clinically indicated. Same as tumor/response assessment above.

Table 5.1-3: On-treatment Procedural Outline (Part 1B and Part 2 - Q2W Regimen)

Procedure	Cycle 1 (C1) (28 days)		Cycle 2 (C2) Onward (28 days each)[a]			
	D1	D15	D1	D15	EOT[b]	Notes
Study Drug Administration						
BMS-986179 (Q2W)	X	X	X	X		Possible treatment regimen for Part 1B and Part 2
Nivolumab						Possible treatment regimen for Part 1B and Part 2. Nivolumab may be administered either Q2W or Q4W in combination with BMS- 986179 Q2W in Part 1B and Part 2.
Q2W	X	X	X	X		
Q4W	X		X			

[a] Cycle 6 will be 15 days duration only, and the last visit in Cycle 6 will be on C6 D15 if the treatment ends on Cycle 6. If additional cycles after Cycle 6 are approved, Cycle 6 should be 28 days long. The first additional cycle should follow Cycle 2 procedures.

[b] End of treatment (EOT) procedures should be performed when it is determined that the subject will no longer be treated with study drug. However, if the decision to discontinue study treatment is made more than 21 days after the last administered treatment, the EOT procedures are no longer required; all Safety Follow-up visits should be completed as detailed in Table 5.1-10.

Table 5.1-4: On-treatment Procedural Outline (Part 1B and Part 2 - Q3W Regimen)

Procedure	Cycle 1 (42 days)		Cycle 2 (C2) Onward (42 days each)[a]			
	D1	D22	D1	D22	EOT[b]	Notes
IVRS (or Equivalent System) Assignment						
IVRS (or Equivalent System) Assignment	X					Once subject eligibility has been confirmed, IVRS (or equivalent system) assignment can be performed prior to the first study drug administration.
Safety Assessments						
Complete Physical Examination (PE)	X		X			Predose. See note in Table 5.1-1.
Symptom-Directed PE		X		X	X	
Weight Measurement	X		X		X	
ECOG Performance Status	X		X			Predose.
Vital Signs	X	X	X	X	X	Vital signs (body temperature, seated blood pressure, heart rate, and respiratory rate) will be obtained before the first infusion, every 15 minutes (+/- 5 minutes) during the infusions, during the interval between the 2 infusions, at the end of the last infusion, 30 minutes (+/- 5 minutes) and 60 minutes (+/- 5 minutes) post the last infusion.
Oxygen Saturation	X	X	X	X	X	
Electrocardiogram	X		X			See note in Table 5.1-1
Laboratory Tests						C1D1 laboratory tests are not required if the screening laboratory test is performed **within 48 hours** prior to dosing, with the exception of pregnancy testing, which must be performed within 24 hours prior to dosing. Subsequent on-treatment laboratory tests may be performed **within 24 hours** prior to dosing. See Section 5.3.2 for further details.
Chemistry (Excluding Liver Function Tests)	X	X	X	X	X	Predose.

Table 5.1-4: On-treatment Procedural Outline (Part 1B and Part 2 - Q3W Regimen)

Procedure	Cycle 1 (42 days)		Cycle 2 (C2) Onward (42 days each)[a]			
	D1	D22	D1	D22	EOT[b]	Notes
Complete Blood Count with Differential and Platelets	X	X	X	X	X	Predose.
Liver Function Test Assessments	X	X	X	X	X	Predose.
Urinalysis	X	X	X	X	X	Predose.
Thyroid Function Tests	X		X		X	Predose on Day 1 every other cycle. See note in Table 5.1-1.
Pregnancy Test (WOCBP)	X	X	X	X	X	Per Section 6.4.
Tumor Marker Assessments	X		X		X	Predose on Day 1 of each cycle; see Section 5.3.2. For subjects with CRPC: PSA predose on Day 1 of each cycle. See note in Table 5.1-1.
Adverse Event Reporting and Concomitant Medication Assessments						
Concomitant Medication Assessments	X	X	X	X	X	Review prior to each dosing.
Monitor for Non-serious Adverse Events	X	X	X	X	X	See note in Table 5.1-2.
Monitor for Serious Adverse Events	X	X	X	X	X	See note in Table 5.1-1.
Sample Collection						
Pharmacokinetic Assessments	See Section 5.5.1, Table 5.5.1-3 (Part 1B), Table 5.5.1-6 (Part 2), Table 5.5.1-9 (Part 1B and Part 2 for BMS-986179 monotherapy) [redacted].					Performed in all subjects.
Immunogenicity Assessments	See Section 5.5.1, Table 5.5.1-3 (Part 1B), and Table 5.5.1-6 (Part 2), Table 5.5.1-9 (Part 1B and Part 2 for BMS-986179 monotherapy) [redacted].					Performed in all subjects.

Table 5.1-4: On-treatment Procedural Outline (Part 1B and Part 2 - Q3W Regimen)

Procedure	Cycle 1 (42 days)		Cycle 2 (C2) Onward (42 days each)[a]			
	D1	D22	D1	D22	EOT[b]	Notes
Biomarker Assessments						
Tumor Biopsy	Day 63 (Cycle 2 Day 21 before next dose)					See Section 5.6.
PD biomarkers	See Section 5.7, Table 5.6-3 (Part 1B), and Table 5.6-5 (Part 2).					
[redacted]						
Efficacy Assessments						
Tumor/Response Assessment	See note.					See note in Table 5.1-1. Assessments must be completed every 9 weeks (± 7 days) starting from date of first dose, up to 7 days before the next dosing, until participant discontinues treatment. Results must be reviewed prior to the dosing.
Brain Imaging	See note.					Participants with a history of brain metastasis or symptoms should have surveillance MRI per standard of care (approximately every 12 weeks), or sooner if clinically indicated
Bone Scan	See note.					As clinically indicated per local standards. Same as tumor/response assessment above.

Table 5.1-4: On-treatment Procedural Outline (Part 1B and Part 2 - Q3W Regimen)

Procedure	Cycle 1 (42 days)		Cycle 2 (C2) Onward (42 days each)[a]			
	D1	D22	D1	D22	EOT[b]	Notes
Study Drug Administration						
BMS-986179 (Q3W)	X	X	X	X		Expected treatment for Part 1B and possible treatment for Part 2.
Nivolumab (Q3W)	X	X	X	X		Expected treatment for Part 1B and possible treatment for Part 2.

[a] Cycle 4 will be 22 days duration only if the treatment ends on Cycle 4. If additional cycles after Cycle 4 are approved, Cycle 4 should be 42 days long. The first additional cycle should follow Cycle 2 procedures.

[b] End of treatment (EOT) procedures should be performed when it is determined that the subject will no longer be treated with study drug. However, if the decision to discontinue study treatment is made more than 21 days after the last administered treatment, the EOT procedures are no longer required; all Safety Follow-up visits should be completed as detailed in Table 5.1-10.

Table 5.1-5: On-treatment Procedural Outline (Part 1B and Part 2 - Q4W Regimen)

Procedure	Cycle 1 (C1) (28 days) D1	Cycle 2 (C2) Onward (28 days each)[a] D1	EOT[b]	Notes
IVRS (or Equivalent System) Assignment				
IVRS (or Equivalent System) Assignment	X			Once subject eligibility has been confirmed, IVRS (or equivalent system) assignment can be performed within 3 days prior to the first study drug administration (discuss with the Sponsor if institutional policies and procedures require additional lead-time).
Safety Assessments				
Complete Physical Examination (PE)	X	X		Predose. See note in Table 5.1-1.
Symptom-Directed PE	X	X	X	
Weight Measurement	X	X	X	
ECOG Performance Status	X	X		Predose. See Appendix 3.
Vital Signs	X	X X	X	Vital signs (body temperature, seated blood pressure, heart rate, and respiratory rate) will be obtained before the first infusion, every 15 minutes (+/- 5 minutes) during the infusions, during the interval between the 2 infusions, at the end of the last infusion, and at 30 minutes (+/- 5 minutes) and 60 minutes (+/- 5 minutes) after the last infusion.
Oxygen Saturation	X	X	X	
Electrocardiogram	X	X		See note in Table 5.1-1.

Table 5.1-5: On-treatment Procedural Outline (Part 1B and Part 2 - Q4W Regimen)

Procedure	Cycle 1 (C1) (28 days) D1	Cycle 2 (C2) Onward (28 days each)[a] D1	EOT[b]	Notes
Laboratory Tests				C1D1 laboratory tests are not required if the screening laboratory test is performed **within 48 hours** prior to dosing, with the exception of pregnancy testing, which must be performed within 24 hours prior to dosing. Subsequent on-treatment laboratory tests may be performed **within 24 hours** prior to dosing. See Section 5.3.2 for further details.
Chemistry (Excluding Liver Function Tests)	X	X	X	Predose.
Complete Blood Count with Differential and Platelets	X	X	X	Predose.
Liver Function Test Assessments	X	X	X	Predose.
Urinalysis	X	X	X	Predose.
Thyroid Function Tests	X	X	X	Predose on Day 1 of every other cycle. See note in Table 5.1-1.
Pregnancy Test (WOCBP)	X	X	X	Per Section 6.4.
Tumor Marker Assessments	X	X	X	Predose on Day 1 of each cycle; see Section 5.3.2. For subjects with CRPC: PSA predose on Day 1 of each cycle. See note in Table 5.1-1 and Table 5.1-2.
Adverse Event Reporting and Concomitant Medication Assessments				
Concomitant Medication Assessments	X	X	X	Review prior to each dosing.

Table 5.1-5: On-treatment Procedural Outline (Part 1B and Part 2 - Q4W Regimen)

Procedure	Cycle 1 (C1) (28 days) D1	Cycle 2 (C2) Onward (28 days each)[a] D1	EOT[b]	Notes
Monitor for Non-serious Adverse Events	X	X	X	Non-serious AEs will be collected starting with the first dose of the study drug through 100 days after discontinuation of dosing.
Monitor for Serious Adverse Events	X	X	X	See note in Table 5.1-1.
Sample Collection				
Pharmacokinetic Assessments	See Section 5.5.1, Table 5.5.1-5 (Part 2), Table 5.5.1-7 (Part 1B and Part 2), Table 5.5.1-10 (Part 1B and Part 2 for BMS-986179 monotherapy IV [redacted].			Performed in all subjects.
Immunogenicity Assessments	See Section 5.5.1, Table 5.5.1-5 (Part 2), Table 5.5.1-7 (Part 1B and Part 2), Table 5.5.1-10 (Part 1B and Part 2 for BMS-986179 monotherapy IV [redacted].			Performed in all subjects.
Biomarker Assessments				
Tumor Biopsy	Day 56 - 5 days (Cycle 3 Day 1 before next dose)			See Section 5.6.
[redacted]				
PD Biomarkers	See Section 5.7, Table 5.6-2 (Part 1B), and Table 5.6-4 (Part 2).			See Section 5.7.
Efficacy Assessments				
Tumor/Response Assessment	See note.			See note in Table 5.1-1 and Table 5.1-2.
Brain Imaging	See note.			As clinically indicated. Same as tumor/response assessment above.
Bone Scan	See note.			As clinically indicated. Same as tumor/response assessment above.

Table 5.1-5: On-treatment Procedural Outline (Part 1B and Part 2 - Q4W Regimen)

Procedure	Cycle 1 (C1) (28 days) D1	Cycle 2 (C2) Onward (28 days each)[a] D1	EOT[b]	Notes
Study Drug Administration				
BMS-986179 (Q4W)	X	X		Possible Q4W regimen for Part 2 only.
Nivolumab (Q4W)	X	X		Possible Q4W regimen for Part 2 only.

[a] Cycle 6 will be 28 days in duration only, and the last visit in Cycle 6 will be on C6 D28 if the treatment ends on Cycle 6. If additional cycles after Cycle 6 are approved, Cycle 6 should be 28 days long. The first additional cycle should follow Cycle 2 procedures.

[b] End of treatment (EOT) procedures should be performed when it is determined that the subject will no longer be treated with study drug. However, if the decision to discontinue study treatment is made more than 21 days after the last administered treatment, the EOT procedures are no longer required; all Safety Follow up visits should be completed as detailed in Table 5.1-10.

Table 5.1-6: Re-treatment Day 0 Procedural Outline (CA013004)

Procedure	Day 0[a]	Notes
Eligibility Assessments		
Eligibility Verification	X	Ensure subject continues to meet eligibility for protocol treatment.
Safety Assessments		
Physical Examination	X	See note in Table 5.1-1.
ECOG Performance Status	X	See Appendix 3.
Weight Measurement	X	Includes weight.
Vital Signs	X	See note in Table 5.1-1.
Oxygen Saturation	X	
Electrocardiogram	X	See note in Table 5.1-1.
Laboratory Tests		See note in Table 5.1-1.
Chemistry (Excluding Liver Function Tests)	X	Details are in Section 5.3.2.
Complete Blood Count with Differential and Platelets	X	
Liver Function Test Assessments	X	See note in Table 5.1-1.
Urinalysis	X	Details are in Section 5.3.2.
Thyroid Function Tests	X	See note in Table 5.1-1.
Serology Tests	X	Details are in Section 5.3.2.
Pregnancy Test	X	See note in Table 5.1-1.
Follicle Stimulating Hormone	X	Women only, if needed to document post-menopausal status (Section 3.3.2).
Concomitant Medication Assessments		
Concomitant Medications	X	See note in Table 5.1-1.

Table 5.1-6: Re-treatment Day 0 Procedural Outline (CA013004)

Procedure	Day 0[a]	Notes
Efficacy Assessments		
Tumor Assessments	X	See note in Table 5.1-1.
Brain Imaging	X	See note in Table 5.1-1.
Bone Scan	X	See note in Table 5.1-1.

[a] All procedures for re-treatment eligibility will be performed within 28 days of re-treatment Day 1 dosing.

Re-treatment will be limited to subjects as described in Section 3.1.6.

Table 5.1-7: Re-treatment Procedural Outline (Part 1A - Q1W Regimen)

Procedure	Cycle 1 (C1) Onward[a]					
	Day 1	Day 8	Day 15	Day 22	EOT[b]	Notes
Safety Assessments						
Complete Physical Examination (PE)	X					Predose. See note in Table 5.1-1.
Symptom-Directed PE		X	X	X	X	
Weight Measurement	X				X	On Day 1 of every cycle
ECOG Performance Status	X					Predose. See Appendix 3.
Vital Signs	X	X	X	X	X	See note in Table 5.1-3.
Oxygen Saturation	X	X	X	X	X	
Electrocardiogram	X					See note in Table 5.1-1.
Laboratory Tests						See note in Table 5.1-3.
Chemistry (Excluding Liver Function Tests)	X	X	X	X	X	Predose.
Complete Blood Count with Differential and Platelets	X	X	X	X	X	Predose.
Liver Function Test Assessments	X	X	X	X	X	Predose.
Urinalysis	X	X	X	X	X	Predose.
Thyroid Function Tests	X				X	Predose. Cycles 1, 3, and 5 only. See note in Table 5.1-1.
Pregnancy Test (WOCBP)	X		X		X	See Section 6.4.
Tumor Marker Assessments	X					Predose on Day 1 of each cycle; see Section 5.3.2. See note in Table 5.1-1.
Adverse Event Reporting & Concomitant Medication Assessments						
Concomitant Medication Assessments	X	X	X	X	X	Review prior to each dosing.
Monitor for Non-serious Adverse Events	X	X	X	X	X	See note in Table 5.1-2.
Monitor for Serious Adverse Events	X	X	X	X	X	See note in Table 5.1-1.

Table 5.1-7: Re-treatment Procedural Outline (Part 1A - Q1W Regimen)

Procedure	Cycle 1 (C1) Onward[a]					
	Day 1	Day 8	Day 15	Day 22	EOT[b]	Notes
Sample Collection						
Pharmacokinetic Assessments	See Section 5.5.1 and Table 5.5.1-5.					Perform in all subjects.
Immunogenicity Assessments	See Section 5.5.1 and Table 5.5.1-5.					Perform in all subjects.
Tumor Biopsy	See Section 5.7 and Table 5.6-8.					
PD biomarkers	See Section 5.7 and Table 5.6-8.					
[redacted]						
Efficacy Assessments						
Tumor/Response Assessment	See note.					See note in Table 5.1-1 and Table 5.1-2.
Brain Imaging	See note.					As clinically indicated.
Bone Scan	See note.					As clinically indicated.
Study Drug Administration						
BMS-986179						
Q1W	X	X	X	X		
Nivolumab (Q2W)	X		X			

[a] Cycle 6 will be 28 days if the treatment ends in Cycle 6. If additional cycles after Cycle 6 are approved, Cycle 6 should be 28 days long. The first additional cycle should follow Cycle 2 procedures.

[b] End of treatment (EOT) procedures should be performed when it is determined that the subject will no longer be treated with study drug. However, if the decision to discontinue study treatment is made more than 21 days after the last administered treatment, the EOT procedures are no longer required; all Safety Followup- visits should be completed as detailed in Table 5.1-10.

Re-treatment will be limited to subjects as described in Section 3.1.6.

Table 5.1-8: Re-treatment Procedural Outline (Part 1B/Part 2 - Q2W Regimen)

Procedure	Cycle 1 (C1) Onward[a]			
	Day 1	Day 15	EOT[b]	Notes
Safety Assessments				
Complete Physical Examination (PE)	X			Predose. See note in Table 5.1-1.
Symptom-Directed PE		X	X	
Weight Measurement	X		X	On Day 1 of every cycle.
ECOG Performance Status	X			Predose. See Appendix 3.
Vital Signs	X	X	X	See note in Table 5.1-3
Oxygen Saturation	X	X	X	
Electrocardiogram	X			See note in Table 5.1-1.
Laboratory Tests				See note in Table 5.1-3.
Chemistry (Excluding Liver Function Tests)	X	X	X	Predose.
Complete Blood Count with Differential and Platelets	X	X	X	Predose.
Liver Function Test Assessments	X	X	X	Predose.
Urinalysis	X	X	X	Predose.
Thyroid Function Tests	X		X	Predose. Cycles 1, 3, and 5 only. See note in Table 5.1-1.
Pregnancy Test (WOCBP)	X	X	X	See Section 6.4.
Tumor Marker Assessments	X			Predose on Day 1 of each cycle; see Section 5.3.2. See note in Table 5.1-1.
Adverse Event Reporting & Concomitant Medication Assessments				
Concomitant Medication Assessments	X	X	X	Review prior to each dosing.
Monitor for Non-serious Adverse Events	X	X	X	See note in Table 5.1-2.
Monitor for Serious Adverse Events	X	X	X	See note in Table 5.1-1.

Table 5.1-8: Re-treatment Procedural Outline (Part 1B/Part 2 - Q2W Regimen)

Procedure	Cycle 1 (C1) Onward[a]			
	Day 1	Day 15	EOT[b]	Notes
Sample Collection				
Pharmacokinetic Assessments	See Section 5.5.1 and Table 5.5.1-5.			Perform in all subjects.
Immunogenicity Assessments	See Section 5.5.1 and Table 5.5.1-5.			Perform in all subjects.
Tumor Biopsy	See Section 5.7 and Table 5.6-8.			
PD biomarkers	See Section 5.7 and Table 5.6-8.			
[redacted]				
Efficacy Assessments				
Tumor/Response Assessment	See note.			See note in Table 5.1-1 and Table 5.1-2.
Brain Imaging	See note.			As clinically indicated.
Bone Scan	See note.			As clinically indicated.
Study Drug Administration				
BMS-986179 (Q2W)	X	X		Expected treatment for Part 1B, and possible treatment for Part 2.
Nivolumab (Q2W)	X	X		Expected treatment for Part 1B and possible treatment for Part 2.
Nivolumab (Q4W)	X			For Part 2 only.

[a] Cycle 6 will be 15 days if the treatment ends in Cycle 6. If additional cycles after Cycle 6 are approved, Cycle 6 should be 28 days long. The first additional cycle should follow Cycle 2 procedures.

[b] End of treatment (EOT) procedures should be performed when it is determined that the subject will no longer be treated with study drug. However, if the decision to discontinue study treatment is made more than 21 days after the last administered treatment, the EOT procedures are no longer required; all Safety Follow-up visits should be completed as detailed in Table 5.1-10.

Re-treatment will be limited to subjects as described in Section 3.1.6.

Table 5.1-9: Re-treatment Procedural Outline (Part 1B/Part 2 - Q3W Regimen)

Procedure	Cycle 1 Onward[a]			
	Day 1	Day 22	EOT[b]	Notes
Safety Assessments				
Complete Physical Examination (PE)	X			Predose. Also, see note in screening procedures.
Symptom-Directed PE		X	X	
Weight Measurement	X		X	On Day 1 of every cycle.
ECOG Performance Status	X			Predose. See Appendix 3
Vital Signs	X	X	X	See note in Table 5.1-3.
Oxygen Saturation	X	X	X	
Electrocardiogram	X			See note in Table 5.1-1.
Laboratory Tests				See note in Table 5.1-3.
Chemistry (Excluding Liver Function Tests)	X	X	X	Predose.
Complete Blood Count with Differential and Platelets	X	X	X	Predose.
Liver Function Test Assessments	X	X	X	Predose.
Urinalysis	X	X	X	Predose.
Thyroid Function Tests	X		X	Predose. Cycles 1 and 3 only. See note in Table 5.1-1.
Pregnancy Test (WOCBP)	X	X	X	See Section 6.4.
Tumor Marker Assessments	X			See note in Table 5.1-1.
Adverse Event Reporting and Concomitant Medication Assessments				
Concomitant Medication Assessments	X	X	X	Review prior to each dosing.
Monitor for Non-serious Adverse Events	X	X	X	See note in Table 5.1-2.
Monitor for Serious Adverse Events	X	X	X	See note in screening procedures.

