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Clinical Protocol CA224020

A Phase 1/2a Dose Escalation and Cohort Expansion Study of the Safety, Tolerability, and Efficacy of Anti-LAG-3 Monoclonal Antibody (BMS-986016) Administered Alone and in Combination with Anti-PD-1 Monoclonal Antibody (Nivolumab, BMS-936558) in Advanced Solid Tumors

Revised Protocol Number: 07
Incorporates Amendment 11

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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 versions.

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised protocol 07	20-Dec-2016	Incorporates Amendment 11
Amendment 11	20-Dec-2016	<p>The following changes were made:</p> <ul style="list-style-type: none"> Updated Nivolumab and BMS 986016 safety information Added a Q4W dosing regimen in Part B of the study Updated dose delay guidelines and study discontinuation criteria to align with Nivolumab program Modified inclusion/exclusion criteria for Part C of study Modified to mandate fresh tumor biopsy collection from every subject Updated statistical section and made administrative changes as applicable
Revised protocol 06	25-May-2016	Incorporates Amendment 07 and Administrative letter 03
Amendment 07	25-May-2016	<p>The following changes were made:</p> <ul style="list-style-type: none"> Revision of exclusion criteria regarding cardiovascular history Addition of echocardiogram and troponin level monitoring at baseline Addition of ECG and troponin level monitoring through Cycle 1 Correction of typographical errors
Revised protocol 05	12-Feb-2016	Incorporates Amendment 06 and Administrative letter 02
Amendment 06	12-Feb-2016	<p>The following changes were made:</p> <ul style="list-style-type: none"> Revised study design to remove Parts D, E, F and G, and updated Part C expansion cohort populations. Updated DLT criteria Included adaptive language for dose selection for Part C of the study Nivolumab infusion time was reduced from 60 minutes to 30 minutes starting for Part C of the study Updated statistical sections, to align with revised study design
Administrative letter 02	20-Nov-2015	Change of Medical Monitor/Study Director
Revised protocol 04	24-Aug-2015	Incorporates Amendment 04
Amendment 04	24-Aug-2015	<p>The following changes were made:</p> <ul style="list-style-type: none"> Revised study design to include new Parts/cohorts and updated expansion cohort populations; introduced adaptive design of Stage 1 and Stage 2. Updated biomarker and pharmacokinetic collections Updated anti-LAG-3 and nivolumab safety information Updated statistical sections to reflect new study design

Document	Date of Issue	Summary of Change
Revised protocol 03	08-Sep-2014	Incorporates Amendment 03 and Administrative letter 01
Amendment 03	08-Sep-2014	The following changes were made: <ul style="list-style-type: none"> Revised the starting dose of anti-LAG-3 in the first combination cohort of Part B from 3mg to 20mg. Removed the 3mg anti-LAG-3/240mg nivolumab cohort in Part B
Administrative letter 01	16-Jul-2014	Addition of EUDRACT number and minor clerical edits.
Revised Protocol 02	23-May-2014	Incorporates Amendment 02
Amendment 02	23-May-2014	The following changes were made: <ul style="list-style-type: none"> Addition of fourth additional subject at beginning of each dose level Revision of inclusion and exclusion criteria Updated WOCBP definition and contraception methods, and revised Appendix 1 Revised DLT criteria Added study drug dosing instructions for combination of anti-LAG-3 and nivolumab. Incorporated new biomarker sample collections for Part C of study Revised subject criteria for Part B and expansion cohorts in Part C of study Modified PK and ADA Table 5.5.1-1 Added Appendix 4- Nivolumab Management Algorithms
Revised Protocol 01	11-Sep-2013	Incorporates Amendment 01
Amendment 01	11-Sep-2013	The following changes were made: <ul style="list-style-type: none"> Addition of Grade 4 anemia to dose-limiting toxicity criteria Addition of neurological examination performed by a neurologist for subjects in Part B or C who develop study drug-related Grade 2 or higher neurological AEs Extension of vital sign monitoring on Cycle 1 Day 1 from 60 minutes to 120 minutes for subjects in the first cohort in Part B Modifications to inclusion criteria to specify that subjects in all parts of the study must have an incurable solid malignancy and that subjects in Parts B and C may have refused standard therapy for advanced or metastatic disease
Original Protocol	10-Jul-2013	Not applicable

SYNOPSIS

Clinical Protocol CA224020

Protocol Title: A Phase 1/2a Dose Escalation and Cohort Expansion Study of the Safety, Tolerability, and Efficacy of Anti-LAG-3 Monoclonal Antibody (BMS-986016) Administered Alone and in Combination with Anti-PD-1 Monoclonal Antibody (Nivolumab, BMS-936558) in Advanced Solid Tumors

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s):

BMS-986016 (anti-LAG-3 antibody) is supplied as a sterile 10mg/mL or 11mg/mL formulation to be administered as an intravenous (IV) infusion.

Nivolumab (BMS-936558) is available as a sterile 10-mg/mL formulation to be administered as an IV infusion.

In Part A, monotherapy dose escalation, BMS-986016 will be administered at doses of 20, 80, 240, and 800 mg once every 2 weeks, in 8-week cycles, for up to 12 cycles of study therapy.

In Part A1, monotherapy cohort expansion, BMS-986016 will be administered at the maximum administered dose (MAD) of 800 mg as determined in Part A. Study therapy will be administered once every 2 weeks, in 8-week cycles, for up to 12 cycles.

In Part B, dose escalation of combination with nivolumab administered by sequential infusion, nivolumab will be administered at a dose of either 80 mg or 240 mg followed by infusion of BMS-986016 at doses of 20, 80, and 240, once every 2 weeks, in 8-week cycles, for up to 12 cycles of study therapy. This part of the study will also have a dose escalation with a nivolumab dose of 480mg followed by infusion of BMS-986016 at doses of 160, 240 and 320mg once every 4 weeks, in 8-week cycles for up to 12 cycles of study therapy.

In Part C, cohort expansion of combination with nivolumab administered by sequential infusion nivolumab and BMS-986016 will be administered at the combination doses selected from Part B, which may represent the maximum tolerated dose (MTD), maximum administered dose (MAD), or an alternative dose selected from dose escalation. Study therapy will be administered once every 2 weeks with infusion of nivolumab first followed by BMS-986016 administration, in 8-week cycles, for up to 12 cycles.

Study Phase: Phase 1/2a

Research Hypothesis: It is anticipated that anti-LAG-3 antibody (BMS-986016), administered as a single agent or in combination with anti-PD-1 antibody (nivolumab), 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 determine the safety, tolerability, dose-limiting toxicities (DLTs), and MTD of BMS-986016 administered alone and in combination with nivolumab in subjects with advanced solid tumors.

The co-primary objective in Dose Expansion Part C is to investigate the preliminary efficacy of BMS-986016 in combination with nivolumab as measured by objective response rate, disease control rate and duration of response.

Secondary Objectives:

The secondary objectives are:

- To characterize the pharmacokinetics (PK) of BMS-986016 administered alone and in combination with nivolumab.
- To investigate the preliminary objective response rate (ORR) and/ or disease control rate (DCR) of BMS-986016 administered alone and in combination with nivolumab in subjects with advanced solid tumors in Parts

A and B Dose Escalation. To characterize the immunogenicity of BMS-986016 administered alone and in combination with nivolumab.

- To characterize the immunogenicity of BMS-986016 administered alone and in combination with nivolumab.
- In Parts A and B, to assess the effect of BMS-986016 administered alone and in combination with nivolumab on QTc.

Exploratory Objectives:

- To evaluate safety and tolerability of combination therapy using sequential infusion therapy.
- To assess the pharmacodynamic effects of BMS-986016 alone and in combination with nivolumab based on select biomarkers in the peripheral blood and tumor biopsy specimens.
- To characterize T cell function during both BMS-986016 monotherapy and combination therapy with BMS-986016 and nivolumab.
- To assess the 1-year and 2-year landmark overall survival in subjects treated with BMS-986016 alone and in combination with nivolumab.
- To explore exposure-response relationships in subjects treated with BMS-986016 as monotherapy or in combination with nivolumab.
- To investigate the relationship between clinical efficacy and peripheral and tumor biomarkers

Study Design:

This is a Phase 1/2a, open-label study of BMS-986016 administered as a single agent and in combination with nivolumab to subjects with advanced solid tumors.