Table 5.1-9: Re-treatment Procedural Outline (Part 1B/Part 2 - Q3W Regimen)

Procedure	Cycle 1 Onward[a]			
	Day 1	Day 22	EOT[b]	Notes
Sample Collection				
Pharmacokinetic Assessments	See Section 5.5.1 and Table 5.5.1-6.			Perform in all subjects.
Immunogenicity Assessments	See Section 5.5.1 and Table 5.5.1-6.			Perform in all subjects.
Tumor Biopsy	See Section 5.7 and Table 5.6-9.			
PD Biomarkers	See Section 5.7 and Table 5.6-9.			
[redacted]				
Efficacy Assessments				
Tumor/Response Assessment				See note in Table 5.1-1 and Table 5.1-4.
Brain Imaging	See note.			As clinically indicated.
Bone Scan	See note.			As clinically indicated.
Study Drug Administration	See note.			See note in Table 5.1-2.
BMS-986179 (Q3W)	X	X		Expected treatment for Part 1B and possible treatment for Part 2.
Nivolumab (Q3W)	X	X		Expected treatment for Part 1B and possible treatment for Part 2.

[a] Cycle 4 will be 22 days duration only.

[b] End of treatment (EOT) procedures should be performed when it is determined that the subject will no longer be treated with study drug. However, if the decision to discontinue study treatment is made more than 21 days after the last administered treatment, the EOT procedures are no longer required; all Safety Follow-up visits should be completed as detailed in Table 5.1-10.

Re-treatment will be limited to subjects as described in Section 3.1.6.

Table 5.1-10: Follow-up Procedural Outline (CA013004)

Procedure	Safety Follow-up (FU)			Response/Survival Follow-up	
	FU 1 30 days[a] (± 7 days)	FU 2 60 days (± 7 days)	FU 3 100 days (± 7 days)	Begins After Completion of Safety Follow-up Until 3 yrs After LAST Dose of Study Drug	Notes
Safety Assessments					
Symptom-Directed Physical Examination	X	X	X		
ECOG Performance Status	X	X	X		See Appendix 3.
Vital Signs	X	X	X		See note in Table 5.1-1.
Oxygen Saturation	X	X	X		
Electrocardiogram	X	X	X		
Laboratory Tests					
Chemistry (Excluding Liver Function Tests)	X	X	X		
Complete Blood Count with Differential and Platelets	X	X	X		
Liver Function Test Assessments	X	X	X		
Urinalysis	X	X	X		Details are in Section 5.3.2.
Thyroid Function Tests	X	X	X		See note in Table 5.1-1.
Pregnancy Test (WOCBP)	X	X	X		Per Section 6.4.
Adverse Event Reporting and Concomitant Medication Assessments					
Concomitant Medication Assessments	X	X	X		
Monitor for Non-serious Adverse Events	X	X	X		See note in Table 5.1-2.
Monitor for Serious Adverse Events	X	X	X		See note in Table 5.1-1.

Table 5.1-10: Follow-up Procedural Outline (CA013004)

Procedure	Safety Follow-up (FU)			Response/Survival Follow-up	
	FU 1 30 days[a] (± 7 days)	FU 2 60 days (± 7 days)	FU 3 100 days (± 7 days)	Begins After Completion of Safety Follow-up Until 3 yrs After LAST Dose of Study Drug	Notes
Sample Collection					
Pharmacokinetic Assessments	See Table 5.5.1-1 through Table 5.5.1-6.				
Immunogenicity Assessments	See Table 5.5.1-1 through Table 5.5.1-6.				
Efficacy Assessments					
Tumor/Response Assessments	During safety follow-up: approximately every 8 weeks (± 7 days) from the last tumor assessment in the treatment period			During response/survival follow-up: approximately every 8 weeks (± 7 days) from the last tumor assessment for the 2 years until progression is confirmed, withdrawal of consent, start of new treatment, whichever comes first. Then as per standard of care guidelines, at a minimum 12 weeks (± 7 days) during the third year until progression is confirmed, withdrawal of consent, start of new treatment, lost to follow up, death, whichever comes first.	See note in Table 5.1-1. Response/Survival Follow-up visits are not required for subjects who discontinue from treatment during BMS-986179 monotherapy treatment in Part 1A
Brain Imaging	See note.				As clinically indicated.
Bone Scan	See note.				As clinically indicated.
Assessment of Subject Survival Status				X	Subject status will be assessed by telephone contact once every 12 weeks if there is no scheduled tumor assessment visit.

Table 5.1-10: Follow-up Procedural Outline (CA013004)

Procedure	Safety Follow-up (FU)			Response/Survival Follow-up	
	FU 1 30 days[a] (± 7 days)	FU 2 60 days (± 7 days)	FU 3 100 days (± 7 days)	Begins After Completion of Safety Follow-up Until 3 yrs After LAST Dose of Study Drug	Notes
New Anti-cancer Therapies	X	X	X	X	Any new anti-cancer therapies (including surgery and radiotherapy) will be recorded.

[a] The timing of the Safety Follow-up visits on Days 30, 60, and 100 (± 7 days) should occur relative to the last administered dose of study drug. If the decision to discontinue study treatment is made 38 days or more after the last treatment, Safety Follow-Up 1 should be performed coinciding with the date discontinuation is decided or as soon as possible thereafter; Safety Follow-ups 2 and 3 should continue to be performed on 60 ± 7 days and 100 ± 7 days from the last treatment, respectively.

5.1.1 Retesting During Screening

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

Any new result will override the previous result (ie, the most current result prior to treatment) and is the value by which study inclusion will be assessed, as it represents the subject's most current clinical state.

Laboratory parameters and/or assessments that are included in Table 5.1-1 may be repeated in an effort to find all possible well-qualified subjects. Retesting is limited to these specific laboratory parameters and/or assessments required by this protocol. Consultation with the BMS Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

5.2 Study Materials

The site will provide all required materials for the tests performed locally (ie, relevant clinical laboratory tests and urine drug screens). The site will have available a well-calibrated scale for recording body weight, a 12-lead electrocardiogram machine, and a calibrated sphygmomanometer and thermometer for vital signs assessments. A current and fully-stocked (advanced cardiac life support [ACLS]) cart will be immediately available on the premises. The site will have urine collection containers, a refrigerated centrifuge, a monitored and alarmed refrigerator, and freezer (-20°C or below), as well as containers and dry ice for shipment and storage of blood samples. The site will provide all materials required for accurate source documentation of study activities and for housing the subjects during the study.

BMS will provide a BMS-approved protocol and any amendments or administrative letters (if required), and IB. CRFs (electronic or hard copy) will be provided by BMS. BMS/The Central Laboratory will provide labels and tubes for the collection of blood samples for PD, PK, anti-drug antibody (ADA) [redacted] analysis.

Additionally, the Central Laboratory Manual, IVRS Manual, Pharmacy Manual, and Imaging Manual will also be provided.

5.3 Safety Assessments

AEs will be assessed continuously during the study and for 100 days after the last dose of study drug. AEs will be evaluated according to the NCI CTCAE v4.03 and should be followed per requirements in Section 6.1.1 and Section 6.2.1. AEs will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA) and reviewed for potential significance and importance. Subjects should be followed until all treatment-related AEs have recovered to baseline or are deemed irreversible by the investigator.

Protocol-specified assessments are described in Table 5.1-1 through Table 5.1-4.

5.3.1 Imaging Assessment for the Study

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

medical/clinical judgment. All imaging assessments related to incidental findings should be evaluated by the study investigator for potential identification/confirmation of disease progression (See Sections 8.3.2.2 [redacted] and 8.4.2).

Images will be submitted to an imaging core lab and may be reviewed by blinded independent central review (BICR) at any time during the study. Sites should be qualified prior to scanning the first participant and understand the image acquisition guidelines and submission process as outlined in the CA013004 Imaging Manual to be provided by the imaging core lab.

Contrast-enhanced CT of the chest, abdomen, pelvis, and all other known/suspected sites of disease should be performed for tumor assessments. Images should be acquired with slice thickness of 5 mm or less with no intervening gap (contiguous). Every attempt should be made to image each participant using an identical acquisition protocol on the same scanner for all imaging time points. Tumor measurements should be made by the same investigator or radiologist for each assessment whenever possible. Change in tumor measurements and tumor response to guide ongoing study treatment decisions will be assessed by the Investigator using the RECIST 1.1 criteria.

Should a participant have contraindication for CT intravenous 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.

Should a participant have contraindication for both MR and CT intravenous 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.

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

Use of CT component of a PET-CT scanner: Combined modality scanning such as with PET-CT is increasingly used in clinical care, and is a modality/technology that is in rapid evolution; therefore, the recommendations outlined here may change rather quickly with time. At present, low dose or attenuation correction CT portions of a combined PET-CT are of limited use in anatomically-based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for anatomically-based RECIST 1.1 measurements. However, if a site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the PET-CT can be used for RECIST 1.1 measurements. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed

Bone scan or PET scan is not adequate for assessment of RECIST 1.1 response in target lesions. In selected circumstances where such modalities are the sole modality used to assess certain non-target organs, those non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

MRI of brain should be acquired as outlined in Table 5.1-1 through Table 5.1-4. CT of the Brain (without and with contrast) can be performed if MRI is contraindicated.

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

5.3.2 Laboratory Test Assessments

A local laboratory will perform the analyses and will provide reference ranges for these tests. All on-treatment pre-dose laboratory tests may be performed up to 48 hours prior to the first dose of the study and up to 24 hours prior to sequential doses, and the results MUST be reviewed prior to each infusion. Exceptions: certain laboratory tests (i.e. tumor markers, etc.) may be performed earlier if longer turnaround time is needed to ensure availability and review of the results prior to dosing. However, pregnancy testing must be done within 24 hours prior to all doses.

The following clinical laboratory tests will be performed:

Hematology

Hemoglobin
Hematocrit
Total leukocyte count, including differential
Platelet count
HbA1c

Serum Chemistry

Aspartate aminotransferase (AST)
Alanine aminotransferase (ALT)
Total bilirubin
Direct bilirubin
Alkaline phosphatase
Lactate dehydrogenase (LDH)
Creatinine
Blood urea nitrogen (BUN)
Uric acid (for screening only)
Glucose
Amylase
Lipase
Gamma-glutamyl transferase (GGT) (only when alkaline phosphatase is abnormal)
Cardiovascular lipid profile
Total protein
Albumin
Sodium
Potassium
Chloride
Bicarbonate
Calcium
Phosphorus
Magnesium
Creatine kinase
Creatinine clearance (for screening only)
Activated partial thromboplastin time (aPTT)
International normalized ratio (INR)
Prothrombin time

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 (or other appropriate evaluation, if not routinely performed)

Serology
Serum for hepatitis C antibody (if hepatitis C antibody is positive reflex to hepatitis C RNA) or hepatitis C RNA if hepatitis C antibody test is not available, hepatitis B surface antigen, and HIV-1 and -2 antibodies

Other Analyses

Pregnancy test (WOCBP only)
Thyroid-stimulating hormone (TSH) with reflex to T3 and T4 (T3 and T4: standard at screening; reflex all other time points)
Follicle-stimulating hormone (FSH) (screening only for post-menopausal women only)
CA19-9 (pancreatic adenocarcinoma subjects only, predose on Day 1 of each cycle if elevated at baseline)
PSA (CRPC subjects only, predose on Day 1 of each cycle)

Results of all laboratory tests required by this protocol must be provided to BMS, either recorded 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 test results 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 (see Section 6.3).

5.4 Efficacy Assessments

Disease assessment with CT and/or MRI scans as appropriate will be performed at baseline and every 8 weeks from the start of combination treatment for the Q1W, Q2W and Q4W regimens or every 9 weeks from the start of combination treatment for the Q3W regimen during treatment period until disease progression per RECIST v1. 1 (see Appendix 2), or until additional disease progression for subjects treated beyond progression (defined as 5 mm or greater increase in tumor burden volume from time of initial progression [including all measurable lesions]), discontinuation of treatment or withdrawal from study. Tumor assessments at other time points may be performed if the investigator is concerned about tumor progression.

Tumor assessment schedules during follow-up period after discontinuation of therapy are outlined in Table 5.1-10.

Changes in tumor measurements and assessment of tumor response will be reported by the investigator as defined by RECIST v1.1[87] (see Appendix 2). Investigators will also report the number and size of new lesions that appear while on study. The timepoint tumor assessments will be reported on the CRF based on investigators' assessment using RECIST criteria. Within each subject, the same imaging modality should be used for all assessments. Section 8.3.2.2 describes the endpoints associated with RECIST.

Tumor assessments for all participants should continue as per protocol even if dosing is delayed or discontinued. Tumor measurements should be made by the same investigator or radiologist for each assessment whenever possible.

5.4.1 Primary Efficacy Assessment

Not applicable.

5.4.2 Secondary Efficacy Assessments

The efficacy assessments will include the ORR (ie, PR + CR), DOR, and PFSR at time points (eg, 24 weeks) based on assessment of tumor response using RECIST v1.1. [redacted]

5.5 Pharmacokinetic Assessments

The PK of BMS-986179 will be derived for monotherapy and combination therapy, if feasible, from serum concentration versus time data. The PK parameters to be assessed, if data permit, include but are not limited to:

Cmax	Maximum observed serum concentration
Tmax	Time of maximum observed serum concentration
AUC(0-T)	Area under the serum concentration-time curve from time zero to time of the last quantifiable concentration
AUC(TAU)	Area under the serum concentration-time curve in 1 dosing interval
T-HALF	Apparent terminal half-life
AUC(INF)	Area under the serum concentration-time curve from time zero extrapolated to infinite time
T-HALFeff	Effective elimination half-life that explains the degree of accumulation observed for a specific exposure measure [exposure measure includes AUC(TAU), Cmax, and Ctau]
Ctau	Concentration at the end of the dosing interval
Ctrough	Trough observed serum concentration at the end of the dosing interval
CLT	Total body clearance
Vss	Volume of distribution at steady state
AI	Accumulation index, calculated based on ratio of an exposure measure at steady state to that after the first dose [exposure measure includes AUC(TAU), Cmax, and Ctau]
Vz	Apparent volume of distribution of terminal phase
DF	Degree of fluctuation or fluctuation index (to be calculated at steady state)

Individual subject PK parameter values will be derived by non-compartmental methods by a validated PK analysis program. Actual times will be used for the analyses.

[redacted]

5.5.1 Pharmacokinetics and Immunogenicity: Collection and Processing

Table 5.5.1-1 through Table 5.5.1-10 list the sampling schedule to be followed for the assessment of the PK and immunogenicity of BMS-986179. All time points are relative to the start of BMS-986179 administration. Pre-dose samples should be taken within 30 minutes before the start of dose administration. End-of-infusion samples should be taken just prior to the end of infusion (preferably within 2 minutes). On-treatment PK samples are intended to be drawn relative to actual dosing days. If it is known that a dose is going to be delayed, then the pre-dose sample should be collected just prior to the delayed dose. However, if a pre-dose sample is collected but the dose is subsequently delayed, an additional pre-dose sample should not be collected. Further details of blood collection and processing will be provided to the site in the procedure manual. Additional samples for immunogenicity assessments, referred to as "ADA Event Driven" samples may be justified in cases of Grade 3/4 infusion or hypersensitivity reactions (see Section 4.5.7). The immunogenicity (and corresponding drug exposure) data from these samples will be reported as part of a subject's overall immunogenicity assessment. Uniquely identified specimen collection kits and instructions for collection of "ADA Event Driven" samples will be provided by the central laboratory vendor.

Table 5.5.1-1: Pharmacokinetic and Immunogenicity Sampling Schedule for BMS-986179 [redacted] (Part 1A Q1W Regimen with Monotherapy Lead-in)

Study Day of Sample Collection (Cycle 0 = 14 days Cycle 1 = 28 days)	Event	Time (Relative To BMS-986179 Infusion) Hour: Min	Serum Samples for BMS-986179 PK	[redacted]	BMS-986179 Immuno-genicity Sample	Nivolumab Immuno-genicity Sample
Monotherapy Lead-in						
C0D1	Predose[a]	00:00	X		X	
	EOI[b]	01:00/02:00[c]	X			
		04:00	X			
		08:00	X			
C0D2		24:00	X			
C0D3		48:00	X			
C0D5		96:00	X			
C0D8	Predose[a]	00:00	X			
	EOI[b]	01:00/02:00[c]	X			
C0D10	Biopsy Sampling[d]	Varied 48:00	X			
Combination treatment with nivolumab						
C1D1	Predose[a]	00:00	X		X	X
C1D1	EOI[b]	01:00/02:00[c]	X			
C1D15	Predose[a]	00:00	X		X	X
C1D22	Predose[a]	00:00	X			
	EOI[b]	01:00/02:00[c]	X			
		04:00	X			
		08:00	X			
C1D24		48:00	X			
C1D26		96:00	X			
C2D1	Predose[a]	00:00	X			
C3D1	Predose[a]	00:00	X			

Table 5.5.1-1: Pharmacokinetic and Immunogenicity Sampling Schedule for BMS-986179 and Nivolumab (Part 1A Q1W Regimen with Monotherapy Lead-in)

Study Day of Sample Collection (Cycle 0 = 14 days Cycle 1 = 28 days)	Event	Time (Relative To BMS-986179 Infusion) Hour: Min	Serum Samples for BMS-986179 PK	[redacted]	BMS-986179 Immuno-genicity Sample	Nivolumab Immuno-genicity Sample
C4D1	Predose[a]	00:00	X		X	X
C6D15	Predose[a]	00:00	X		X	X
Additional treatment (if applicable) C4D1	Predose[a]	00:00	X		X	X
End of treatment (EOT) and follow-up period (FU)						
EOT			X		X	X
30-day FU			X		X	X
60-day FU			X		X	X
100-day FU			X		X	X

[a] Predose: All predose samples for [redacted] BMS-986179 should be taken prior to the start of nivolumab infusion.

[b] EOI: End of infusion [redacted] BMS-986179 EOI samples should be taken immediately prior to stopping the BMS-986179 infusion (preferably within 2 minutes prior to the EOI). If the infusion is delayed to beyond the normal infusion duration, the collection of this sample should also be delayed accordingly.

[c] EOI is 01:00 h for BMS-986179 dose ≤ 800 mg, and 02:00 h for BMS-986179 dose > 800 mg.

[d] Biopsy sampling: On-treatment biopsy taken at C0D10 ± 1D =D9 to D11 of study. The serum samples should be taken at the time of biopsy sampling or as close as feasible to the biopsy date, and these can be taken together with the serum samples for biomarker testing.

Abbreviations: C = cycle; D = day; EOI = end of infusion.

Table 5.5.1-2: Pharmacokinetic and Immunogenicity Sampling Schedule for BMS-986179 [redacted] (Part 1B Q2W Regimen)

Study Day of Sample Collection (1 Cycle = 28 days)	Event	Time (Relative To BMS-986179 Infusion) Hour: Min	Serum Samples for BMS-986179 PK	[redacted]	BMS-986179 Immuno-genicity Sample	Nivolumab Immuno-genicity Sample
Combination treatment with nivolumab						
C1D1	Predose[a]	00:00	X	[redacted]	X	X
	EOI[b]	01:00/02:00[c]	X			
C1D15	Predose[a]	00:00	X		X	X
C2D14	Biopsy Sampling[d]	Varied 312:00	X			
C2D15	Predose[a]	00:00	X			
	EOI[b]	01:00/02:00[c]	X			
C2D20		120:00	X			
C2D24		216:00	X			
C3D1	Predose[a]	00:00	X			
C4D1	Predose[a]	00:00	X		X	X
C6D15	Predose[a]	00:00	X		X	X
Additional treatment (if applicable) C4D1	Predose[a]	00:00	X		X	X
End of treatment (EOT) and follow-up period (FU)						
EOT			X	[redacted]	X	X
30-day FU			X		X	X
60-day FU			X		X	X
100-day FU			X		X	X

[a] Predose: All predose samples for [redacted] BMS-986179 should be taken prior to the start of nivolumab infusion.

[b] EOI: End of infusion. [redacted] BMS-986179 EOI samples should be taken immediately prior to stopping the BMS-986179 infusion (preferably within 2 minutes prior to the EOI). If the infusion is delayed to beyond the normal infusion duration, the collection of this sample should also be delayed accordingly.

[c] EOI is 01:00 h for BMS-986179 dose ≤ 800 mg, and 02:00 h for BMS-986179 dose > 800 mg.

[d] Biopsy sampling: On-treatment biopsy taken at C2D14 - 5D (D38 to D42) of study The serum samples should be taken at the time of biopsy sampling or as close as feasible to the biopsy date, and these can be taken together with the serum samples for biomarker testing.

Abbreviations: C = cycle; D = day; EOI = end of infusion.

Table 5.5.1-3: Pharmacokinetic and Immunogenicity Sampling Schedule for BMS-986179 [redacted] (Part 1B Q3W Regimen)

Study Day of Sample Collection (1 Cycle = 42 days)	Event	Time (Relative To BMS-986179 Infusion) Hour: Min	Serum Samples for BMS-986179 PK	[redacted]	BMS-986179 Immunogenicity Sample	Nivolumab Immunogenicity Sample
Combination treatment with nivolumab						
C1D1	Predose[a]	00:00	X	[redacted]	X	X
	EOI[b]	01:00/02:00[c]	X			
C1D22	Predose[a]	00:00	X		X	X
C2D1	Predose[a]	00:00	X			
	EOI[b]	01:00/02:00[c]	X			
C2D21	Biopsy Sampling[d]	Varied 480:00	X			
C3D1	Predose[a]	00:00	X		X	X
C4D1	Predose[a]	00:00	X			
C4D22	Predose[a]	00:00	X		X	X
Additional treatment (if applicable) C3D1	Predose[a]	00:00	X		X	X
End of treatment (EOT) and follow-up period (FU)						
EOT			X	[redacted]	X	X
30-day FU			X		X	X
X60-day FU			X		X	X
100-day FU			X		X	X

[a] Predose: All predose samples for [redacted] BMS-986179 should be taken prior to the start of nivolumab infusion.

[b] EOI: [redacted] BMS-986179 EOI samples should be taken immediately prior to stopping the BMS-986179 infusion (preferably within 2 minutes prior to the EOI). If the infusion is delayed to beyond the normal infusion duration, the collection of this sample should also be delayed accordingly.

[c] EOI is 01:00 h for BMS-986179 dose ≤ 800 mg, and 02:00 h for BMS-986179 dose > 800 mg.

[d] Biopsy sampling: On-treatment biopsy taken at C2D21 - 5D (D59 to D63) of study. The serum samples should be taken at the time of biopsy sampling or as close as feasible to the biopsy date, and these can be taken together with the serum samples for biomarker testing.

Abbreviations: C = cycle; D = day; EOI = end of infusion.

Table 5.5.1-4: Pharmacokinetic and Immunogenicity Sampling Schedule for BMS-986179 [redacted] (Re-treatment Q1W Regimen)

Study Day of Sample Collection (1 Cycle = 28 days)	Event	Time (Relative To BMS-986179 Infusion) Hour: Min	Serum Samples for BMS-986179 PK	[redacted]	BMS-986179 Immuno-genicity Sample	Nivolumab Immuno-genicity Sample
Combination treatment with nivolumab						
C1D1	Predose[a]	00:00	X	[redacted]	X	X
C2D15	Predose[a]	00:00	X		X	X
C5D15	Predose[a]	00:00	X		X	X
Additional treatment (if applicable) C4D1	Predose[a]	00:00	X		X	X
End of treatment (EOT) and follow-up period (FU)						
EOT			X	[redacted]	X	X
30-day FU			X		X	X
60-day FU			X		X	X
100-day FU			X		X	X

[a] Predose: All predose samples for [redacted] BMS-986179 should be taken prior to the start of nivolumab infusion.

Abbreviations: C = cycle; D = day.

Table 5.5.1-5: Pharmacokinetic and Immunogenicity Sampling Schedule for BMS-986179 [redacted] (Part 2 Q2W Regimen, Re-treatment Q2W Regimen, and Post-progression Combination Therapy[a] Q2W Regimen)

Study Day of Sample Collection (Cycle 1 = 28 days)	Event	Time (Relative To BMS-986179 Infusion) Hour: Min	Serum Samples for BMS-986179 PK	[redacted]	BMS-986179 Immuno-genicity Sample	Nivolumab Immuno-genicity Sample
Combination treatment with nivolumab						
C1D1	Predose[b]	00:00	X		X	X
C2D1	Predose[b]	00:00	X		X	X
C2D14	Biopsy Sampling[c]	Varied 312:00	X			
C2D15	Predose[b]	00:00	X		X	
C5D15	Predose[b]	00:00	X		X	
Additional treatment (if applicable) C3D1	Predose[a]	00:00	X		X	X
End of treatment (EOT) and follow-up period (FU)						
EOT			X		X	X
30-day FU			X		X	X
60-day FU			X		X	X
100-day FU			X		X	X

[a] BMS-986179 therapy in combination with nivolumab after disease progression on monotherapy

[b] Predose: All predose samples for [redacted] BMS-986179 should be taken prior to the start of nivolumab infusion (preferably within 30 minutes).

[c] PK sample on C2D14 - 5D (D38 to D42) will be collected only for Part 2 Q2W. The samples should be collected on the day of biopsy or as close as feasible to the biopsy date. These samples will not be collected during re-treatment because no biopsy sample collection is required.

Abbreviations: C = cycle; D = day.

Table 5.5.1-6: Pharmacokinetic and Immunogenicity Sampling Schedule for BMS-986179 [redacted] (Part 2 Q3W Regimen, Re-treatment Q3W Regimen, and Post-progression Combination Therapy[a] Q3W Regimen)

Study Day of Sample Collection (Cycle 1 = 42 days)	Event	Time (Relative To BMS-986179 Infusion) Hour: Min	Serum Samples for BMS-986179 PK	[redacted]	BMS-986179 Immuno-genicity Sample	Nivolumab Immuno-genicity Sample
Combination treatment with nivolumab						
C1D1	Predose[b]	00:00	X	[redacted]	X	X
C2D1	Predose[b]	00:00	X	[redacted]	X	X
C2D21	Biopsy Sampling[c]	Varied 480:00	X	[redacted]		
C4D1	Predose[b]	00:00	X	[redacted]	X	X
Additional treatment (if applicable) C3D1	Predose[b]	00:00	X	[redacted]	X	X
End of treatment (EOT) and follow-up period (FU)						
EOT			X	[redacted]	X	X
30-day FU			X	[redacted]	X	X
60-day FU			X	[redacted]	X	X
100-day FU			X	[redacted]	X	X

[a] BMS-986179 therapy in combination with nivolumab after disease progression on monotherapy

[b] Predose: All predose samples for [redacted] BMS-986179 should be taken prior to the start of nivolumab infusion (preferably within 30 minutes).

[c] PK sample on C2D21 - 5D (D59 to D63) will be collected only for Part 2 Q3W. The samples should be collected on the day of biopsy or as close as feasible to the biopsy date. These samples will not be collected because no biopsy sample collection is required during re-treatment.

Abbreviations: C = cycle; D = day.

Table 5.5.1-7: Pharmacokinetic and Immunogenicity Sampling Schedule for BMS-986179 [redacted] (Part 1B or Part 2 Q4W Regimen, Re-treatment Q4W Regimen and Post-progression Combination Therapy[a] Q4W Regimen)

Study Day of Sample Collection (Cycle 1 = 28 days)	Event	Time (Relative To BMS-986179 Infusion) Hour: Min	Serum Samples for BMS-986179 PK	[redacted]	BMS-986179 Immuno-genicity Sample	Nivolumab Immuno-genicity Sample
Combination treatment with nivolumab						
C1D1	Predose[b]	00:00	X	[redacted]	X	X
C2D1	Predose[b]	00:00	X		X	X
C3D1	Biopsy Sampling[c]	Varied	X			
C5D1	Predose[b]	00:00	X		X	X
Additional treatment (if applicable) C4D1	Predose[a]	00:00	X		X	X
End of treatment (EOT) and follow-up period (FU)						
EOT			X	[redacted]	X	X
30-day FU			X		X	X
60-day FU			X		X	X
100-day FU			X		X	X

[a] BMS-986179 therapy in combination with nivolumab after disease progression on monotherapy

[b] Predose: All predose samples for [redacted] BMS-986179 should be taken prior to the start of nivolumab infusion (preferably within 30 minutes).

[c] PK sample on C3D1 - 5D (D51 to D56) will be collected only for Part 2 Q4W. The samples should be collected on the day of biopsy or as close as feasible to the biopsy date. These samples will not be collected if no biopsy sample collection is required during re-treatment.

Abbreviations: C = cycle; D = day.

Table 5.5.1-8: Pharmacokinetic and Immunogenicity Sampling Schedule for BMS-986179 Monotherapy (Part 1B or Part 2 Q2W Regimen)

Study Day of Sample Collection (Cycle 1 = 28 days)	Event	Time (Relative To BMS-986179 Infusion) Hour: Min	Serum Samples for BMS-986179 PK	BMS-986179 Immunogenicity Sample
Monotherapy treatment				
C1D1	Predose[a]	00:00	X	X
C1D1	EOI[b]	01:00/02:00[c]	X	
C1D1		04:00	X	
C1D1		08:00	X	
C1D2		24:00	X	
C1D3 - C1D5		48:00 - 96:00	X	
C1D8		168:00	X	
C1D15	Predose[a]	336	X	
	EOI[b]	01:00/02:00[c]	X	
C2D1	Predose[a]	00:00	X	X
C2D14	Biopsy sampling[d]	Varied	X	
C2D15	Predose[a]	00:00	X	
C3D1	Predose[a]	00:00	X	
C4D1	Predose[a]	00:00	X	X
C4D15	Predose[a]	00:00	X	
C4D15	EOI[b]	01:00/02:00[c]	X	
C4D15		04:00	X	
C4D15		08:00	X	
C4D16		24:00	X	
C4D17 - C4D19		48:00 - 96:00	X	
C4D21		168:00	X	
C5D1	Predose[a]	00:00	X	X
Additional treatment (if applicable) C4D1	Predose[a]	00:00	X	X

Table 5.5.1-8: Pharmacokinetic and Immunogenicity Sampling Schedule for BMS-986179 Monotherapy (Part 1B or Part 2 Q2W Regimen)

Study Day of Sample Collection (Cycle 1 = 28 days)	Event	Time (Relative To BMS-986179 Infusion) Hour: Min	Serum Samples for BMS-986179 PK	BMS-986179 Immunogenicity Sample
End of treatment (EOT) and follow-up period (FU)				
EOT			X	X
30-day FU			X	X
60-day FU			X	X
100-day FU			X	X

[a] Predose: All predose samples for BMS-986179 should be taken prior to the start of infusion (preferably within 30 minutes).

[b] EOI: BMS-986179 EOI samples should be taken immediately prior to stopping the BMS-986179 infusion (preferably within 2 minutes prior to the EOI). If the infusion is delayed to beyond the normal infusion duration, the collection of this sample should also be delayed accordingly.

[c] EOI is 01:00 h for BMS-986179 dose ≤ 800 mg, and 02:00 h for BMS-986179 dose > 800 mg.

[d] Biopsy sampling: On-treatment biopsy taken at C2D14 - 5D (D38 to D42) of study. The serum samples should be taken at the time of biopsy sampling or as close as feasible to the biopsy date, and these can be taken together with the serum samples for biomarker testing.

Abbreviations: C = cycle; D = day; EOI = end of infusion.

Table 5.5.1-9: Pharmacokinetic and Immunogenicity Sampling Schedule for BMS-986179 Monotherapy (Part 1B or Part 2 Q3W Regimen)

Study Day of Sample Collection (Cycle 1 = 42 days)	Event	Time (Relative To BMS-986179 Infusion) Hour: Min	Serum Samples for BMS-986179 PK	BMS-986179 Immunogenicity Sample
Monotherapy treatment				
C1D1	Predose[a]	00:00	X	X
	EOI[b]	01:00/02:00[c]	X	
		04:00	X	
		08:00	X	
C1D2		24:00	X	
C1D3-C1D5		48:00 - 96:00	X	
C1D8		168:00	X	
C1D15		336	X	
C1D22	Predose[a]	00:00	X	X
C2D1	Predose[a]	00:00	X	X
C2D22	Biopsy sampling[d]	Varied	X	
C2D22	Predose[a]	00:00	X	
C3D1	Predose[a]	00:00	X	X
C3D22	Predose[a]	00:00	X	
C3D22	EOI[b]	01:00/02:00[c]	X	
C3D22		04:00	X	
C3D22		08:00	X	
C3D23		24:00	X	
C3D24-C3D26		48:00 - 96:00	X	
C3D29		168.00	X	
C3D36		336.00	X	
C4D1	Predose[a]	00:00	X	X
Additional treatment (if applicable) C3D1	Predose[a]	00:00	X	X

Table 5.5.1-9: Pharmacokinetic and Immunogenicity Sampling Schedule for BMS-986179 Monotherapy (Part 1B or Part 2 Q3W Regimen)

Study Day of Sample Collection (Cycle 1 = 42 days)	Event	Time (Relative To BMS-986179 Infusion) Hour: Min	Serum Samples for BMS-986179 PK	BMS-986179 Immunogenicity Sample
End of treatment (EOT) and follow-up period (FU)				
EOT			X	X
30-day FU			X	X
60-day FU			X	X
100-day FU			X	X

[a] Predose: All predose samples for BMS-986179 should be taken prior to the start of infusion (preferably within 30 minutes).

[b] EOI: BMS-986179 EOI samples should be taken immediately prior to stopping the BMS-986179 infusion (preferably within 2 minutes prior to the EOI). If the infusion is delayed to beyond the normal infusion duration, the collection of this sample should also be delayed accordingly.

[c] EOI is 01:00 h for BMS-986179 dose ≤ 800 mg, and 02:00 h for BMS-986179 dose > 800 mg.

[d] Biopsy sampling: On-treatment biopsy taken at C2D21 - 5D (D59 to D63) of study. The serum samples should be taken at the time of biopsy sampling or as close as feasible to the biopsy date, and these samples can be taken together with the serum samples for biomarker testing.

Abbreviations: C = cycle; D = day; EOI = end of infusion.

Table 5.5.1-10: Pharmacokinetic and Immunogenicity Sampling Schedule for BMS-986179 Monotherapy (Part 1B or Part 2 Q4W IV Regimen)

Study Day of Sample Collection (Cycle 1 = 28 days)	Event	Time (Relative To BMS-986179 Infusion) Hour: Min	Serum Samples for BMS-986179 PK	BMS-986179 Immunogenicity Sample
Monotherapy treatment				
C1D1	Predose[a]	00:00	X	X
C1D1	EOI[b]	01:00/02:00[c]	X	
C1D1		04:00	X	
C1D1		08:00	X	
C1D2		24:00	X	
C1D3-C1D5		48:00 - 96:00	X	
C1D8		168.00	X	
C1D15		336	X	
C1D21		504	X	
C2D1	Predose[a]	00:00	X	X
C3D1	Biopsy sampling[d]	Varied	X	
C3D1	Predose[a]	00:00	X	
C4D1	Predose[a]	00:00	X	X
C5D1	Predose[a]	00:00	X	
C5D1	EOI[b]	01:00/02:00[c]	X	
C5D1		04:00	X	
C5D1		08:00	X	
C5D2		24:00	X	
C5D3-C5D5		48:00 - 96:00	X	
C5D8		168:00	X	
C5D15		336	X	
C5D21		504	X	
C6D1	Predose[a]	00:00	X	X
Additional treatment (if applicable) C4D1	Predose[a]	00:00	X	X

Table 5.5.1-10: Pharmacokinetic and Immunogenicity Sampling Schedule for BMS-986179 Monotherapy (Part 1B or Part 2 Q4W IV Regimen)

Study Day of Sample Collection (Cycle 1 = 28 days)	Event	Time (Relative To BMS-986179 Infusion) Hour: Min	Serum Samples for BMS-986179 PK	BMS-986179 Immunogenicity Sample
End of treatment (EOT) and follow-up period (FU)				
EOT			X	X
30-day FU			X	X
60-day FU			X	X
100-day FU			X	X

[a] Predose: All predose samples for BMS-986179 should be taken prior to the start of infusion (preferably within 30 minutes).

[b] EOI: BMS-986179 EOI samples should be taken immediately prior to stopping the BMS-986179 infusion (preferably within 2 minutes prior to the EOI). If the infusion is delayed to beyond the normal infusion duration, the collection of this sample should also be delayed accordingly.

[c] EOI is 01:00 h for BMS-986179 dose ≤ 800 mg, and 02:00 h for BMS-986179 dose > 800 mg.

[d] Biopsy sampling: On-treatment biopsy taken at C3D1 - 5D (D51 to D56) of study. The serum samples should be taken at the time of biopsy sampling or as close as feasible to the biopsy date, and these can be taken together with the serum samples for biomarker testing.

Abbreviations: C = cycle; D = day; EOI = end of infusion.

[redacted]

[redacted]

[redacted]

5.5.2 Pharmacokinetic Sample Analyses

The serum samples will be analyzed for BMS-986179 [redacted] by a validated assay.

5.5.3 Labeling and Shipping of Biological Samples

Detailed instructions for biological sample collection, labeling, processing, storage, and shipping will be provided to the site in the procedure manual.

5.6 Biomarker Assessments

Blood and tumor biopsies will be collected at the times indicated in Table 5.6-1 through Table 5.6-9 for the measurement of biomarkers relevant to dose selection, mechanism of action, and prediction of clinical benefit. If relevant biomarker data is available from existing samples at sites (EGFR/KRAS mutations, HPV, microsatellite instability, etc.), sponsor may request details. Further details of blood and tumor biopsy collection and processing will be provided to the site in the procedure manual.

Table 5.6-1: BMS-986179 Plus Nivolumab Dose Escalation Biomarker Sampling Schedule (Part 1A Q1W Regimen with Monotherapy Lead-in)

Study Day	Time (Event) Hour	Time (Relative to Dosing) Hour: Min	PD Serum	PD Tumor Biopsy	[redacted]
C0D1	0 (predose)	00:00	X	X[a]	
C0D1	6	06:00	X		
C0D2	0 (predose)	00:00	X		
C0D8	0 (predose)	00:00	X		
C0D10			X[b]	X[b]	
C1D1	0 (predose)	00:00	X		
C2D1	0 (predose)	00:00	X		
C3D1	0 (predose)	00:00	X		
Unscheduled/EOT/ at progression[c]			X[c]	X[c]	

[a] This is the same mandatory pre-treatment biopsy as the fresh pre-treatment tumor biopsy listed in Table 5.1-1. May be collected at any time during screening or on C0D1 prior to study drug administration.

[b] Ontreatment- biopsy taken at C0D10 ± 1D =D9 to D11 of study. [redacted] PD serum samples to be collected on the day of biopsy or as close as feasible to the biopsy date.

[c] Unscheduled visit included to allow for biopsy and mandatory biomarker sample collection during re-treatment or at progression. Biomarker samples are required even if tumor biopsy is not collected. If tumor biopsy is collected, PD serum [redacted] samples should be collected on the same day or as close as feasible to the biopsy date.

Abbreviations: [redacted] EOT = end of treatment.

Table 5.6-2: BMS-986179 Plus Nivolumab PD Sub-study Biomarker Sampling Schedule (Part 1B Q2W Regimen)

Study Day	Time (Event) Hour	Time (Relative to Dosing) Hour: Min	PD Serum	PD Tumor Biopsy	[redacted]
C1D1	0 (predose)	00:00	X	X[a]	
C2D1	0 (predose)	00:00	X		
C2D14			X[b]	X[b]	
C3D1	0 (predose)	00:00	X		
Unscheduled/EOT / at progression[c]			X[c]	X[c]	

[a] This is the same mandatory pre-treatment biopsy as the fresh pre-treatment tumor biopsy listed in Table 5.1-1. May be collected at any time during screening or on C1D1 prior to study drug administration.

[b] On-treatment biopsy taken at C2D14 - 5D (D38 to D42) of study. [redacted] PD serum samples to be collected on the day of biopsy or as close as feasible to the biopsy date.

[c] Unscheduled visit included to allow for biopsy and mandatory biomarker sample collection during re-treatment or at progression. Biomarker samples are required even if tumor biopsy is not collected. If tumor biopsy is collected, PD serum [redacted] samples should be collected on the same day or as close as feasible to the biopsy date.

Abbreviations: [redacted] EOT = end of treatment.

Table 5.6-3: BMS-986179 Plus Nivolumab PD Sub-study Biomarker Sampling Schedule (Part 1B Q3W Regimen)

Study Day	Time (Event) Hour	Time (Relative to Dosing) Hour: Min	PD Serum	PD Tumor Biopsy	[redacted]
C1D1	0 (predose)	00:00	X	X[a]	
C2D1	0 (predose)	00:00	X		
C2D21			X[b]	X[b]	
C3D1	0 (predose)	00:00	X		
Unscheduled/EOT /at progression[c]			X[c]	X[c]	

[a] This is the same mandatory pre-treatment biopsy as the fresh pre-treatment tumor biopsy listed in Table 5.1-1. May be collected at any time during screening or on C1D1 prior to study drug administration.

[b] On-treatment biopsy taken at C2D21-5D (D59 to D63) of study. [redacted] PD serum samples to be collected on the day of biopsy or as close as feasible to the biopsy date.

[c] Unscheduled visit included to allow for biopsy and mandatory biomarker samples collection during re-treatment or at progression. Biomarker samples are required even if tumor biopsy is not collected. If tumor biopsy is collected, PD serum [redacted] samples should be collected on the same day or as close as feasible to the biopsy date.

Abbreviations: [redacted] EOT = end of treatment.

Table 5.6-4: BMS-986719 Monotherapy or BMS-986179 Plus Nivolumab Cohort Expansion Biomarker Sampling Schedule (Part 2 Q2W Regimen)

Study Day	Time (Event) Hour	Time (Relative to Dosing) Hour: Min	PD Serum	[redacted]	PD Tumor Biopsy	[redacted]
C1D1	0 (predose)	00:00	X		X[a]	
C2D1	0 (predose)	00:00	X			
C2D14			X[b]		X[b]	
C3D1	0 (predose)	00:00	X			
Unscheduled/ EOT/at progression[c]			X[c]		X[c]	

[a] This is the same mandatory pre-treatment biopsy as the fresh pre-treatment tumor biopsy listed in Table 5.1-1. May be collected at any time during screening or on C1D1 prior to study drug administration.

[b] On-treatment biopsy taken at C2D14 - 5D (D38 to D42) of study. [redacted] PD serum [redacted] samples to be collected on the day of biopsy or as close as feasible to the biopsy date.