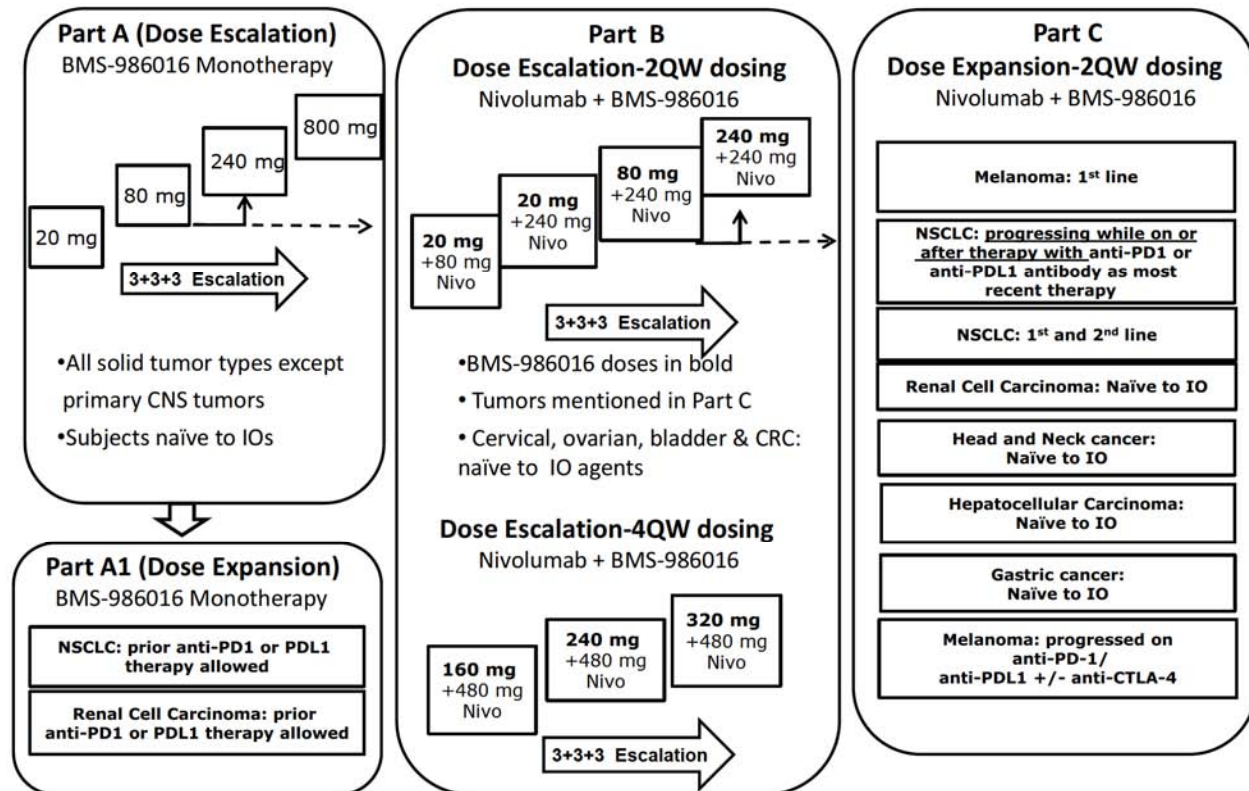
Part A and Part B consist of a 3 + 3 + 3 dose escalation design with BMS-986016 administered as a single agent (Part A) or in combination with nivolumab (Part B) as sequential infusions in subjects with advanced solid tumors. Treatment in Part B will be initiated upon the decision to escalate to the third dose cohort in Part A (in accordance with dose escalation rules); subsequently, escalation in the 2 parts will proceed in parallel. At no point will the dose of BMS-986016 administered in combination with nivolumab (Part B) exceed doses of BMS-986016 that have been demonstrated previously to be safe on the monotherapy dose escalation arm (Part A). Testing of the Q2W and Q4W dosing schedules in Part B can proceed concurrently with independent escalation decisions based upon review of the current total safety experience and following consultation and agreement between Investigators and the Sponsor.