[c] Unscheduled visit included to allow for biopsy and mandatory biomarker sample collection during re-treatment or at progression. Biomarker samples are required even if tumor biopsy is not collected. If tumor biopsy is collected, PD serum [redacted] samples should be collected on the same day or as close as feasible to the biopsy date.

[redacted]

Abbreviations: [redacted] EOT = end of treatment.

Table 5.6-5: BMS-986719 Monotherapy or BMS-986179 Plus Nivolumab Cohort Expansion Biomarker Sampling Schedule (Part 2 Q3W Regimen)

Study Day	Time (Event) Hour	Time (Relative to Dosing) Hour: Min	PD Serum	[redacted]	PD Tumor Biopsy	[redacted]
C1D1	0 (predose)	00:00	X		X[a]	
C2D1	0 (predose)	00:00	X			
C2D21			X[b]		X[b]	
C3D1	0 (predose)	00:00	X			
Unscheduled/EOT/at progression[c]			X[c]		X[c]	

[a] This is the same mandatory pre-treatment biopsy as the fresh pre-treatment tumor biopsy listed in Table 5.1-1. May be collected at any time during screening or on C1D1 prior to study drug administration.

[b] On-treatment biopsy taken at C2D21 - 5D (D59 to D63) of study. [redacted] PD serum [redacted] samples to be collected on the day of biopsy or as close as feasible to the biopsy date.

[c] Unscheduled visit included to allow for biopsy and mandatory biomarker samples collection during re-treatment or at progression. Biomarker samples are required even if tumor biopsy is not collected. If tumor biopsy is collected, PD serum [redacted] samples should be collected on the same day or as close as feasible to the biopsy date.

[redacted]

Abbreviations: [redacted] EOT = end of treatment.

Table 5.6-6: BMS-986719 Monotherapy or BMS-986179 Plus Nivolumab Cohort Expansion Biomarker Sampling Schedule (Part 1B or Part 2 Q4W Regimen)

Study Day	Time (Event) Hour	Time (Relative to Dosing) Hour: Min	PD Serum	[redacted]	PD Tumor Biopsy	[redacted]
C1D1	0 (predose)	00:00	X		X[a]	
C2D1	0 (predose)	00:00	X			
C3D1	0 (predose)	0	X[b]		X[b]	
C4D1 to C5D1	0 (predose)	00:00	X[c]			
Unscheduled /EOT/at progression[c]			X[d]		X[d]	

[a] This is the same mandatory pre-treatment biopsy as the fresh pre-treatment tumor biopsy listed in Table 5.1-1. May be collected at any time during screening or on C1D1 prior to study drug administration.

[b] On-treatment biopsy taken at C3D1 - 5D (D51 to D56) of study. [redacted] PD serum [redacted] samples to be collected on the day of biopsy or as close as feasible to the biopsy date.

[c] Mandatory biomarker sample collection at C4D21 - 4D and C5D1 -4D (D80-84 and D108-112) of study: PD serum [redacted] samples.

[d] Unscheduled visit included to allow for biopsy and mandatory biomarker sample collection during re-treatment or at progression. Biomarker samples are required even if tumor biopsy is not collected. If tumor biopsy is collected, PD serum [redacted] samples should be collected on the same day or as close as feasible to the biopsy date.

[redacted]

Abbreviations: [redacted] EOT = end of treatment.

Table 5.6-7: BMS-986179 Plus Nivolumab Biomarker Sampling Schedule (Re-treatment Part 1A Q1W Regimen)

Re-treatment Study Day	Time (Event) Hour	Time (Relative to Dosing) Hour:Min	PD Serum	PD Tumor Biopsy	[redacted]
Re-treatment C1D1	0 (predose)	00:00	X		
Re-treatment C3D1	0 (predose)	00:00	X		
Unscheduled/EOT/at progression (optional)[a]			X[a]	X[a]	

[a] One tumor biopsy can be collected any time pre, during, or post re-treatment. Unscheduled visit included to allow for biopsy and mandatory biomarker sample collection. Biomarker samples are required even if tumor biopsy is not collected. If tumor biopsy is collected, PD serum [redacted] samples should be collected on the same day or as close as feasible to the biopsy date.

Abbreviations: EOT = end of treatment.

Table 5.6-8: BMS-986179 Plus Nivolumab Biomarker Sampling Schedule (Re-treatment for Parts 1B and 2 Q2W Regimen)

Re-treatment Study Day	Time (Event) Hour	Time (Relative to Dosing) Hour: Min	PD Serum	[redacted]	PD Tumor Biopsy	[redacted]
Re-treatment C1D1	0 (predose)	00:00	X			
Re-treatment C2D1	0 (predose)	00:00	X			
Re-treatment C3D1	0 (predose)	00:00	X			
Unscheduled/EOT/at progression (optional) [b]			X[b]		X[b]	

[redacted]

[b] One tumor biopsy can be collected any time pre, during, or post re-treatment. Unscheduled visit included to allow for biopsy and mandatory biomarker sample collection. Biomarker samples are required even if tumor biopsy is not collected. If tumor biopsy is collected, PD serum [redacted] samples should be collected on the same day or as close as feasible to the biopsy date.

[redacted]

Abbreviations: [redacted] EOT = end of treatment.

Table 5.6-9: BMS-986179 Plus Nivolumab Biomarker Sampling Schedule (Re-treatment for Parts 1B and 2 Q3W Regimen)

Re-treatment Study Day	Time (Event) Hour	Time (Relative to Dosing) Hour: Min	PD Serum	[redacted]	PD Tumor Biopsy	[redacted]
Re-treatment C1D1	0 (predose)	00:00	X			
Re-treatment C3D1	0 (predose)	00:00	X			
Unscheduled/EOT/at progression (optional)[b]			X[b]		X[b]	

[redacted]

[b] One tumor biopsy can be collected any time pre, during, or post re-treatment. Unscheduled visit included to allow for biopsy and mandatory biomarker sample collection. Biomarker samples are required even if tumor biopsy is not collected. If tumor biopsy is collected, PD serum [redacted] samples should be collected on the same day or as close as feasible to the biopsy date.

[redacted]

Abbreviations: [redacted] EOT = end of treatment.

5.7 Exploratory Biomarker Assessments

[redacted]

[redacted]

5.7.2 Tissue Markers from Fresh Tumor Biopsies

Tracking changes in biomarkers measured in tumor tissue during treatment is instrumental to determining the mechanisms of action of cancer therapeutics. To monitor the presence (or absence) of infiltrating lymphocytes and to track other molecular changes within tumors in response to CD73 inhibition in combination with nivolumab, tumor biopsies will be collected as outlined in Table 5.6-1 through Table 5.6-9. **All subjects must have soft-tissue tumor lesions that can be biopsied or collected via core needle at acceptable clinical risk (as judged by the investigator) at baseline (pre-treatment). On-treatment biopsies at time points as indicated in Table 5.6-1 through Table 5.6-6 are required for all subjects.** On-treatment biopsies in the re-treatment phase or additional 80-week treatment phase may be collected as indicated in Table 5.6-6 through Table 5.6-9. Please notify the BMS Medical Monitor if biopsy on-treatment may pose unacceptable clinical risk or if the tumor at the time of on-treatment biopsy is not accessible for sampling.

A third optional biopsy specimen may be collected (for subjects in Part 1B or 2 only) at the time of disease progression or during another clinically meaningful event (eg, response or AE).

Biopsies may be excisional, incisional, or core needle. Biopsies from previously irradiated lesions are only suitable if they subsequently progressed. Baseline samples may be obtained at any time following other screening procedures and prior to the first dose of the study drug. Archival specimens may not be substituted for fresh, baseline specimens. On-treatment specimens may be obtained within a collection window of ± 1 day for Part 1A or ± 2 days for Parts 1B and 2. Participating subjects must consent to biopsy procedures.

As described previously, complete instructions on the collection, processing, handling, and shipment of all biomarker specimens will be provided in a separate procedure manual. Please refer to this manual for information pertaining to the collection and processing of tissue via biopsy or core needle. Collection procedures at baseline and on-treatment (and at progression) should be completed on a single, appropriately assessable lesion, when applicable. In the case that the lesion sampled at baseline is no longer accessible or within acceptable clinical risk to re-biopsy during study, tissue from alternative lesion(s) may be obtained. This should be documented. Immediate confirmation for presence of viable tumor cells from collected tissue samples is strongly

recommended. If adequate tissue is not obtained following initial passages of the needle, repeat passages may be completed.

Subjects whose baseline or on-treatment biopsy yields inadequate tissue quantity or quality (lack of tumor) will be allowed to continue in the study and participate in the other biomarker assay collections (eg, blood collections) described in Table 5.6-1 through Table 5.6-9. Tumor tissue will be analyzed as described below. If tissue obtained from a large proportion of subjects is deemed inadequate for testing (eg, possesses low tumor cell content), additional subjects may be enrolled in an attempt to obtain tissue specimens better-suited for testing.

[redacted]

5.7.2.2 Protein Expression [redacted]

First core of each biopsy specimen will be fresh frozen and used to measure CD73 enzyme activity. Second core of each biopsy specimen will be formalin fixed, paraffin embedded, and analyzed by IHC or RNAscope to determine the expression of CD73 and to assess abundance of immunoregulatory proteins present at the tumor site. Such analyses may reflect the presence of tumor-infiltrating immune cells or the expression of immunoregulatory proteins by the tumor and/or surrounding stroma. Analytes may include, but are not limited to [redacted] CD4, CD8, [redacted] and PD-L1. [redacted]

[redacted] PD changes in the presence or abundance of immunoregulatory (listed above) and other proteins such as but not limited A2AR [redacted] and CD39 will be sought. [redacted]

5.7.3 Tissue Markers from Archived Tumor Samples

In addition to fresh tumor biopsy as described above, an archival, formalin-fixed, paraffin-embedded tumor tissue block or 15 to 20 unstained sections from the archival tissue block are required for all subjects, if available. For tracking purposes, the availability of the tissue must be confirmed and the tissue shipped to a central laboratory as soon as possible after signing the consent. Molecular characterization of archival specimens will be similar to the characterizations described above but is likely to focus on the expression of PD-L1 and/or CD73 as candidate markers associated with response to combination therapy. [redacted]

5.8 Outcomes Research Assessments

Not applicable.

5.9 Other Assessments

Not applicable.

[redacted]

6 ADVERSE EVENTS

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a clinical investigation subject administered study drug and that

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

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The causal relationship can be one of the following:

Related: There is a reasonable causal relationship between study drug administration and the AE.

Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

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

BMS will be reporting adverse events to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/EC and FDA Code of Federal Regulations 21 CFR Parts 312 and 320.

6.1 Serious Adverse Events

A ***Serious Adverse Event (SAE)*** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject 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)
- 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 subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization.) pDILI is also considered an important medical event. (See Section 6.6 for the definition of pDILI.)

Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy, overdose, cancer, and pDILI are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 6.1.1 for reporting pregnancies).

Any component of a study endpoint that is considered related to study drug (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported) should be reported as an SAE (see Section 6.1.1 for reporting details.

NOTE:

The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)
- admission for administration of anti-cancer therapy in the absence of any other SAEs (applies to oncology protocols)

6.1.1 Serious Adverse Event Collection and Reporting

Section 5.6.1 and Section 5.6.2 in the IB represent the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting. Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 100 days of discontinuation of dosing.

The investigator must report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure.

An SAE report must be completed for any event where doubt exists regarding its seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship must be specified in the narrative section of the SAE Report Form.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS or designee within 24 hours of awareness of the event. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). The preferred method for SAE data reporting collection is through the electronic CRF (eCRF). The paper SAE/pregnancy surveillance forms are only intended as a back-up option when the eCRF system

is not functioning. In this case, the paper forms are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

For studies capturing SAEs through electronic data capture (EDC), electronic submission is the required method for reporting. In the event the electronic system is unavailable for transmission, paper forms must be used and submitted immediately. When paper forms are used, the original paper forms are to remain on site

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

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

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

All SAEs must be followed to resolution or stabilization.

6.2 Nonserious Adverse Events

A ***nonserious adverse event*** is an AE not classified as serious adverse event.

6.2.1 Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 6.1.1). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic).

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

For subjects receiving study treatment, all nonserious AEs (not only those deemed to be treatmentrelated-) should be collected continuously during the treatment period and for a minimum of 100 days following discontinuation of study treatment.

Every AE must be assessed by the investigator with regard to whether it is considered immunemediated-. For AEs that are potentially immunemediated-, additional information will be collected on the subject's CRF.

6.3 Laboratory Test Result Abnormalities

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

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

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

6.4 Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half-lives after product administration, the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to the BMS designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Section 6.1.1.

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

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

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

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

6.5 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section 6.1.1 for reporting details.).

6.6 Potential Drug Induced Liver Injury

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a pDILI event. All occurrences of pDILIs, meeting the defined criteria, must be reported as SAEs (see Section 6.1.1 for reporting details).

Potential drug induced liver injury is defined as:

1) Aminotransaminases (ALT or AST) elevation > 3 times ULN if liver chemistries are normal at baseline; if liver chemistries are abnormal at baseline, then > 2 × baseline values or any value > 8 × ULN should be used as cutoffs

   AND

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

   AND

3) No other immediately apparent possible causes of aminotransaminase 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.

6.7 Other Safety Considerations

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

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

Not applicable.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

8.1.1 Part 1A (Dose Escalation)

As a Phase 1 dose-escalation trial, the sample size at each dose depends on observed toxicity and posterior inference. For BMS-986179 in combination with nivolumab (with BMS-986179 monotherapy lead-in), approximately 30 to 60 subjects are expected to be treated during the dose-escalation period. Initially, approximately 3 subjects will be treated at the starting dose levels of BMS-986179 and then in combination with nivolumab. Due to the potential for early discontinuation, additional subjects may be enrolled at the current dose level, before the initially enrolled subjects have completed the [redacted] period, to ensure 3 evaluable subjects at each dose level. Additional subjects will be treated in recommended dose levels per BLRM (-Copula) model during the dose escalation period (see Appendix 4). [redacted]

Additional subjects (up to 12 in total) may be treated at any dose level at or below the estimated MTD/recommended dose for further evaluation of safety and PD/PK parameters as needed.

8.1.2 Part 1B (PD Substudy)

Total 6 regimen cohorts will be included in Part 1B with approximately 10 subjects each except for the subcutaneous with approximately 16 subjects.

To assess the PD effects of BMS-986179-nivolumab combination as stated in the secondary objective, pre- and on-treatment whole blood samples, serum samples, and tumor biopsies will be required. It is of interest to ensure the precision of the estimate of the ratio of on-treatment biomarker assessments to pre-treatment (baseline) levels. Assuming that a biomarker is measured as a continuous variable, a given number of subjects per treatment arm will provide the confidence that the estimate of the ratio of on-treatment to baseline values will be within 20% of the true value, as shown in Table 8.1.2-1.

Table 8.1.2-1: Probability That Estimated Ratio of On-treatment to Pre-treatment (Baseline) Value Is Within 20% of True Value

Intra-subject Standard Deviation (Log-scale)		0.2	0.3	0.4	0.5	0.6	0.7	0.8
Probability	N = 6	92%	75%	61%	52%	44%	38%	34%
	N = 7	94%	79%	65%	55%	47%	41%	36%
	N=8	96%	82%	68%	58%	50%	44%	39%
	N = 9	97%	84%	71%	61%	53%	46%	41%
	N = 10	97%	86%	74%	63%	55%	48%	43%

For example, for a biomarker [redacted] with an intra-subject standard deviation of 0.3 (second column above), if the true ratio of post-baseline to baseline geometric means is 1.2 (increase from baseline is 20%), there is 75% probability that the estimated ratio would be within 0.96 and 1.44 (or a percent change between -4% and 44%) with 6 subjects per treatment arm. If the true increase from baseline is 60%, for a biomarker with the same variability, then there is 75% probability that the estimated percent increase would be between 28% and 92% with 6 subjects per treatment arm. To account for potential missing data, approximately 10 subjects will be dosed for each of the arms except for the subcutaneous dosing arm.

Sample size calculations for the subcutaneous dosing arm are based on width of the confidence interval for the geometric mean ratio (GMR) of exposures for IV and SC dosing. The PK parameters are assumed to be distributed log-normally, with an inter-subject coefficient of variation of 50-60%, and an intra-subject correlation of the logged values of 0.5 - 0.6. With 14 subjects, the lower bounds for the 90% CI range from 77% - 82% of the point estimate for the GMR and the upper bounds for the 90% CI range from 122% - 130% of the point estimate. To account for potential missing data, approximately 16 subjects will be dosed.

8.1.3 Part 2 (Cohort Expansion)

Subjects diagnosed with NSCLC or RCC whose disease has progressed during or after prior anti-PD-(L)1 therapy will be enrolled in cohorts to be administered either BMS-986179 as monotherapy or BMS-986179 in combination with nivolumab in the cohort expansion phase, as described in Table 8.1.3-1. If both monotherapy and combination therapy cohorts are open, assignments within a particular disease type will be made in an alternating manner.

Subjects diagnosed with SCCHN or melanoma who have progressed on prior anti-PD-(L)1 therapy as their most recent therapy will be enrolled in cohorts to be administered BMS-986179 in combination with nivolumab. Subjects diagnosed with CRPC will also be enrolled in a cohorts to be administered BMS-986179 in combination with nivolumab.

A Simon 2-stage (optimal) design will be employed to evaluate initial efficacy across treatment arms within tumor type cohorts receiving BMS-986179 as monotherapy and in combination with nivolumab in these subjects. The total sample size for each expansion cohort will be calculated to provide a reasonable false positive rate (FPR) (≤ 10%) and false negative rate (FNR) (≤ 10%), based on assumptions of true (target) and historic ORR for each indication. The sample size and operational characteristics of using a Simon 2-stage design are provided in Table 8.1.3-1. While this design includes hypothesis testing with decision rules, the decision to proceed to Stage 2 in a cohort will be based on the totality of available data, in consultation with study investigators.

Table 8.1.3-1: Cohort Expansion: Characteristics of the Simon 2-stage Design for Selected NSCLC, RCC, SCCHN, CRPC and Melanoma Cohorts

Expansion Cohort	Treatment Arm	Historic ORR (%)	Target ORR (%)	Stage 1/ Total N	Stage 1/ Overall Responses Futility Boundaries[a]	FPR/ (1-FNR) (%)	Probability of Early Stopping (%)
NSCLC Post-PD-(L)1 Therapy[b,c]	Mono	1	15	15/33	1/2	10/90	86
NSCLC Post-PD-(L)1 Therapy[b,c]	Combo	1	15	15/33	1/2	10/90	86
RCC Post-PD-(L)1 Therapy[b]	Mono	1	15	15/33	1/2	10/90	86
RCC Post-PD-(L)1 Therapy[b]	Combo	1	15	15/33	1/2	10/90	86
Melanoma Post-PD-(L)1 Therapy[d]	Combo	1	15	15/33	1/2	10/90	86

Table 8.1.3-1: Cohort Expansion: Characteristics of the Simon 2-stage Design for Selected NSCLC, RCC, SCCHN, CRPC and Melanoma Cohorts

Expansion Cohort	Treatment Arm	Historic ORR (%)	Target ORR (%)	Stage 1/ Total N	Stage 1/ Overall Responses Futility Boundaries[a]	FPR/ (1-FNR) (%)	Probability of Early Stopping (%)
SCCHN Post-PD-(L)1 Therapy	Combo	1	15	15/33	1/2	10/90	86
CRPC	Combo	4	20	12/29	1/3	10/90	61

[a] Minimum responder count at end of first and second stage to determine treatment is promising, based on historical and target rates, and FPR and (1-FNR).

[b] Progression following prior anti-PD-(L)1 therapy and expected response rates.

[c] Includes EGFR-mutant and/or KRAS-mutant expressors. Enrollment may be extended to include an adequate number (eg. approximately 10) of subjects with mutant expressions of each type in this cohort.

[d] Includes BRAF- and/or NRAS-mutant expressors. Enrollment may be extended to include an adequate number (eg. approximately 10) of subjects with mutant expressions of each type in this cohort.

Abbreviation: CI = confidence interval; Combo = BMS-986179 in combination with nivolumab; Mono = BMS-986179 monotherapy until disease progression; NSCLC = non-small cell lung cancer; RCC = renal cell carcinoma; CRPC = castrate-resistant prostate carcinoma.

The probability of early stopping is based on the true but unknown probability of response in the cohort being evaluated. Subject to the constraints imposed by the error rates (FPR, FNR), and considering the historic ORR to be the best estimate of the probability of response in the population of subjects with the identified tumor type, the probability of early stopping describes the likelihood of failing to observe a responder count that exceeds the Stage 1 futility boundary. The number of subjects receiving treatment at the time of Stage 1 efficacy evaluation is approximate and may exceed the specified minimum number of subjects due to unknown time of response and recruitment.

Additionally, subjects with pancreatic adenocarcinoma will receive BMS-986179 in combination with nivolumab in a single-stage expansion phase design. The total sample size for each expansion cohort will be calculated to provide a reasonable FPR (≤ 10%) and FNR (≤ 13%) based on the assumptions of true (target) ORR and historic ORR for each indication. The sample size and operational characteristics of using a single-stage design are provided in Table 8.1.3-2. Approximately 227 and 19 subjects will be treated using the Simon 2stage (optimal) design or a single-stage design, respectively.

Table 8.1.3-2: Cohort Expansion: Characteristics of the Single-stage Design[a] for Pancreatic Adenocarcinoma

Expansion Cohort	Historic ORR (%)	Target ORR (%)	Total N	FPR/(1-FNR) (%)
Pancreatic adenocarcinoma	8	30	19/4	6/87

[a] All subjects received BMS-986179 therapy in combination with nivolumab.
Abbreviations: FNR = false negative rate; FPR = false positive rate; ORR=objective response rate

Should fewer than 10 subjects with each drivermarker- expression be enrolled in study cohorts, additional markerdriven- enrollment may be permitted. Mutational marker, efficacy, and safety results from these cohorts will guide later subject enrollment, planning/operations, and sponsor decision-making.

8.2 Populations for Analyses

- All enrolled: All subjects who have provided an ICF
- All treated: All subjects who received at least 1 dose of any study medication
- Pharmacokinetic: All subjects who received at least 1 dose of BMS-986179 (as monotherapy or in combination with nivolumab) or nivolumab and have evaluable serum concentration-time data
- Immunogenicity: All treated subjects with BMS-986179 or nivolumab who have baseline and at least 1 post-baseline pre-infusion immunogenicity assessment
- Biomarker: All treated subjects with available biomarker data
- Response Evaluable: All treated subjects who have baseline tumor measurement(s) and at least 1 other tumor measurement after treatment, or clinical progression, or death prior to the first planned on-treatment tumor assessment
- Safety: The "All Treated" analysis population

All available data from subjects who receive BMS-986179 as monotherapy and in combination with nivolumab and who have a sufficient number of serum specimens available will be included in the BMS-986179 PK analysis population. [redacted]

8.3 Endpoints

8.3.1 Primary Endpoints

The primary objective of the study is to assess the safety and tolerability of BMS-986179 administered alone and in combination with nivolumab. The assessment of safety will be based on the incidence of AEs, SAEs, AEs leading to discontinuation, and deaths in relation to initial treatment. In addition, clinical laboratory test abnormalities will be examined.

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

8.3.2 Secondary Endpoints

8.3.2.1 Pharmacodynamics

The first secondary objective (PD effect of CD73 inhibition) will be measured by CD73 enzyme assays and CD73 IHC in pre- and on-treatment tumor biopsies.

8.3.2.2 Efficacy

The anti-tumor activity of BMS-986179 as monotherapy and in combination with nivolumab will be measured by ORR, DOR, and PFSR at 24 weeks and will be based on RECIST 1.1 for solid tumors. [redacted]

Under RECIST v1.1 the following definitions apply:

- Best overall response (BOR) is defined as the best response designation over the study as a whole, recorded between the dates of first dose until the last tumor assessment prior to subsequent therapy. CR or PR determinations included in the BOR assessment must be confirmed by a second scan performed no less than 4 weeks after the criteria for response are first met. For those subjects who received re-treatment, re-treatment will be considered as subsequent therapy.
- ORR is defined as the proportion of all treated subjects whose BOR is either a CR or PR.
- DOR (computed for all treated subjects with a BOR of CR or PR) is defined as the time between the date of first response and the date of disease progression or death, whichever occurs first.
- PFSR at 24 weeks is defined as the proportion of treated subjects remaining progression free and surviving at 24 weeks. The proportion will be calculated by the Kaplan-Meier estimate, which takes into account censored data. [redacted]

8.3.2.3 Pharmacokinetics and Immunogenicity

The PK will be characterized by assessment of PK parameters of BMS-986179 as listed in Section 5.5.1, and immunogenicity will be assessed by the frequency of positive ADA to BMS-986179 [redacted]

[redacted]

8.4 Analyses

8.4.1 Demographics and Baseline Characteristics

Frequency distributions of gender and race will be tabulated. Summary statistics for age, body weight, height, and body mass index will be tabulated.

8.4.2 Efficacy Analyses

A listing of tumor measurements will be provided by subject and study day in each dose level. Individual subjects' BOR will be listed based on RECIST 1.1 for solid tumor.

To describe the anti-tumor activity of BMS-986179 in monotherapy or in combination with nivolumab, ORR will be calculated. ORR and corresponding 2-sided exact 95% exact CI by the Clopper-Pearson method will be provided by treatment, and/or dose level, and tumor type. Median DOR and corresponding 2-sided 95% CI will be reported by treatment, and/or dose level and tumor type. DOR will be analyzed using the Kaplan-Meier method.

In addition, PFSR, the probabilities of a subject remaining progression free and surviving to 24 weeks, will be estimated by the Kaplan-Meier methodology, by treatment, tumor type, prior PD-(L)1 exposure status, and dose level. The corresponding 95% CIs will be derived based on the Greenwood formula.

[redacted]

Subjects treated in monotherapy cohorts who receive combination therapy upon progression will be considered failures for purposes of initial efficacy assessment.

Additional details will be provided in the Statistical Analysis Plan.

8.4.3 Safety Analyses

All recorded AEs will be listed and tabulated by system organ class, preferred term, treatment arm, and dose level and coded according to the most current version of MedDRA. Vital signs, electrocardiograms, ECOG performance status, and clinical laboratory test results will be listed and summarized by treatment. Safety events will be summarized overall and within monotherapy and combined therapy settings as appropriate.

Any significant PE findings and clinical laboratory results will be listed.

8.4.4 Pharmacokinetic Analyses

All individual PK parameters for BMS-986179 will be listed including any exclusions and reasons for exclusion from summaries. Summary statistics will be tabulated for each PK parameter, if feasible, and wherever applicable, by treatment and dosing regimen. Geometric means and coefficients of variation will be presented for Cmax, Ctrough, Ctau, AUC(0-T), AUC(TAU), AUC(INF), CLT, [redacted] Vz, and Vss after single or multiple dose PK. Medians and

ranges will be presented for Tmax. Means and standard deviations will be presented for all other PK parameters, such as T-HALF, T-HALFeff, DF, and AI.

BMS-986179 dose dependency will be accessed in Part 1A. To describe the dependency on dose of BMS-986179, scatter plots of Cmax, AUC(0-T), and AUC(TAU) versus dose may be provided for each day measured. [redacted]

[redacted]

8.4.5 Biomarker Analyses

Summary statistics for biomarkers and their corresponding changes (or percent changes) from baseline will be tabulated by planned study day and dose in each arm. The time course of biomarker measures will be investigated graphically. If there is indication of a meaningful pattern over time, further analysis (eg, by linear mixed model) may be performed to characterize the relationship. Methods such as, but not limited to, logistic regression will be used to explore possible associations between biomarker measures from peripheral blood or tumor biopsy and clinical outcomes.

[redacted]

8.4.7 Outcomes Research Analyses

Not applicable.

8.4.8 Other Analyses

8.4.8.1 Immunogenicity Analyses

A listing of all available immunogenicity data (BMS-986179 and nivolumab) will be provided by treatment, dose, and immunogenicity status. The frequency of subjects with a baseline and/or at least 1 positive ADA assessment of BMS-986179 and nivolumab or BMS-986179 will be summarized. [redacted]

8.5 Interim Analyses

Interim analysis for internal decision making or external publication purposes may be performed. No formal inferences requiring any adjustment to statistical significance level will be performed.

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, BMS. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects.

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

- IRB/IEC for review and approval/favorable opinion
- BMS
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to BMS.

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

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

9.1.2 Monitoring

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

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

In addition, the study may be evaluated by BMS 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 BMS.

9.1.2.1 Source Documentation

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.

9.1.3 Investigational Site Training

Bristol-Myers Squibb will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent, and enrollment of WOCBP.

9.2 Records

9.2.1 Records Retention

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS, whichever is longer. The investigator must contact BMS prior to destroying any records associated with the study and BMS will notify the investigator 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, IRB). Notice of such transfer will be given in writing to BMS.

9.2.2 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of study drug (inventoried and dispensed) is maintained at the study site to include the following investigational product. 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 subject, including unique subject 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
- retained samples for bioavailability, if applicable
- dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

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

9.2.3 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 BMS 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 or 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 BMS.

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

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

The completed CRF, SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form. 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 BMS training requirements and must only access the BMS electronic data capture tool using the unique user account provided by BMS. User accounts are not to be shared or reassigned to other individuals.

9.3 Clinical Study Report and Publications

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

For this protocol, the signatory investigator will be selected as appropriate based on the following criteria:

- Subject recruitment (eg, among the top quartile of enrollers)

- Involvement in trial design
- Other criteria (as determined by the study team)

The data collected during this study are confidential and proprietary to BMS. Any publications or abstracts arising from this study require approval by BMS prior to publication or presentation and must adhere to BMS's publication requirements as set forth in the approved clinical trial agreement (CTA). All draft publications, including abstracts or detailed summaries of any proposed presentations, must be submitted to BMS at the earliest practicable time for review, but at any event not less than 30 days before submission or presentation unless otherwise set forth in the CTA. BMS shall have the right to delete any confidential or proprietary information contained in any proposed presentation or abstract and may delay publication for up to 60 days for purposes of filing a patent application.

10 GLOSSARY OF TERMS

Term	Definition
Complete Abstinence	Complete Abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. This also means that abstinence is the preferred and usual lifestyle of the subject. This does not mean periodic abstinence (eg, calendar, ovulation, symptothermal, profession of abstinence for entry into a clinical trial, post-ovulation methods) and withdrawal, which are not acceptable methods of contraception. Women must continue to have pregnancy tests. Acceptable alternate methods of highly or less effective contraception's must be discussed in the event that the subject chooses to forego complete abstinence.

11 LIST OF ABBREVIATIONS

Term	Definition
A2AR	A2A adenosine receptor
A2ARi	adenosine A2A receptor inhibitor
ADA	anti-drug antibody
AE	adverse event
AI	accumulation index
ALT	alanine aminotransferase
AMP	adenosine monophosphate
APC	antigen-presenting cell
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the serum concentration-time curve
AUC(0-T)	area under the serum concentration-time curve from time zero to the time of the last quantifiable concentration
AUC(INF)	area under the serum concentration-time curve from time zero extrapolated to infinite time
AUC(TAU)	area under the serum concentration-time curve in 1 dosing interval
BLRM	Bayesian Logistic Regression Method
BMS	Bristol-Myers Squibb
BOR	best overall response
BRAF	B-Raf oncogene
C	Cycle
CA19-9	cancer antigen 19-9
Cavgss	steady-state average concentration
CABG	Coronary Artery Bypass Grafting
[redacted]	[redacted]
CI	confidence interval
[redacted]	[redacted]
CLT	total body clearance

Term	Definition
Cmax	maximum observed serum concentration
Cmaxss	steady-state maximum observed concentration
CNS	central nervous system
CR	complete response
CrCl	creatinine clearance
CRF	Case Report Form, paper or electronic
CRPC	castrate-resistant prostate carcinoma
CT	computed tomography
CTA	clinical trial agreement
Ctau	concentration at the end of the dosing interval
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
CTLA-4	cytotoxic T-lymphocyte-associated antigen 4
Ctrough	trough observed serum concentration at the end of the dosing interval
[redacted]	[redacted]
D	Day
DF	degree of fluctuation
DLT	dose-limiting toxicity
[redacted]	[redacted]
DOR	duration of response
ECD	extracellular domain
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EGFR	epidermal growth factor receptor
[redacted]	[redacted]
EOI	end of infusion
EOT	end of treatment
ERK	extracellular signal-regulated kinase
[redacted]	[redacted]

Term	Definition
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FNR	false negative rate
FPR	false positive rate
FSH	follicle-stimulating hormone
FU	follow-up
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HIF	hypoxia-inducible factor
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
IEC	Independent Ethics Committee
IFNγ	interferon gamma
IgG	immunoglobulin G
IHC	immunohistochemistry
IMP	investigational medicinal product
IO	immuno-oncology
[redacted]	[redacted]
IP	investigational product
[redacted]	[redacted]
[redacted]	[redacted]
IRB	Institutional Review Board
[redacted]	[redacted]
[redacted]	[redacted]

Term	Definition
IV	intravenous(ly)
IVRS	Interactive Voice Response System
KRAS	K-RAS oncogene
MAPK	mitogen-activated protein kinase
MedDRA	Medical Dictionary for Regulatory Activities
MEK	MAPK/ERK kinase
MEL	melanoma
[redacted]	[redacted]
MMR	mismatch repair
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MST	Medical Surveillance Team
MTD	maximum tolerated dose
NCI	National Cancer Institute
NK	natural killer
NOAEL	no-observed-adverse-effect-level
NRAS	neuroblastoma RAS oncogene
NSCLC	non-small cell lung cancer
NT5E	ecto-5'-nucleosidase
ORR	objective response rate
OS	overall survival
PCI	Percutaneous Coronary Intervention
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PD-1	programmed death-1
pDILI	potential drug-induced liver injury
PD-(L)1	either programmed death-1 or programmed death ligand-1
PD-L1	programmed death ligand-1
PD-L2	programmed death ligand-2
PE	physical examination

Term	Definition
PFSR	progression-free survival rate
PK	pharmacokinetic(s)
PPK	population pharmacokinetics
PR	partial response
PSA	prostate specific antigen
Q1W	weekly
Q2W	every 2 weeks
Q3W	every 3 weeks
Q4W	every 4 weeks
RCC	renal cell cancer
rHuPH20	Recombinant human hyaluronidase PH20
RECIST	Response Evaluation Criteria in Solid Tumors
[redacted]	[redacted]
SAE	serious adverse event
SC	subcutaneous
SCCHN	squamous cell carcinoma of the head and neck
SD	stable disease
[redacted]	[redacted]
T3	free triiodothyronine
T4	free thyroxine
TCGA	The Cancer Genome Atlas
T-HALF	apparent terminal half-life
T-HALFeff	effective elimination half-life
Tmax	time of maximum observed serum concentration
TMB	tumor mutational burden
ULN	upper limit of normal
US	United States
VNL	von Hippel-Lindau
Vss	volume of distribution at steady state
Vz	apparent volume of distribution of terminal phase

Term	Definition
WOCBP	women of childbearing potential

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[redacted]

APPENDIX 1 MANAGEMENT ALGORITHMS FOR IMMUNO-ONCOLOGY AGENTS

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology agents and regimens.

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

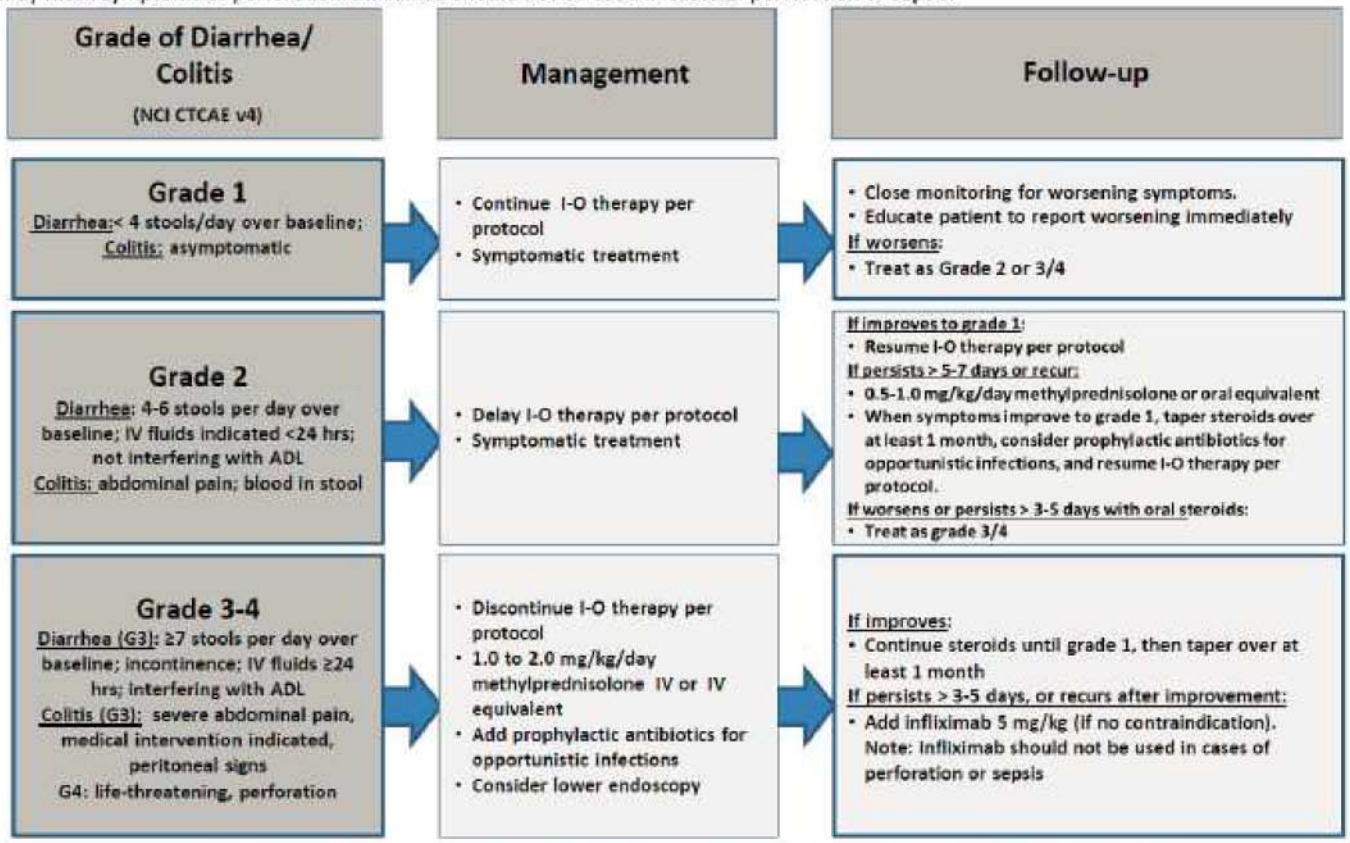
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