Part A1 consists of cohort expansion with BMS-986016 monotherapy in 2 disease-restricted cohorts of approximately 6-12 subjects each. Treatment in Part A1 will be initiated at the maximum administered dose (MAD) determined in Part A (i.e., 800mg). The dose selected for Part A1 will not exceed the MAD in Part A, but dose selection may change according to assessment of other data including toxicities and PK and pharmacodynamic data from Parts A and A1. Subjects in Part A1 may crossover to combination therapy with nivolumab and BMS-986016 in sequential infusion if they meet pre-defined criteria.

Part C consists of cohort expansion in disease-restricted cohorts using a multi-stage approach, treated with sequential infusion of nivolumab and BMS-986016. Cohorts deemed futile (see sample size section for further details) at Stage 1 will be discontinued, while those deemed promising may be expanded further up to 90 to 120 subjects in total after careful evaluation of all available data including the totality of efficacy, safety profile, and PK/PD. Otherwise, additional subjects may be treated to collect more data during Stage 2 in order to make decision for further expansion. The doses selected for Part C will not exceed the Part B MTD or MAD, and specific doses selected may incorporate assessment of other data including toxicities, PK and pharmacodynamic data from Parts A and B. Subjects in Part C cannot crossover to Part A1 either.

A schematic of the study is provided in Figure A.

Figure A: Study Schematic



IO = immuno-oncology agents (such as, but not limited to, anti-CTLA-4, anti-PD-1, anti-PD-L1, anti-PD-L2, anti-KIR, anti-CD137, and/or anti-OX40 antibodies)

Subjects will complete up to 4 periods of the study: **Screening** (up to 28 days), **Treatment** (up to a maximum of twelve 8-week cycles of study therapy), **Clinical Follow-up** (135 days), and **Survival Follow-up** (up to 2 years following the first dose of study drug, however, additional survival follow-up may continue for up to 5 years from the first dose). Two independent periods, **Cross-Over** and **Re-challenge**, may be conducted in selected cases at progression.

The **Treatment Period** consists of up to twelve 8-week treatment cycles. Each treatment cycle comprises 4 doses of either BMS-986016 alone (Parts A and A1) or in combination with nivolumab (Part B and C), administered on Days 1, 15, 29, and 43 of each treatment cycle. In Part B, every 4 week dosing, BMS-986016 and nivolumab will be administered on Days 1 and 29 of each treatment cycle. In Parts B and C when both study drugs are given as sequential infusion, nivolumab will be given first followed by BMS-986016 within 15 to 30 minutes of completing the infusion of nivolumab. Tumor response will be evaluated using Response Evaluation Criteria for Solid Tumors version 1.1 (RECIST v1.1). Subjects will be allowed to continue study therapy until the first occurrence of either: (1) confirmed complete response (CR), (2) completion of the maximum number of twelve 8-week cycles, (3) progressive disease (PD), (4) clinical deterioration, and/or (5) meeting other criteria for discontinuation ([Section 3.5](#)). Treatment beyond progression may be allowed in select subjects with initial RECIST v1.1-defined PD who are receiving clinical benefit as assessed by the Investigator, tolerating treatment, and meeting other criteria specified in [Section 4.3.4](#). Subjects who discontinue treatment will enter a 135-day Clinical Follow-up period.

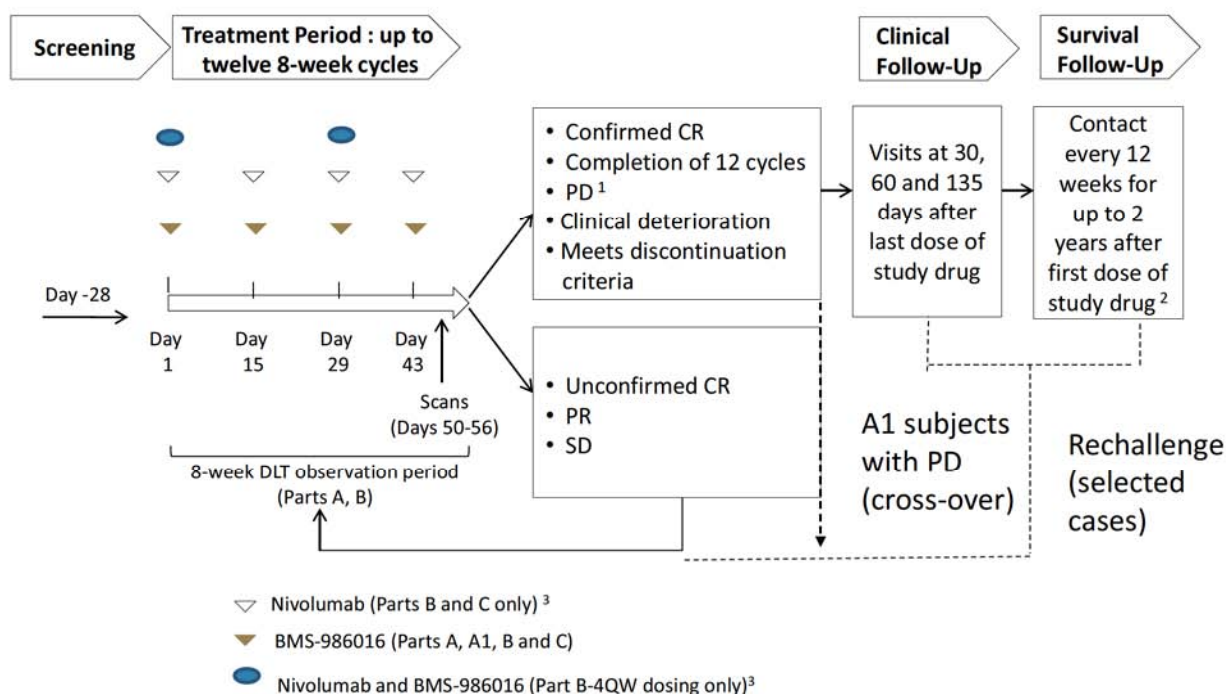
After completion of the **Clinical Follow-up period**, subjects will enter the **Survival Follow-up period**. During this period, clinic visits or telephone contact every 12 weeks will be performed to assess survival status. The duration of

this period is up to 2 years following the first dose of study drug, however, additional survival follow-up may continue for up to 5 years from the first dose. Diagnostic imaging must be performed every 12 weeks until progression in subjects who discontinue due to CR, and in subjects with PR or SD at the end of Cycle 12. If subjects progress during the clinical follow-up period or the survival follow-up period, they could further receive therapy with BMS-986016 alone or in combination therapy (**Re-challenge period**) as long as the risk:benefit ratio is considered favorable by the Investigator and the Medical Monitor and eligibility criteria is met ([Section 3.1.2.4](#)). The original dose and schedule and protocol rules would apply accordingly. Thus, subjects could receive therapy for up to 12 additional eight-week cycles. Subjects will not be re-challenged a second time. Collection of archival tissue (baseline) and tumor biopsies (baseline and on-treatment) will be optional for subjects enrolled for re-challenge. PK and biomarker monitoring will be limited ([Sections 5.5](#) and [5.7](#)).

Also, subjects receiving therapy with BMS-986016 alone in expansion Part A1, may **Cross-Over** to combination therapy at confirmed progression ([Section 3.1.2.1](#)).

A study schematic is shown in Figure B.

Figure B: Detailed Study Schematic



¹ Treatment beyond progression may be considered in select subjects as described in [Section 4.3.4](#).

² Diagnostic imaging must be performed every 12 weeks until progression in subjects who discontinue due to CR, and in subjects with PR at the end of Cycle 12.

³ For treatment visits in Parts B and C where BMS-986016 and nivolumab are administered sequentially, nivolumab will be administered first followed by BMS-986016 within 15 to 30 minutes after completion of the nivolumab infusion.

Study Parts:

Dose Escalation Part A: In Part A, a 3 + 3 + 3 design will be used to assess the safety of BMS-986016 given as single agent. A fourth subject may be enrolled at the beginning of a dose escalation cohort following agreement between the Investigator and the Sponsor/Medical Monitor, if subject is able to start the first day of dosing within approximately one week of the third subject in the same dose escalation cohort. The dosages during dose escalation are provided in Table -1. Three subjects (or 4, if applicable) will initially be treated in each dose cohort; in Dose Cohort 1, each of the first 3 subjects (or 4, if applicable) will be designated as sentinel subjects and will begin treatment at least 5 days apart. Subjects in subsequent cohorts will not be required to observe the 5-day interval between treatment start dates.