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

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

GI Adverse Event Management Algorithm

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

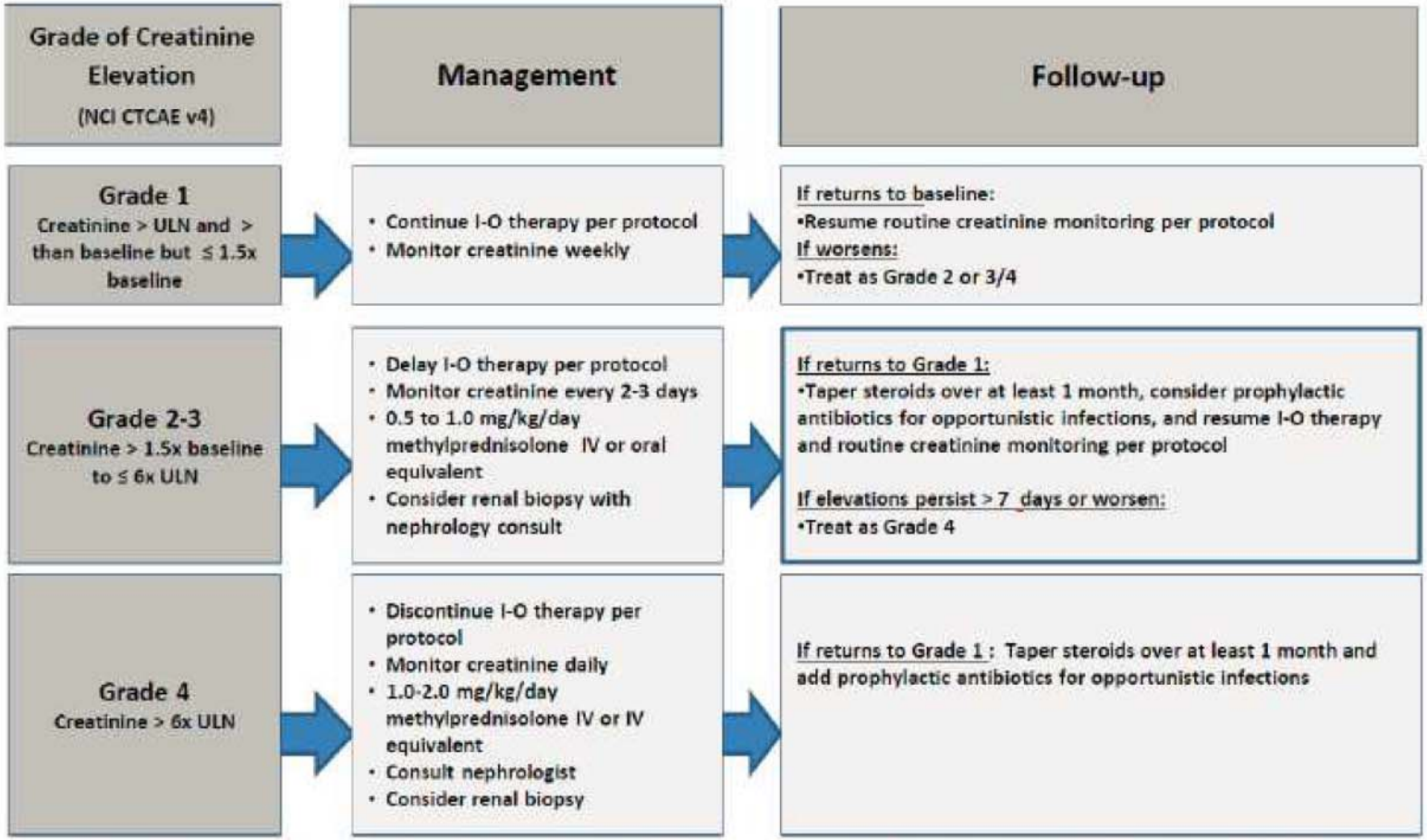


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

27-Jun-2018

Renal Adverse Event Management Algorithm

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

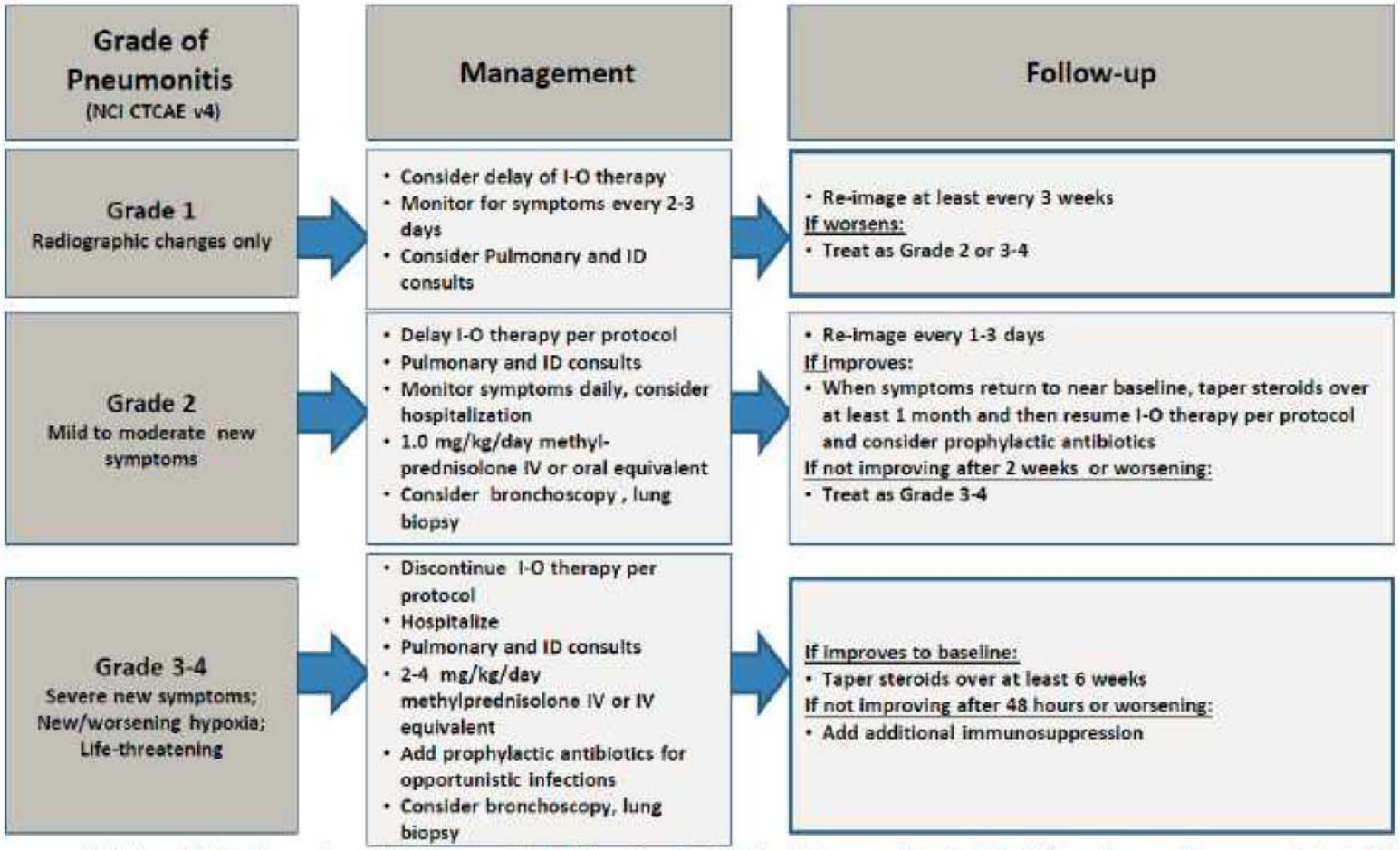


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

27-Jun-2018

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.

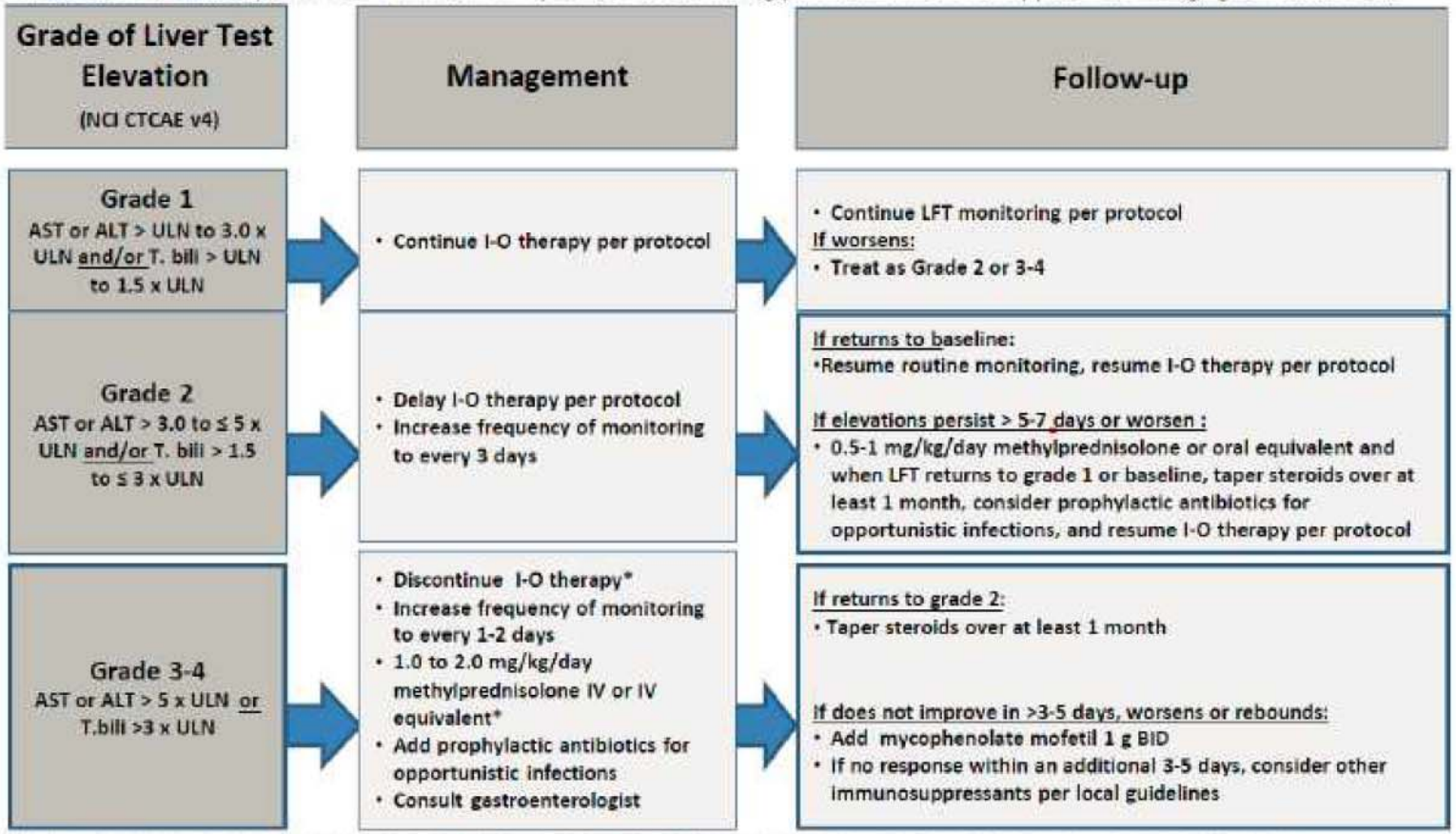


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

27-Jun-2018

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.



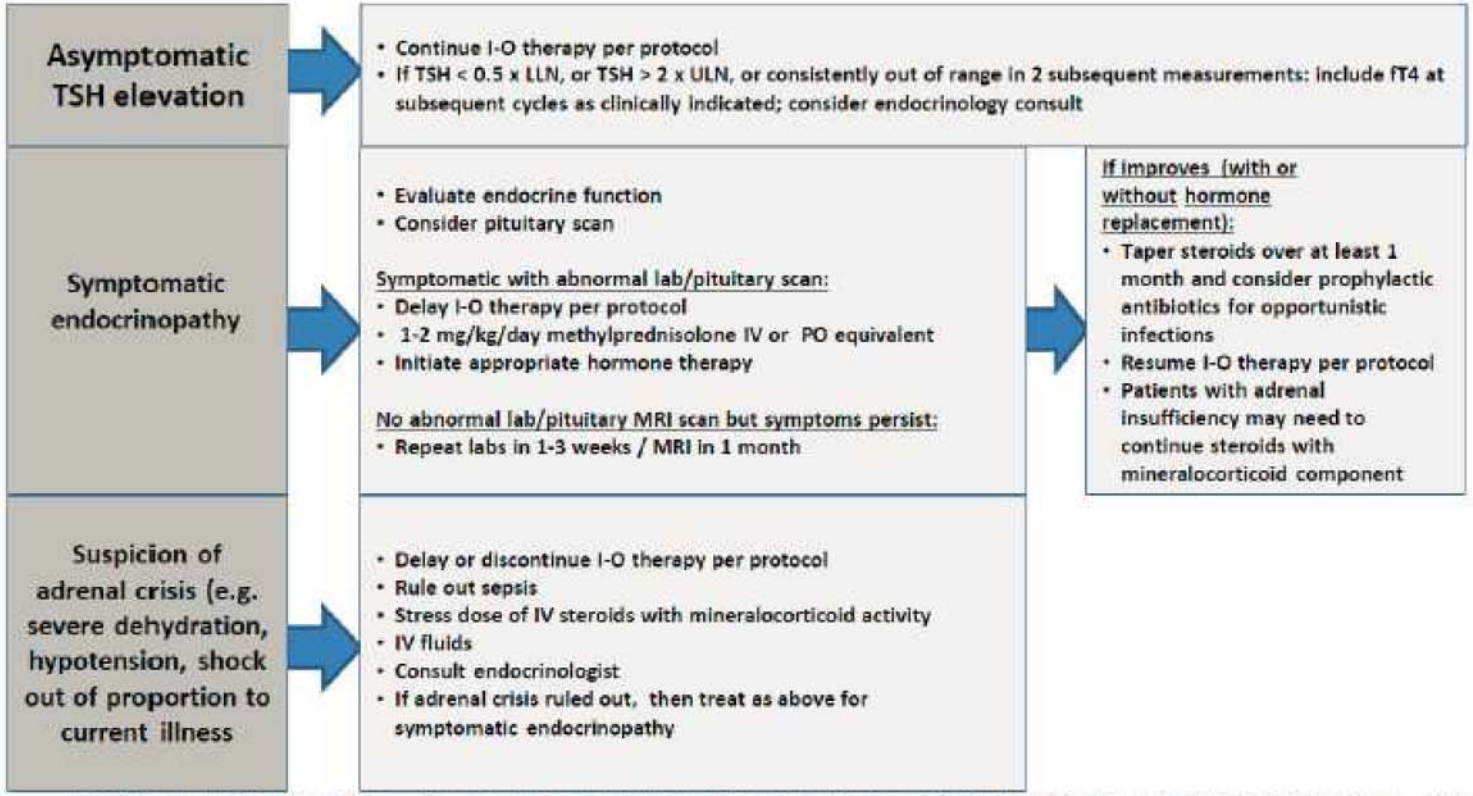
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

*The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

27-Jun-2018

Endocrinopathy Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.

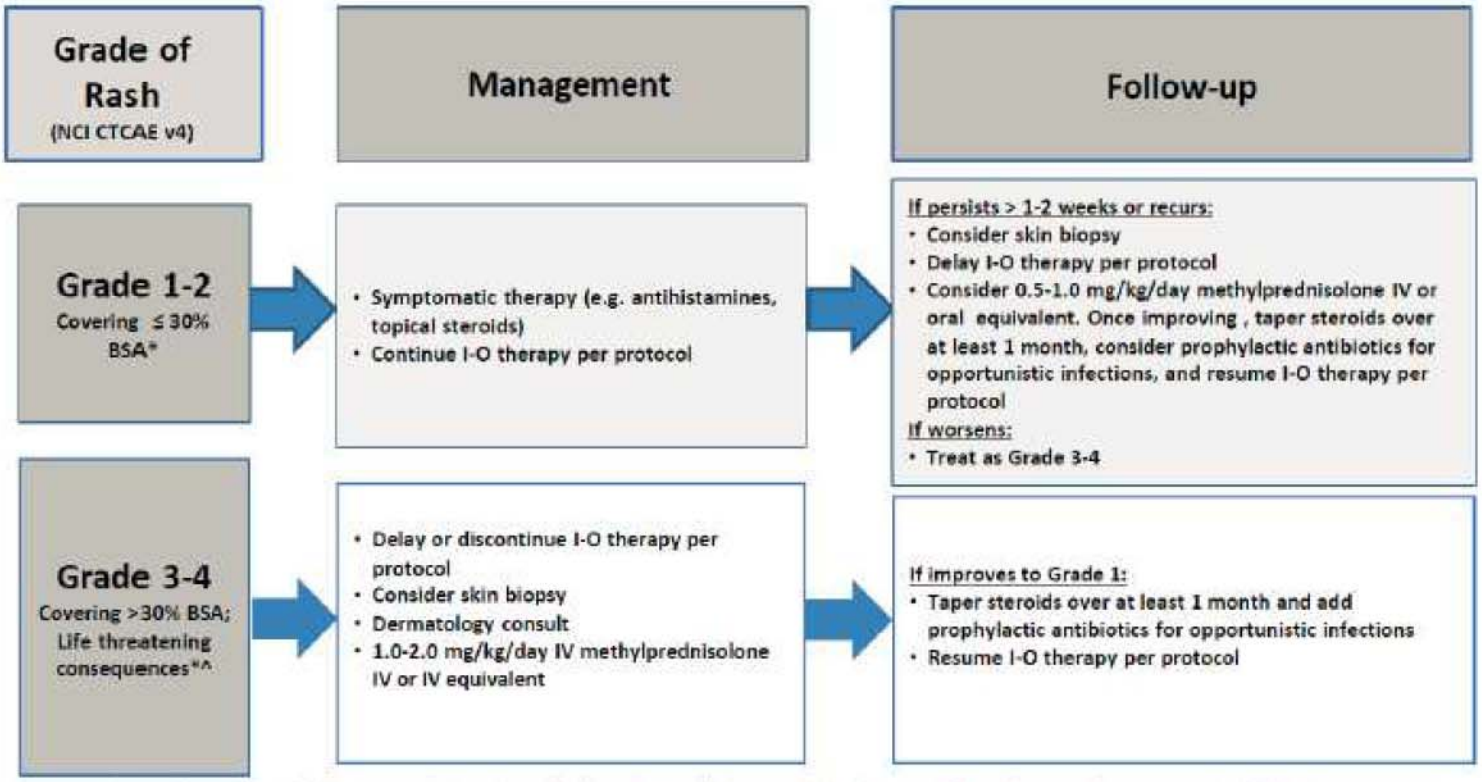


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

27-Jun-2018

Skin Adverse Event Management Algorithm

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



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

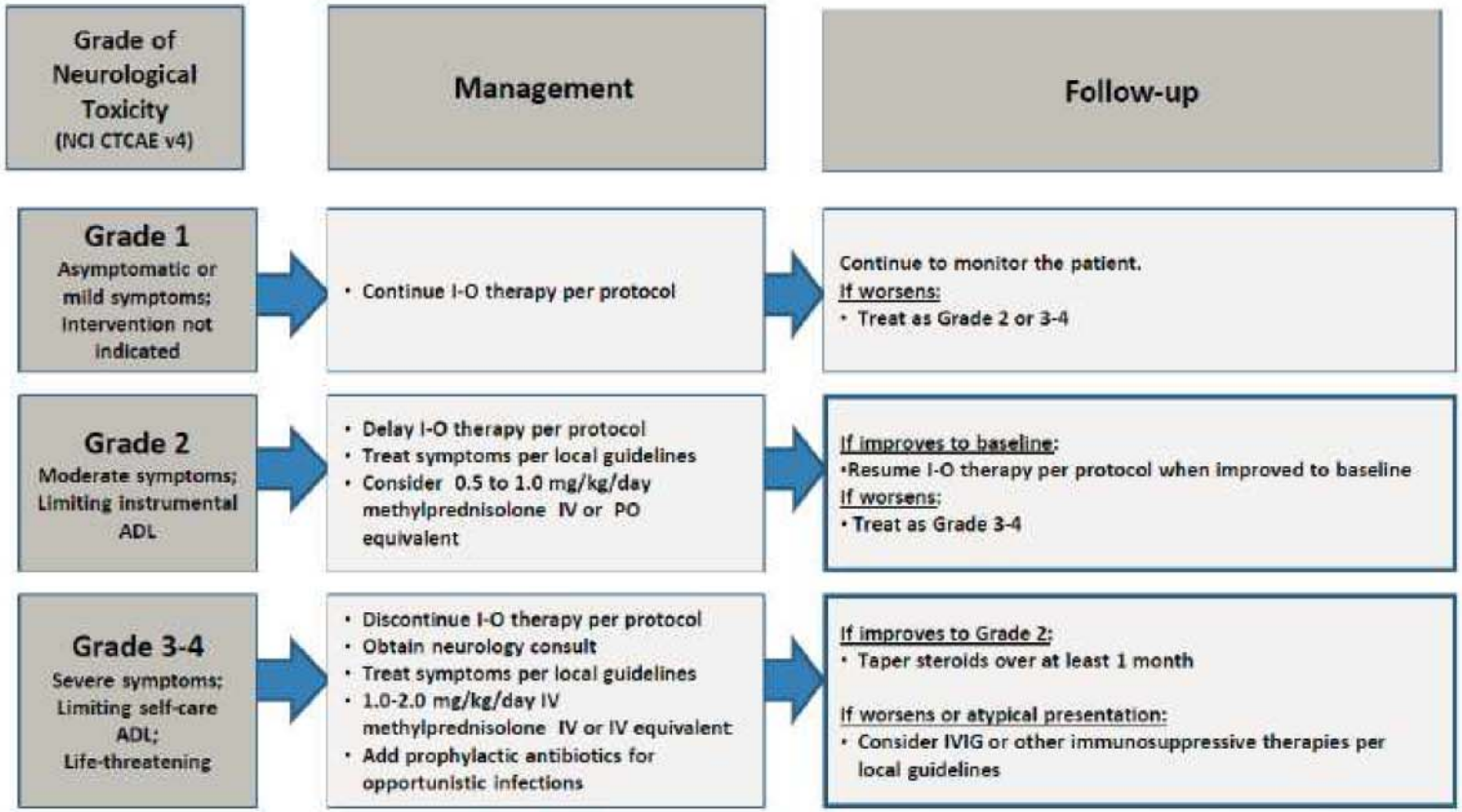
*Refer to NCI CTCAE v4 for term-specific grading criteria.

^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

27-Jun-2018

Neurological Adverse Event Management Algorithm

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



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

27-Jun-2018

APPENDIX 2 RECIST 1.1

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 one measurable tumor lesion. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

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

1.1 Measurable lesions

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

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

1.2 Non-measurable lesions

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

1.3 Special considerations regarding lesion measurability

1.3.1 Bone lesions

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

1.3.2 Cystic lesions

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

1.3.3 Lesions with prior local treatment

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

1.4 Specifications by methods of measurements

1.4.1 Measurement of lesions

All measurements should be recorded in metric notation (mm). All baseline evaluations should be performed as close as possible to the treatment start and never more than 28 days before the beginning of the treatment.

1.4.2 Method of assessment

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

1.4.2.1 CT/MRI scan

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

1.4.2.2 Chest X-ray

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

1.4.2.3 Clinical lesions

Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers. For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As previously noted,

when lesions can be evaluated by both clinical exam 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.

1.4.2.6 Tumor markers

Tumor markers ***alone*** cannot be used to assess objective tumor response.

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

2.1 Target lesions

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

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

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

2.1.1 Lymph nodes

Lymph nodes merit special mention since they are normal anatomical structures 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 scan**. Only the *short* axis of these nodes will contribute to the baseline sum. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

2.2 Non-target lesions

All other lesions (or sites of disease) including pathological lymph nodes should be identified as *non-target lesions* and should also be recorded at baseline. Measurements are not required and

these lesions should be followed as **'present', 'absent', or in rare cases 'unequivocal progression'.** In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

3. TUMOR RESPONSE EVALUATION

3.1 Evaluation of target lesions

Complete Response (CR): **Disappearance of all target lesions.** Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a **30% decrease in the sum of diameters of target lesions,** taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a **20% increase in the sum of diameters of target lesions, taking as reference the *smallest sum on study*** (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an **absolute increase of at least 5 mm**. (*Note:* the appearance of 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.

3.1.1 Special notes on the assessment of target lesions

3.1.1.1 Lymph nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded and should be 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.

3.1.1.2 Target lesions that become 'too small to measure'

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

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

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

3.1.1.3 Target lesions that split or coalesce on treatment

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

3.2 Evaluation of non-target lesions

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

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

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

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

3.2.1 Special notes on assessment of non-target lesions

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

3.2.1.1 When the subject also has measurable disease

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

3.2.1.2 When the subject has only non-measurable disease

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

3.3 New lesions

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

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

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

3.3.1 FDG-PET evaluation

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

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

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

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

Table 1. Time point response: subjects with target (+/– non-target) disease.

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

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE =not evaluable.

4.1.1 Missing assessments and not evaluable designation

When no imaging/measurement is done at all at a particular time point, the subject is **not evaluable (NE)** at that time point. If only a subset of lesion measurements are made at an assessment, the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not have changed the assigned time point response.