Dose escalation in Part A will proceed as follows: if none of the 3 (or 4, if applicable) subjects experiences a DLT, a new cohort of 3 subjects (or 4, if applicable) will be treated at the next higher dose level. If 1 of 3 (or 4, if applicable) subjects experiences a DLT, that cohort will be expanded to 6 subjects (or 7, if applicable). If 2 of 6 (or 7, if applicable) subjects experience a DLT, that cohort will be expanded to 9 subjects. If ≥ 2 of 3 (or 4, if applicable), ≥ 3 of 6 (or 7, if applicable), or ≥ 3 of 9 subjects experience DLTs within a cohort, then that dose level will be determined to have exceeded the MTD.

Table 1: Dose Escalation and Dose Expansion Schedules for Part A and Part A1 BMS-986016 Monotherapy

Part A Dose Escalation Cohort Number	Total Subjects	BMS-986016 Dose (IV; mg)
1	n = approximately 3-9	20
2	n = approximately 3-9	80
3	n = approximately 3-9	240
4	n = approximately 3-9	800
Total	N=approximately 12-36	
Part A1: Dose Expansion Cohorts		
NSCLC: prior anti-PD1 or PDL1 therapy allowed ^a	n = approximately 6-12	800
Renal Cell Carcinoma: prior anti-PD1 or PDL1 therapy allowed ^a	n = approximately 6-12	800
Total	N = approximately 12-24	

^asee [section 3.3](#) for detailed eligibility criteria

Prior to declaring the MTD (or MAD), and in consultation with Investigators, the Sponsor has the option to expand any cohort previously established to be safe in order to obtain additional experience or to investigate dose levels intermediate to those defined in the protocol. Dose escalation rules (cohort size, observation for DLTs, etc.) will apply to these expanded or additional cohorts. A maximum of 9 subjects will be enrolled in any additional or expanded dose cohorts.

Cohort Expansion Monotherapy (Part A1): The purpose of cohort expansion is to gather additional safety, tolerability, preliminary efficacy, PK, and pharmacodynamic information of BMS-986016 monotherapy. The doses selected for Part A1 will not exceed the MTD or MAD in Part A, but may incorporate assessment of other data including toxicities and PK and pharmacodynamic data from Part A. Doses to be considered may include doses intermediate to those evaluated in Part A, if recommended by the Investigators and the Sponsor. Modeling may be

used to help inform the selection of the combination dose level to carry forward in Part A1 if a dose below the MTD is chosen. Two expansion cohorts will be restricted to the tumor types listed in [Table -1](#).

Subjects in Part A1 may crossover to Part C if all of the following criteria are met: 1) Subject has confirmed disease progression (investigator-assessed RECIST 1.1-defined progression confirmed at least 4 weeks after the initial tumor assessment showing progression; 2) Subject has not experienced BMS-986016 related adverse events leading to permanent discontinuation; 3) Subject is not continuing to derive any clinical benefit from BMS-986016 single agent therapy as assessed by the investigator; 4) The individual case has been discussed with the medical monitor prior to cross over ([Section 3.1.2.1](#)); 5) At least an 8 week period in between the last dose of monotherapy and the first dose of combination therapy. Subjects will not be re-challenged a second time. Subjects crossing over to combination therapy will start treatment at Cycle 1 Day 1 as described for subjects in Part C. Subjects who crossover will receive combination therapy in sequential infusion at the doses that have been declared safe in dose escalation and/ or dose expansion parts at the time of cross-over. The original protocol rules will apply accordingly. Combination therapy may thus be administered for up to 12 additional eight week cycles according to the protocol rules. Subjects who crossed over and subsequently have an objective response in combination therapy will not be considered in the decision making for Part C proceeding to Stage 2. Subjects in Part C cannot crossover to Part A1.

Dose Escalation Sequential (Part B): Treatment in Part B will be initiated upon the decision to escalate to the third dose cohort in Part A in accordance with dose escalation rules. Subsequently, escalation in the 2 parts will proceed in parallel. At no point will the dose of BMS-986016 administered in combination with nivolumab (Part B) exceed doses of BMS-986016 that have been demonstrated previously to be safe on the monotherapy dose escalation arm (Part A). Treatment assignments for subjects eligible for both Part A and Part B will alternate between the 2 parts, with consecutively treated subjects assigned to different parts through interactive voice response system (IVRS), whenever possible. If there are no openings available in the part to which the subject would be assigned by this algorithm, then the subject will be assigned to the next open cohort or part.