4.1.2 Confirmation Scans

- **Verification of Response**: Confirmation of PR and CR is required at least 4 weeks later to ensure responses identified are not the result of measurement error. To be assigned a status of CR or PR, changes in tumor measurements must be confirmed by consecutive repeat assessments that should be performed no less than 28 days after the criteria for response are first met. For this study, the next scheduled tumor assessment can meet this requirement.
- **Verification of Progression**: Not required.

4.2 Best overall response: All timepoints

The *best overall response* is determined once all the data for the subject is known. It is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. The subject's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

Best response is defined as the best response across all time points with subsequent confirmation. Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later).

In this circumstance, the best overall response can be interpreted as specified in Table 2. 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 weeks) that is defined in the study protocol.

Table 2. Best overall response when confirmation of CR and PR IS required.

Overall response	Overall response	BEST overall response
First time point	Subsequent time point	
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD

Table 2. Best overall response when confirmation of CR and PR IS required.

Overall response	Overall response	BEST overall response
First time point	Subsequent time point	
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable.

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 subject 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.

4.3 Duration of response

4.3.1 Duration of overall response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

4.3.2 Duration of stable disease

Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

APPENDIX 3 ECOG PERFORMANCE STATUS

STATUS	SCALES		STATUS
	KARNOFSKY	ZUBROD-ECOG-WHO	
Normal, no complaints	100	0	Normal activity
Able to carry on normal activities Minor signs or symptoms of disease	90	1	Symptoms, but fully ambulatory
Normal activity with effort	80		
Cares for self. Unable to carry on normal activity or to do active work	70	2	Symptomatic, but in bed < 50% of the day.
Requires occasional assistance, but able to care for most of his needs	60		
Requires considerable assistance and frequent medical care	50	3	Needs to be in bed > 50% of the day, but not bedridden
Disabled. Requires special care and assistance	40		
Severely disabled. Hospitalization indicated though death non imminent	30	4	Unable to get out of bed
Very sick. Hospitalization necessary. Active supportive treatment necessary	20		
Moribund	10		
Dead	0	5	Dead

From: Minna JD, Higgins GA and Glatstein EJ. Cancer of the lung. In: DeVita V, Hellman S, Rosenberg S (Eds.). Cancer: Principles and Practice of Oncology, Lippincott, Philadelphia, 1984, p. 536.

APPENDIX 4 STATISTICAL METHODOLOGY

Statistical Details for Bayesian Logistic Regression Model (BLRM and BLRM-Copula) and Priors for Dose Escalation

1 MODEL SETUP FOR BMS-986179 LEAD-IN (MONOTHERAPY)

1.1 Monotherapy Methodology Description

An adaptive 2-parameter Bayesian Logistic Regression Model (BLRM) guided by the escalation with overdose control (EWOC) principle[1,2,3] will be used to guide the dose escalation of BMS-986179 alone in the lead-in phase, providing dose recommendation during dose escalation.

The BLRM will be fitted on the dose limiting toxicity (DLT) data for BMS-986179 within the 2-week lead-in throughout the dose escalation to model the dose-toxicity relationship of BMS-986179 in the lead-in phase.

The dose-toxicity relationship for BMS-986179 alone 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-986179 (refer to the meaning of α_1 and β_1 in Section 1.2.1 for detailed implementation).

1.2 Prior Specification for BMS-986179 Monotherapy

The Bayesian approach requires the specification of prior distributions for model parameters, which include parameters (α_1, β_1) for BMS-986179. The prior distributions for BMS-986179 single agent activity were derived using a weakly informative prior.

Derivation of prior distribution of these parameters is provided in the following subsections.

1.2.1 Prior Derivation for BMS-986179 Parameters ($log\ (\alpha_1), log\ (\beta_1)$)

A weakly informative prior will be used for parameters (α_1, β_1) for BMS-986179 to reflect the potential of different toxicity of BMS-986179.

Further details are provided below.

Weakly Informative Prior

The median DLT rate at the reference dose (BMS-986179 at 1600 mg QD) was assumed to be 30%, eg, mean ($\log(\alpha_1)$) = logit(0.3) = log(0.3/0.7) = -0.847.

A doubling in dose was assumed to double the odds of DLT, ie, mean($\log(\beta_1)$) = 0.

The standard deviation of $\log(\alpha_1)$ was set to 1.532 using the following steps:

- Toxicity probability range was set to be [1%, 99%], then the toxicity interval would be logit(0.99) - logit(0.01) = 9.190.
- To cover 99.7% of the variance, the toxicity interval will cover 6*sd($\log(\alpha_1)$).

Correspondingly, the standard deviation of $\log(\beta_1)$ was set to 1, which allows for considerable prior uncertainty for the dose toxicity.

1) The correlation between $\log(\alpha_1)$ and $\log(\beta_1)$ was set to 0.
2) $\log(\alpha_1)$ and $\log(\beta_1)$ follow a bivariate normal distribution.

Table 1: Prior Distribution for Model Parameters for BMS-986179

Parameter	Means	Standard Deviations	Correlation
$\log(\alpha_1)$, $\log(\beta_1)$	(-0.847, 0)	(1.532 1)	0

2 MODEL SETUP FOR BMS-986179 AND NIVOLUMAB COMBINATION

2.1 Methodology Description for Combination therapy

Toxicity profiles of both BMS-986179 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 2 treatments will be explored using a Bayesian hierarchical model by utilizing the toxicity profiles of 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:

$$p_{ij} = 1 - exp(-\left[\{-log(1-{p_i}^m)\}^{1/\gamma} + \{-log(1-{q_j}^n)\}^{1/\gamma}\right]^{\gamma}),$$

where p_i is the prespecified best guess toxicity probability for agent A, q_j is the prespecified best guess toxicity probability for agent B, m and n characterize the individual drug effect, and γ characterizes drug-drug interactive effect.

The joint toxicity framework models toxicity rates of both agents as well as their interaction effects in a 7-parameter hierarchical model, where each monotherapy dose-toxicity relationship will be characterized by a 2-parameter BLRM model (see Section 1.1). There are 3 additional parameters for the copula-type model, 1 for each agent as well as 1 for the interaction term. A dose-toxicity surface will be characterized for different dose combinations of these 2 agents.

As there is currently no historical data or prior knowledge to indicate how much information 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:

$$p_{ij} = 1 - exp(-\left[\{-log(1-p_i)\}^{1/\gamma} + \{-log(1-q_j)\}^{1/\gamma}\right]^{\gamma}$$

Since only a fixed nivolumab dose (240 mg) will be used in BMS-986179 and nivolumab combination, this surface will be simplified into a 2-dimensional dose-toxicity curve. Posteriors for the corresponding 5 parameters (2 logistic regression parameters $[\alpha_1, \beta_1]$ for BMS-986179 and 2 logistic regression parameters for nivolumab $[\alpha_2, \beta_2]$, as well as 1 interaction parameter for

the copula-type model [γ, which will be discussed in detail in the following session]) will be fit into the in-house developed model, which implements the above described theoretical setup.

2.2 Priors Specification for Combination Studies

2.2.1 Prior for BMS-986179

Posterior information on $\log(\alpha_1)$ and $\log(\beta_1)$ from the lead-in part of the study will be used as marginal BMS-986179 prior for combination with nivolumab. This prior information is not prespecified and will be continuously updated when additional toxicity (DLT) information from the lead-in is available. In the simulation (see Section 2.4), the prior of BMS-986179 as described in Section 1.2.1 (Table 1) is used for illustration purposes, as no real-time DLT data are available at this time.

2.2.2 Prior Derivation for Nivolumab Parameters ($\log(\alpha_2)$,$\log(\beta_2)$)

Similar to BMS-986179 monotherapy in the lead-in phase, the logistic model for nivolumab is as follows:

$$logit(q_j) = log(\alpha_2) + \beta_2 log(^{d_{2j}}/_{d_2^*}),\ where\ \alpha_2,\ \beta_2 > 0.$$

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 ($\log(\alpha_2)$, $\log(\beta_2)$) was obtained by extracting a posterior of nivolumab using DLT and safety data from the Study CA209003, which is used later as the meta-analytical-predictive (MAP) prior for nivolumab.

The MAP prior for the model parameters ($\log(\alpha_2)$, $\log(\beta_2)$) was obtained in the following steps.

First, a prior distribution for nivolumab was developed:

- The median DLT rate at the reference dose (3 mg/kg, equivalent to 240 mg flat dose, every 2 weeks) was assumed to be 10%, ie, mean ($\log(\alpha_2)$) = logit(1/10) = log(1/9) = -2.197.
- A doubling in dose was assumed to double odds of DLT, ie, mean($\log(\beta_2)$) = 0.
- The standard deviation of $\log(\alpha_2)$ was set to 2, and the standard deviation of $\log(\beta_2)$ to 1, which allows for considerable prior uncertainty for the dose-toxicity profile.
- The correlation between $\log(\alpha_2)$ and $\log(\beta_2)$ is assumed to be 0 (assuming independence of $\log(\alpha_2)$ and $\log(\beta_2)$).

- In addition, heterogeneity between the historical study and current study was incorporated using a MAP approach, by defining between-trial standard deviations τ_1 and τ_2 for $\log(\alpha_2)$ and $\log(\beta_2)$, 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 were used to generate the posterior for nivolumab, which is then used as the MAP prior for this study.

Table 2: Data from Single Agent Nivolumab Study CA209003

Dose of Nivolumab (mg/kg)	Every 2 Weeks
	No. of DLTs/No. of Evaluable Patients in Escalation Phase
0.1	0/3
0.3	0/3
1	0/3
3	0/3
10	1/6

Abbreviation: DLT = dose limiting toxicity; No. = number.

Table 3: Prior Distribution for Model Parameters for Nivolumab (ie, Posterior from MAP Method)

Parameter	Means	Standard Deviations	Correlation
$\log(\alpha_2)$, $\log(\beta_2)$	(-3.269, -0.152)	(1.186, 0.771)	-0.369

Abbreviation: MAP = meta-analytical-predictive.

Note: Nivolumab prior information was based on mg/kg dosing instead of flat dosing. If real pharmacokinetic (PK) data from this study show difference from mg/kg assumption, the nivolumab prior will be revisited and modified accordingly.

2.2.3 Prior for Interaction Parameters for Joint Toxicity of BMS-986179 and Nivolumab Combination

A gamma prior distribution for the interaction parameter γ is derived to reflect the current uncertainty about the toxicity profile of the combination of BMS-986179 and nivolumab. Although no PK drug-drug interaction is expected, the possibility of significant positive interaction between BMS-986179 and nivolumab cannot be totally excluded. The interaction parameter γ was chosen accordingly but with a degree of uncertainty in order to allow for the possibility that the interaction may be positive or negative. Therefore, the following assumptions are made for the interaction parameter:

- γ follows a gamma distribution and with a mean centered at 1.1, which means the combination of 2 agents is likely to have only a small synergistic effect.

- The 97.5 percentile of γ is log(3), ie, 3-fold increase in odds of DLT due to interaction over independence at the combination starting dose.

This model assigns the highest probability to there being a small synergistic interaction but also allows for the potential of larger synergism of the toxic profiles. It also does not completely ignore the possibility of antagonism since there is a 40% prior probability that γ is less than 1.

2.3 Parameters for Dose Recommendation Decision for the Lead-in Phase and Combination Phase

Dose escalation recommendations for BMS-986179 alone and in combination with nivolumab will be based on inference from the Bayesian posterior, and the probability that the true DLT rate for each dose lies in one of the following categories:

- [0,16%) under-dosing
- [16%,35%) targeted toxicity
- [35%,100%] excessive toxicity

Following the principle of EWOC, after DLT information is obtained from each cohort of subjects, 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.

Any information on the dose-DLT relationship generated by publicly available CD73 clinical trial data as well as nivolumab prior data from Study CA209003 will be incorporated into the prior distribution before the first dose escalation decision is made within this study in order to reflect all relevant information at that time.

The final recommended maximum tolerated dose (MTD)/recommended Phase 2 dose of BMS-986179 in combination with nivolumab for cohort expansion will be based on the recommendation from the BLRM-copula model and a synthesis of all the data available on all dosed subjects, including clinical and laboratory safety assessments and PK and pharmacodynamic and efficacy data from all treated patients at each dose level up to the MTD/MAD. For further details of the BLRM-copula model and results under a variety of scenarios, refer to the simulation results in Section 2.4.

2.4 Operating Characteristics

The BLRM and BLRM-copula models should make reasonable dose escalation recommendations during a study based on the observed toxicities particularly in early cohorts. After completion of a given cohort, the decision to dose escalate and the actual dose chosen for the subsequent cohort will depend on the recommendation of the BLRM (-copula) EWOC principle and medical review of all relevant data available to date. Simulated operating characteristics of the BLRM-copula model of BMS-986179 in combination with nivolumab are shown in this section. The provisional dose levels for BMS-986179 are 150, 300, 600, 1200, and 1600 mg. Nivolumab is fixed at a 240-mg flat dose.

In order to show how the design performs, 4 hypothetical scenarios were investigated (please refer to Table 4 for more details):

- Scenario 1: General dose-DLT relationship with the assumption that the higher doses will have higher DLT rates, with the highest dose reaching the target toxicity rate (**Additive**)
- Scenario 2: Toxicity rates 25% higher than the additive scenario 1 with increased dose levels, with the highest dose toxicity level above 33% (**Synergistic Effect**)
- Scenario 3: All dose levels with toxicities 25% lower than the additive scenario 1 (**Subadditive effect**)
- Scenario 4: All dose levels with toxicities 50% lower than the additive scenario 1 (**Strong Cancellation effect**)

Table 4: Toxicity Rates for Each Simulated Scenario For 5 Pre-specified Dose Levels

Scenario/Dose Level	150 mg BMS-986179 + 240 mg Nivolumab	300 mg BMS-986179 + 240 mg Nivolumab	600 mg BMS-986179 + 240 mg Nivolumab	1200 mg BMS-986179 + 240 mg Nivolumab	1600 mg BMS-986179 + 240 mg Nivolumab
Scenario 1 Additive	0.110	0.140	0.175[a]	0.250[a]	0.400
Scenario 2 Synergistic	0.1375	0.175[a]	0.2188[a]	0.3125[a]	0.500
Scenario 3 Subadditive effect	0.082	0.105	0.131	0.188[a]	0.300[a]
Scenario 4 Strong Cancellation effect	0.055	0.007	0.088	0.125	0.200[a]

[a] Doses with true toxicity rate within the target toxicity interval [16%, 35%).

Simulation Parameters

One thousand trial simulations were used for each scenario. The number of subjects to be treated in each patient cohort in a specific dose level and the stopping rules used to declare MTD were defined as:

I. Fixed cohort size: 3
II. Probability of overdosing: < 35%
III. Maximum number of subjects treated: 30
IV. Probability of target toxicity: > 50%
V. Minimum number of subjects treated at a given dose level in order to declare MTD: 6

All simulations were run using in house-developed code via R and Openbugs, and EAST 6.3.1® software.

Simulation Results

Operating characteristics from the simulations were reviewed to assess the relative performance under each true scenario. The metrics reviewed are:

1. Percentage of trials with MTD being selected whose true toxicity is in the range of [16%, 35%) (**Correct MTD)**
2. Percentage of trials with MTD being selected in the range of [35%, 100%] (**MTD Too High**)
3. Percentage of trials with MTD being selected in the range of [0%, 16%) (**MTD Too Low**)
4. Percentage of trials with MTD being selected at the dose level with the true toxicity closest to 33% and ≤ 33% (**MTD Point**)
5. The 25% quantile of 1000 trials' fitted MTDs derived by solving the logistic regression formula using posterior medians of parameters, as well as the 33% as target DLT rate (**Fitted MTD**)
6. Percentage of trials stopped before declaring MTD due to the reason that MTD is below the lowest dose level (simulation parameter II) (**EWOC Stop**)
7. Percentage of trials stopped because of sufficient posterior probability that the toxicity is in the desired range (simulation parameter IV) and a minimum sample size of N = 6 at the declared MTD (simulation parameter V) (**Target Range Stop**)
8. Percentage of trials stopped because the maximum sample size of N = 30 was reached (simulation parameter III) (**MaxN Stop**)
9. Average sample size for each scenario (**Average Sample Size**)

Below (Table 5) summarizes the simulated operating characteristics of the model for the 4 different scenarios studied. One thing to note is that the following simulation results are only for illustrative purposes. This might not fully represent real trial conduct because the potential for the clinical team to override the BLRM recommendation is not taken into account.

Table 5: Simulation Results for Operating Characteristics

	MTD Range			Point Estimate		Good Stopping		Bad Stopping	Average Sample Size
	Correct MTD (%)	MTD Too High (%)	MTD Too Low (%)	MTD Point (%)	Fitted MTD (True MTD) (mg)	EWOC Stop (%)	Target Range Stop (%)	MaxN Stop (%)	
Scenario 1: Additive	66.7	19.7	8.6	43.2	1166.4 (< 1200)	5.0	94.2	0.8	14.7
Scenario 2: Synergistic	77.4	8.6	6.2	36.0	927.8 (< 1200)	7.8	91.7	0.4	14.2
Scenario 3: Subadditive effect	82.3	NA[a]	15.0	42.1	1582.4 (1200, 1600)[b]	2.7	95.4	1.9	15.8
Scenario 4: Strong Cancellation effect	68.4	NA[a]	30.5	68.4	2192.4 (> 1600)	1.1	84.0	14.9	18.5

[a] NA because pre-specified toxicity are all below [16%, 35%) target toxicity range.

[b] Means the true MTD falls into the range between 1200 and 1600 mg.

Abbreviations: EWOC = escalation with overdose control; MTD = maximum tolerated dose; NA = not applicable.

Overall, from the scenarios illustrated above, it can be seen that the model performs acceptably under the hypothetical scenarios investigated. The model allows for high MTD identification accuracy (using the MTD range), a relatively small average sample size (< 19), a high probability of good stopping with good confidence (> 85%), and a low probability of bad stopping (≤ 15%) when all of the subjects have been used.

In this simulation, different angles have been investigated regarding the performance of the model in terms of identifying the true MTDs under different scenarios. For scenario 2, the MTD point estimate is the lowest (36.0%) across all 4 scenarios. This means the dose level (1600 mg) corresponding to the toxicity rate of 0.33 has only been identified 36.0% times as the MTD among all 1000 simulations. When it comes to the "correct MTD" (considering the MTD range), which is the accumulated percentages, scenario 3 is the highest among all 4 scenarios (82.3%). This can possibly be attributable to the discrepancy between the prior and simulated toxicity rates, requiring a larger sample size to overcome. Since prior specification plays such an important role in the performance of this design, care has been taken to develop the priors used in this study; if a large discrepancy later becomes apparent, additional subjects could be needed for clarification.

For "MTD too high" cases, scenarios 3 and 4 show a small possibility of overdosing. On the other hand, scenarios 1 and 2 show overdosing rates of 19.7% and 8.6%, respectively. The toxicity rates for 1600 mg are above the target interval of [16%, 35%). The model fitted MTD at 1166.4 mg for scenario 1 and 1582.4 mg for scenario 3 falls in the range of the hypothetical true MTD (between 1200 and 1600 mg). The estimated MTD might be ascribed to the deviation of the prior distribution from the true underlying dose-DLT relationship. There is only 30% of the DLT rate assumed as current prior at the reference dose level of 1600 mg, which is much lower than the true toxicity rate (50%) at this dose level. As in all parametric models, the prior distribution plays an important role in the performance of the BLRM-copula model under each scenario.

For "MTD too low" cases, scenarios 1 to 3 show fairly low percentages of under-dosing (all < 16%), which is consistent with the hypothetical Pr (DLT). This also benefits from the properly defined overdose control probability of (Pr(overdose) < 35%). In scenario 4, a very strong cancellation effect has been investigated with the highest toxicity level set at 0.2. In this case, the "fitted MTD" of 2192.4 mg could provide more guidance for the clinical team during trial conduction.

Different reasons for stopping have been investigated to obtain a deeper understanding of the operating characteristics of the BLRM-copula model. The performance of a "Good Stopping/Target Range Stop" (a stop due to high confidence about the recommended MTD fall in the prespecified target toxicity interval) is good across all 4 scenarios (all high above 85%). Another indicator of "Good Stopping" is the EWOC Stop, wherein the overdosing control is low (< 8%) across all 4 scenarios. Low values are good because all of the toxicities among the 4 scenarios that correspond to the starting dose are relatively low (ranging from 0.05 to 0.14). Therefore, the chance of stopping early and declaring the MTD lower than the prespecified lowest dose level should rarely happen. This is consistent with our hypothetical scenarios.

Additionally, "Bad Stopping" due to reaching the maximum pre-assigned sample size (max N = 30) is < 15% for all 4 scenarios, which is good for early phase trials.

The average sample size from all 1000 simulations for each scenario is below 19, which is less than the pre-specified maximum sample size (N = 30). To control the possible heterogeneity between the prior distribution and the underlying true dose-DLT relationship, more information from the current study is warranted. Increasing the "total maximum number of subjects" for the trial or adding a stopping rule for the "maximum number of subjects enrolled for a next to-be dose level," or adding a restriction for "dose skipping," might be implemented during the conduction of the trial to gain more information from the trial. Also, intermediate dose levels and/or flexible cohort sizes might be investigated in the real study.