In Part B, a 3 + 3 + 3 design will also be used to assess the safety of BMS-986016 given in combination with nivolumab as a sequential infusion every 2 weeks and every 4 weeks. A fourth subject may be enrolled at the beginning of a dose escalation cohort following agreement between the Investigator and the Sponsor/Medical Monitor, if subject is able to start the first day of dosing within approximately one week of the third subject in the same dose escalation cohort. The potential dose levels evaluated during dose escalation are provided in [Table -2](#). Intermediate and lower dose levels may be assessed following agreement between the Investigator and the Sponsor/Medical Monitor based upon ongoing review of safety data. As in Part A, each of the first 3 subjects (or 4, if applicable) in the first dose cohort in Part B will be designated as sentinel subjects and will begin treatment at least 5 days apart.

Table 2: Dose Escalation Schedule for Part B — BMS-986016 in Combination with Nivolumab every 2 week dosing

Dose Cohort Number	Total Subjects	BMS-986016 Dose (IV; mg)	Nivolumab Dose (IV; mg)
1	n = approximately 3-9	20	80
2	n = approximately 3-9	20	240
3	n = approximately 3-9	80	240
Intermediate	n = approximately 3-9	160	240
4	n = approximately 3-9	240	240

Table 2: Dose Escalation Schedule for Part B — BMS-986016 in Combination with Nivolumab every 2 week dosing

Dose Cohort Number	Total Subjects	BMS-986016 Dose (IV; mg)	Nivolumab Dose (IV; mg)
Dose Escalation Schedule for Part B — BMS-986016 in Combination with Nivolumab <u>every 4 week dosing</u>			
1	n = approximately 3-9	160	480
2	n = approximately 3-9	240	480
3	n = approximately 3-9	320	480
Total	N = approximately 24-72		

If the MTD is exceeded in Dose Cohort 2, the subsequent cohort will be treated with 80 mg of BMS-986016 and 80 mg of nivolumab. If this dose combination is found to be safe, and following consultation and agreement between Investigators and the Sponsor, escalation may proceed at the previously defined BMS-986016 doses, maintaining the nivolumab dose at 80 mg, or an intermediate dose level. Testing of the Q2W and Q4W dosing schedules can proceed concurrently with independent escalation decisions based upon review of the current total safety experience and following consultation and agreement between Investigators and the Sponsor.

Prior to declaring the MTD (or MAD), and in consultation with Investigators, the Sponsor has the option to expand any cohort previously established to be safe in order to obtain additional experience or to investigate dose levels intermediate to those defined in the protocol. Dose escalation rules (cohort size, observation for DLTs, etc.) will apply to these expanded or additional cohorts. A maximum of 9 subjects will be enrolled in any additional or expanded dose cohorts.

Cohort Expansion Sequential (Part C): The purpose of cohort expansion is to gather additional safety, tolerability, preliminary efficacy, PK, and pharmacodynamic information in subjects treated with sequential infusion of nivolumab first followed by administration of BMS-986016. The initial doses selected for specific Part C cohorts will not exceed the MTD or MAD in Part B, but may incorporate consideration of other data including (but not necessarily limited to) toxicities, PK and pharmacodynamic data from Parts A and B and can be chosen while additional Part B dose escalation cohorts continue to be explored. Part C expansion cohort doses to be considered will include those doses shown to be safe in Part B (or intermediate to those doses) as recommended by the Investigators and the Sponsor. Dosing of subsequent patients within an expansion cohort, or between cohorts, can be increased (if deemed safe in Part B) or decreased (based upon ongoing reviews of the totality of the safety data), all to be decided in agreement between the Investigators and the Sponsor. There will be no dose adjustments for individual subjects.

In Part C, a multi-stage design will be used to assess treatment efficacy. Cohorts deemed futile at Stage 1 will be discontinued while those deemed promising may be expanded up to 90 to 120 subjects in total after careful evaluation of all available data including the totality of efficacy, safety profile, and PK/PD. Otherwise, additional subjects may be treated to collect more data during Stage 2 in order to make a decision for further expansion. Enrollment to Stage 2 or further expansion in a given cohort can continue even if the other cohorts are still in Stage 1. Subjects who crossed over to combination therapy in Part A1 and subsequently have an objective response will not be considered in the decision making for Part C. Subjects in Part C cannot crossover to Part A1 either.