3 REFERENCES

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APPENDIX 5 METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

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

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

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

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 5 months after the end of study treatment.*

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[b] – oral – intravaginal – transdermal
• Progestogen-only hormonal contraception associated with inhibition of ovulation[b] – oral – injectable
Highly Effective Methods That Are User Independent

- Implantable progestogen-only hormonal contraception associated with inhibition of ovulation [b]
- Hormonal methods of contraception including oral contraceptive pills containing a combination of estrogen and progesterone, vaginal ring, injectables, implants and intrauterine hormone-releasing system (IUS)[c]
- Intrauterine device (IUD)[c]
- Bilateral tubal occlusion

- Vasectomized partner

A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

- Sexual abstinence

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study 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.

- It is not necessary to use any other method of contraception when complete abstinence is elected.
- WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2.
- Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence

NOTES:

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

[b] Hormonal contraception may be susceptible to interaction with the study 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.

[c] Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness

Unacceptable Methods of Contraception*

- 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

- Periodic abstinence (calendar, symptothermal, 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.**

CONTRACEPTION GUIDANCE FOR MALE PARTICIPANTS WITH PARTNER(S) OF CHILD BEARING POTENTIAL.

Male participants with female partners of childbearing potential are eligible to participate if they agree to the following during the treatment and until the end of relevant systemic exposure.

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Male participants are required to use a condom for study duration and until end of relevant systemic exposure defined as 7 months after the end of study treatment.
- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 7 months after the end of treatment in the male participant.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 7 months after the end of study treatment.
- Refrain from donating sperm for the duration of the study treatment and until 7 months after the end of study treatment.

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy is provided on the Pregnancy Surveillance Form.

APPENDIX 6 COUNTRY SPECIFIC REQUIREMENTS

Criteria for exclusion of HIV-positive subjects in Germany:

	Country-specific language
Section 3.3.2 Exclusion Criteria, criterion 2n	"Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)" has been replaced with "Subjects with a positive test for HIV".
Section 5.1 Flow Chart/Time and Events Schedule, Table 5.1-1: Screening Procedural Outline	For Serology Tests added, "Includes HIV testing at screening."
Section 5.3.2 Laboratory Test Assessments	Added that "HIV testing must be done at screening (within 42 days prior to first dose for Part 2)."

APPENDIX 7 REVISED PROTOCOL SUMMARY OF CHANGE HISTORY

Overall Rationale for the Revised Protocol 07, 28-Feb-2018

Data from Parts 1A and 1B of the protocol identified a recommended phase 2 dose/schedule to evaluate in Part 2 (BMS-986179 600 mg IV Q2W monotherapy or in combination with Nivolumab 480 mg Q4W). Given the unmet medical need in expansion indications, this regimen was taken immediately forward. PK and PD data suggested potential feasibility of a less frequent dosing schedule - Q4W- although this was not in the original study design. Moreover, the opportunity for rHuPH20-enabled subcutaneous administration of BMS-986179 recently became available. Both Q4W and subcutaneous administration offer potential convenience and improved compliance to patients, in revised protocol 07 seeks to confirm feasibility of Q4W dosing by IV and SC routes in the PD substudy (Part 1B), in parallel with previously-planned enrollment to Part 2. The intent is to simultaneously seek initial efficacy signals in Part 2, while obtaining data to enable bridging to Q4W IV or SC in later trials. Sections in the synopsis have been updated to align with the protocol section changes listed below.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 07		
Section Number & Title	**Description of Change**	**Brief Rationale**
Throughout the protocol	Made revision throughout the protocol to add information for Q3W and Q4W regimens not previously included. Clarifications and corrections.	See above rationale
Section 1.1.7 Rationale for Subcutaneous Administration; [redacted] Section 1.4 Product Development Background; Section 3.1 Study Design; Section 4 Study Drug; Section 5.5 Pharmacokinetic Assessments; Section 8.1.2 Part 1B (PD Substudy); Section 8.2 Populations for Analyses; Section 8.4.4 Pharmacokinetic Analyses	Sections added or modified based on addition of objective relating to bioavailability for subcutaneous dosing in Part 1B. Added information about new study drug - Recombinant Human Hyaluronidase PH-20 (rHuPH20) in Section 1.4 and section 4.	Subcutaneous dosing objective has been added to Part 1B of this study to assess a potentially important alternative approach to dosing. Sections in question have been modified or added to provide justification, methods, and assessment of this objective. Added necessary background for rHuPH20, which enables SC administration of BMS-986179.
[redacted]		

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 07		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 1.5.1 Risk/Benefit for Combination with Nivolumab	Modified information about overall safety for nivolumab and "musculoskeleton pain" has been added for most common AE.	Harmonization with known Nivolumab safety profile.
Section 3.1.3 Part 2 (Cohort Expansion)	Added information about TMB	Clarification of intended patient population for expansion cohorts.
Section 3.3.1 Inclusion Criteria	Criteria 2b)ii): Additional for Part 1B (PD Substudy) was added under solid tumor histologies. Criteria 2c)j): Additional information about collection for core biopsy specimen was added. Criteria 3e): The duration of contraception post-treatment completion (7 months for male participants) was added.	Specific changes to better define patient populations and improve quality of PD data. Align with contraceptive language for other BMS early assets.
3.5.2 Stopping Rules during Cohort Expansions	Statement modified to be read as "Depending on the nature and grade of the toxicity and after assessing the risk/benefit ratio, a new dose for all cohorts may be initiated at a previously tested lower dose level or, at a dose level intermediated to previously tested lower dose levels, **or an alternate less frequent treatment regimen**."	The phrase in bold was added per health authority recommendation.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 07		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 4.10 Retained Samples for Bioavailability/ Bioequivalence	Remove "Bioequivalence" from the heading.	Bioequivalence was never being tested; term removed for clarity.
Section 5.5 Pharmacokinetic Assessments	Tables 5.5.1-1 through Table 5.5.1-10: Sample collection for PK/immunogenicity for Grade 3/4 infusion or hypersensitivity reaction was removed from all tables	These samples were mainly collected to evaluate immunogenicity at Grade 3/4 hypersensitivity reaction. However samples might not be necessarily collected at trough samples, so might affect the immunogenicity assessment.
	Tables 5.5.1-5: Removed sample scheduling for PK and immunogenicity for Nivolumab for C2D15 and C5D15	Nivolumab will be administered as Q4W regimen for Part 2. Hence nivolumab PK samples for C2D15 and C5D15 would not be required as these represent predose only for Q2W regimen.
	Table 5.5.1-8: Updated table title to remove RCC and NSCLC subjects and also added Part 1B Removed BMS-986179 immunogenicity sample scheduling for C2D14	The table will be used for both Part 1B and Part 2 Q2W and will apply to other tumor types as well. C2D14 is for biopsy sampling therefore, immunogenicity sample collection is not required for that time point.
	Table 5.5.1-9 Updated for PK sample scheduling for BMS-986179 for C3D22, C3D23, C3D24-C3D26, C3D29 and also added additional cycle for C3D36. Table note "d" was corrected from C2D28 - 5D (D66 -D63) to C2D21-5D (D59 to D63).	In the previous protocol "X" were missing in the BMS-986179 PK sample column. Hence added it now. Also added C3D36 since intensive PK sampling is collected at cycle 3 (C3) and one time point was missing.
	Table 5.5-1.10 updated to remove BMS-986179 immunogenicity samples for C3D1	C3D1 is for biopsy sampling therefore, immunogenicity sample collection is not required for that time point.
Section 5.5 Pharmacokinetic Assessments	New PK/Immunogenicity tables are added for Part 1B Subcutaneous administration at Q2W, Q3W and Q4W regimens.	These PK tables were added to support assessment for PK in subjects receiving subcutaneous dose.
Table 5.6-1 through Table 5.6-9	Footnote for Unscheduled/EOT/at progression was modified to make biomarker sample collection mandatory.	Rate of sample collection was unacceptably low when optional.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 07		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 6.1.1 Serious Adverse Event Collection and Reporting; Section 6.2.1 Nonserious Adverse Event Collection and Reporting	Modified to remove the statement about any SAE occurring after the start of a new treatment that is suspected to be related to BMS study treatment	Harmonization with language for other BMS early oncology assets.
Section 8.1.3 Sample Size Determination (Part 2)	A Simon 2-stage design is now being used to evaluate initial efficacy in subjects with CRPC and Table 8.1.3-1 was updated to reflect this change. The following sentence was also added just prior to Table 8.1.3-1 for clarity: "While the design includes hypothesis testing with decision rules, the decision to proceed to Stage 2 in a cohort will be based on the totality of available data, in consultation with study investigators."	This change is being made per health authority recommendation to implement clear futility stopping rules in dose expansion.
Section 8.4.4 Pharmacokinetic Analyses	Added bioavailability analysis	Bioavailability is the primary endpoint for SC cohort added to Part 1B.
Appendix 5	Updated	Harmonization with Nivolumab standard program.
Appendix 6	New Germany country specific appendix added	[redacted]

Overall Rationale for the Revised Protocol 06, 20-Oct-2017

The protocol has been revised to change the tumor types in Part 2, Cohort Expansion (adding NSCLC, RCC, CRPC, SCCHN, and melanoma, and deleting ovarian cancer, colorectal cancer, and gastric cancer) to allow for monotherapy in Part 2 with BMS-986179 in NSCLC and RCC, with the option for subjects to receive combination therapy with BMS-986179 and nivolumab at disease progression; to extend the treatment duration to 2 years (24 weeks of initial treatment, with the option of an additional 80 weeks), change follow-up to 3 years after initial dose, and add a Q4W regimen for combination therapy with BMS-986179 and nivolumab. In addition, [redacted] laboratory assessments were added to monitor cardiovascular safety.

Revisions apply to future participants enrolled in the study, and where applicable, to all participants currently enrolled.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
All	Minor formatting and typographical corrections	Minor, therefore have not been summarized.
Study title, Section 1 Introduction and Study Rationale, Section 3.1 Study Design and Duration, [redacted] Section 8.3.1 Primary Endpoints, Section 8.4.2 Efficacy Analyses	Added "alone and" to reflect the addition of the monotherapy component.	Clarified that anti-tumor activity of BMS-986179 in monotherapy will also be described.
Section 1.1.1 Rationale for BMS-986179 Therapy	Further description of CD73 expression was added.	Reflects emerging data on tumor types and genotypes where adenosine-targeted therapies may have potential activity.
Section 1.1.2 Rationale for BMS-986179 Monotherapy	Preliminary clinical trial data for A2ARi were added.	Clinical benefit in NSCLC and RCC post-A2ARi monotherapy provides rationale for CD73 monotherapy in biomarker/clinically enriched expansion cohorts.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 1.1.4 Rationale for Tumor Selection	Changed the tumor types included; justification for inclusion in study is given. Information supporting the potential anti-tumor activity of CD73 in prostate carcinoma, SCCHN, RCC, and melanoma was added. Text was added describing MAPK driven CD73 expression, and rationale for adenosine-targeted therapy in this context. Pancreatic "carcinoma" was changed to "adenocarcinoma" throughout the section.	Reflects emerging data on tumor types and genotypes where adenosine-targeted therapies may have potential activity. Change to "pancreatic adenocarcinoma" made to clarify the intended target population.
Section 1.1.5.2 Nivolumab	Dosing regimen updated. Justification for new dosing regimen included.	Updated safety and efficacy data to support Q4W nivolumab dosing. Aligned with Q4W schedule used across current BMS I-O trials. Aligned with Q4W nivolumab monotherapy schedule submitted to FDA as supplemental Biologics License Applications (sBLAs).
Section 1.1.5.3 Rationale for ≥ 24-week Duration of Combination Therapy	Section heading updated to "Rationale for ≥ 24-week Duration." Details of previous treatment regimens clarified. Treatment duration changed to 2 years. Justification for extended treatment regimen given.	Clinical observations from Part 1A supporting longer treatment of subjects with appropriate risk-benefit profile.
Section 1.1.5.4 Rational for Treatment Beyond Progression	Update added on a subject with RCC who fits proposed cohort and demonstrated PR.	Clinical observation from Part 1A supporting inclusion of RCC cohorts.
Section 1.1.6 Rationale for PD Substudy	Nonclinical data and PK modeling influence on dosing schedules added.	Additional details added, supporting dosing schedules under investigation.
Section 1.1.7 Rationale for Sentinel Subject Approach	Monkey type "cynomolgus" added for clarity.	Clarified animal model used.
[redacted]		

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
1.1.9 Rationale for Enrolling Additional Subjects for PD in Dose Escalation Cohorts	Pharmacodynamics listed as an assessment for BMS-986179 in the dose escalation cohorts.	Modified to assure sufficient numbers of evaluable specimens.
[redacted]		
Section 1.5 Overall Risk/Benefit Assessment	Added information about cardiovascular AEs occurring to date in this study.	Updated to support safety.
Section 3.1 Study Design and Duration, Figure 3.1.2-1 Study Design Schematic [Part 1B and Part 2], Table 5.1-1 Screening Procedural Outline, Section 1.1.5.3 Rationale for 24-week Duration	The duration of screening for Part 2 was changed to up to 42 days, and the duration of treatment was changed to up to 2 years (initial treatment period of 24 weeks with an option for treatment for an additional 80 weeks).	Extended screening for Part 2 to accommodate necessary evaluations. Treatment duration was modified to reflect longer treatment of subjects with appropriate risk-benefit profile.
Section 3.1 Study Design and Duration, Section 3.1.5 Treatment with Additional Cycles Beyond 24 Weeks, Section 3.1.6 Re-treatment During Follow-up, Table 5.1-10 Follow-up Procedural Outline	Duration of response/survival follow-up was changed to approximately 3 years from the first dose.	Modified to accommodate the extended duration of treatment.
Section 3.1 Study Design and Duration, Section 3.3.1 Inclusion Criteria, Table 5.1-1 Screening Procedural Outline	Number of core biopsy specimens was increased from 2 to either 3 or 4, depending on tumor types. Details added on order of biopsies.	Modified to ensure sufficient samples for all required analyses.
Section 3.1.1 Part 1A (Dose Escalation)	Enrollment update for Part 1A was included.	Status update.
Section 3.1.3 Part 2 (Cohort Expansion)	The number and subtype of subjects were added. Study design parameters were explained. Study activities for monotherapy subjects were further explained. [redacted] Pancreatic "carcinoma" was changed to "adenocarcinoma."	Changed target tumor types, as above, and provided greater detail regarding study design and activities Part 2. Change to "pancreatic adenocarcinoma" was made to clarify the intended target population.
Section 3.1.5	Added an additional 80 weeks of therapy after the initial 24-week treatment (for a total treatment duration of approximately 2 years).	Modified to reflect longer treatment of subjects with appropriate risk-benefit profile.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 3.1.6	Added a statement that re-treatment is limited to subjects enrolled before this amendment.	Modified for practical considerations due to the lengthened treatment time.
Section 3.1.7 Subject Replacement	A rule on subject replacement was added.	Modified to assure sufficient numbers of evaluable subjects.
Section 3.1.8 End of Study Definition	Added new section defining "end of study."	Clarification
Section 3.3.1 Inclusion Criteria	Under 2. Target Population (c), rules regarding prior treatment regimens were clarified. Under 2. Target Population: Rules for NSCLC, RCC, CRPC, SCCHN, and melanoma participants defined. Deleted criteria for ovarian cancer, colorectal cancer, and gastric cancer.	Modified to reflect expanded potential target diseases; added corresponding eligibility criteria.
Section 3.3.1 Inclusion Criteria, Table 5.1-1 Screening Procedural Outline, Section 5.7.3 Tissue Markers from Archived Tumor Samples	Changed timing of shipment of tissue to the central laboratory from "within 6 weeks after signing consent" to "as soon as possible after signing consent."	Modified to ensure quality of tissue samples.
Section 3.3.1 Inclusion Criteria, Section 3.3.2 Exclusion Criteria, Section 5.3.2 Laboratory Test Assessments, Section 5.1 Flow Chart/Time and Events Schedule (Table 5.1-2)	The word "adenocarcinoma" was added to clarify the pancreatic malignancy subtype.	Clarified intended target population.
Section 3.3.2 Exclusion Criteria	Under 1. Target Disease Exceptions, d): changed "pancreatic carcinoma" to "pancreatic adenocarcinoma."	Changed for consistency.
Section 3.4.1 Prohibited and/or Restricted Treatments	Added statement exempting androgen deprivation therapy for CRPC from the anti-cancer therapies prohibited during the study. Ticagrelor added to list of medications prohibited within 2 weeks prior to the first dose of the study drug or while receiving study drugs.	Aligned CPRC therapy with maintenance androgen deprivation (SOC). Ticagrelor excluded for safety, due to known effects on adenosine signaling.
Section 4 Study Drug	Table 4-1 Number of vials in a treatment clarified.	Clarified operational language.
Section 4.4 Method of Assigning Subject Identification	Rules for replacing subjects clarified.	Modified to assure sufficient numbers of evaluable subjects.
Section 4.5.6 Discontinuation of Subjects Following Any Treatment with Study Drug	Added conditions when cases of discontinuation may be reviewed and allowed to continue treatment with nivolumab monotherapy.	Modified to permit continued monotherapy of selected subjects with appropriate risk-benefit profile after

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
		consultation with medical monitor.
Section 5.1 Flow Chart/Time and Events Schedule	Table 5.1-1 Tumor Marker Assessments for pancreatic carcinoma and CRPC clarified. Table 5.1-1: Cardiovascular lipid profile was added to the Chemistry Laboratory Tests. Table 5.1-1: HbA1c was added to the Hematology Laboratory Tests. Table 5.1-3: Nivolumab (Q4W) was added to the Study Drug Administration list. The notes for the Nivolumab (Q2W) administration were slightly modified. Table 5.1-7: Nivolumab (Q4W) was added to the Study Drug Administration list. The notes for the Nivolumab (Q2W) administration were slightly modified. Tables 5.1-5 and Table 5.1-10 (BMS-986179 Q4W) were added.	Tumor markers added are SOC. Lipid profile and HbA1c added to enhance safety. Nivolumab Q4W, as per above. Updated tables to assure alignment with the body of the protocol.
Section 5.1 Flow Chart/Time and Events Schedule, Section 5.6 Biomarker Assessments, Section 5.7.2 Tissue Markers from Fresh Tumor Biopsies	In Tables 5.1-7 through 5.1-9, Tables 5.6-1 through 5.6-9, and Section 5.7.2, the term "optional" was removed from descriptions of tumor biopsies during the re-treatment phase or additional 80-week treatment phase. In Tables 5.1-2 through 5.1-5, Tables 5.6-1 through 5.6-6, and Tables 5.5.1-1 through 5.5.1-3, the term "mandatory was removed from descriptions of tumor biopsies.	Revised to ensure alignment with laboratory manual regarding biopsy requirements.
Section 5.3.1 Imaging Assessment for the Study	Submission procedures to centralized imaging core lab were added. An imaging manual (CA013 004 Imaging Manual) containing guidelines for image acquisition and submission was identified	Clarifications of operational details.
Section 5.3.2 Laboratory Test Assessments	Laboratory parameters HbA1c, cardiovascular lipid profile, and PSA were added to list.	Added to enhance safety.
[redacted] Section 8.3.2.2 Efficacy	[redacted]	

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
	[redacted] The Q4W regimen was added to list of regimens.	Aligned with Section 1.1.5.2.
Section 5.5.1 Pharmacokinetics and Immunogenicity: Collection and Processing	Tables 5.5.1-1, 5.5.1-2, 5.5.1-3, 5.5.1-4, 5.5.1-5, 5.5.1-6 Hypersensitivity added to "Grade 3/4 infusion of hypersensitivity reaction." Table 5.5.1-5 Crossover Q2W regimen added to title, and C2D1 information added. Predose and PK sampling details clarified in footnotes. Table 5.5.1-6 Crossover Q3W regimen added to title, and C4D1 information added. Predose and PK sampling details clarified in footnotes. Tables 5.5.1-7, 5.5.1-8, 5.5.1-9, and 5.5.1-10 were added.	Updated tables to assure alignment with the body of the protocol.
Section 5.6 Biomarker Assessments	Tables 5.6-4, 5.6-5, 5.6-7, 5.6-8 Plasma biomarker sampling information column added. [redacted]	Updated tables to assure alignment with the body of the protocol.
[redacted]		
Section 6.2.1 Nonserious Adverse Event Collection and Reporting	Additional text regarding collection of information for nonserious AEs and immune-mediated AEs was provided.	Clarified safety data handling processes.
Section 8.1.3 Part 2 (Expansion)	Details for sample size determination in Part 2 of the study for subjects with NSCLC, RCC, pancreatic adenocarcinoma, SCCHN, and CRPC were provided.	Updated to include new cohorts added in Part 2.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
	Table 8.1.3-1 and Table 8.1.3-2 were added.	
Section 8.2 Populations for Analyses	The definitions of population groups was expanded. The Response Evaluable population group was defined. A paragraph on the PK analysis population was added.	Clarified populations to be studied.
Section 8.4.2 Efficacy Analyses	Clarified that anti-tumor activity of BMS-986179 in monotherapy will also be described. Added that PFSR will be estimated by prior PD-(L)1 exposure status. [redacted]	Clarified efficacy analyses to be performed in specified cohorts [redacted]
Section 8.4.3 Safety Analyses	A sentence describing how safety events will be summarized was added.	Clarified presentation of safety analyses for monotherapy, combination, and overall.
Section 8.4.4 Pharmacokinetic Analyses	Added the phrase "wherever applicable" to the statement regarding tabulation of summary statistics for PK parameters.	Clarified language to acknowledge that it may not be possible to calculate all PK parameters in all subjects.
Section 11 List of Abbreviations	Abbreviations added to list.	Added for clarity and consistency with body of the protocol.