All Cohort Expansion Parts (A1 and C)

Continuous evaluation of toxicity events in the cohort expansions will be performed throughout enrollment in the expansion cohorts. If, at any time, the aggregate rate of treatment-related toxicities meeting DLT criteria exceeds 33% across all subjects treated in any of these cohort expansions Parts, the findings will be discussed and further

enrollment must be interrupted in that particular cohort and others. Depending on the nature and grade of the toxicity and after assessing the risk:benefit ratio, a new dose(s) for all cohorts may be initiated at a previously tested lower dose level or at a dose level intermediate to previously tested lower dose levels.

Re-challenge in Dose Escalation (Parts A and B) and Cohort Expansion (Parts A1 and C)

If subjects progress during the clinical follow-up period or the survival follow-up period, they could further receive therapy with BMS-986016 alone or in combination therapy (Re-challenge) as long as the risk:benefit ratio is considered favorable by the Investigator and the Medical Monitor and the following eligibility criteria is met: 1) Subject has confirmed disease progression (investigator-assessed RECIST 1.1-defined progression confirmed at least 4 weeks after the initial tumor assessment showing progression; 2) Subject has not experienced BMS-986016 related adverse events leading to permanent discontinuation;. The original dose and schedule of therapy and protocol rules will apply. Thus subjects could receive therapy for up to 12 additional eight-week cycles. Collection of archival tissue (baseline) and tumor biopsies (baseline and on-therapy) will be optional for subjects crossing-over and PK and biomarker monitoring will be limited ([Sections 5.5](#) and [5.7](#)).

Subjects who are re-challenged and who subsequently have an objective response will not be included in the primary analysis of efficacy. Responses to re-challenge will be evaluated in a separate analysis. Subjects will not be re-challenged a second time.

Dose-Limiting Toxicity: BMS-986016 has the potential to augment the frequency and severity of previously described AEs associated with nivolumab, or to produce new toxicities. For the purpose of guiding decisions regarding dose escalation in Parts A and B dose-limiting toxicity (DLT) will be determined based on the incidence, intensity, and duration of AEs that are related to study drug and that occur within 56 days (8 weeks) of initiation of study drug (i.e., the DLT evaluation interval, through the completion of Cycle 1). The severity of AEs will be graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.0.

No intrasubject dose escalations are allowed. Subjects who withdraw from the study during the DLT evaluation interval for reasons other than a DLT may be replaced at the same dose level. In the case that an infusion cannot be administered at a scheduled visit during the DLT evaluation interval, it must be administered as soon as possible. Subjects may be dosed no less than 12 days from the previous dose during Q2W cycles and no more than 3 days from scheduled dose. If an infusion cannot be administered at a scheduled visit, it should be administered as soon as possible. Subsequent dosing visits will follow every 2 weeks after the delayed dose. A dose given more than 3 days after the intended dose date will be considered a delay. A maximum delay of 6 weeks between doses is allowed. Longer delays may be allowed following discussion with the Medical Monitor. For Q4W dosing cycles, subjects may be dosed within a +/- 3 day window. For the purpose of making decisions on dose escalation from a safety perspective, subjects will be considered evaluable if they have received 3 out of the 4 scheduled BMS-986016 doses in Part A (or 3 out of 4 schedules BMS-986016 and nivolumab doses in Part B) through the 8 week observation period, only if the one missed dose was secondary to progressive disease or non-medical reasons. Unevaluable subjects may be replaced at the same dose level.

For the purpose of subject management, potential DLTs that occur at any time, whether during dose escalation (Part A, B) or cohort expansion (Parts A1, C) will result in all study drug(s) being held pending evaluation of the event's relatedness to study drug, severity, duration, and in accordance with [Section 4.3.2](#). Subjects must meet criteria for re-treatment prior to re-initiation of study treatment (see [Section 4.3.3](#)).

Duration of Study: Subjects will be allowed to continue on therapy for up to twelve 8-week cycles, confirmed CR, or until meeting criteria for discontinuation as described in [Section 3.5](#). Subjects may be on study for a total of up to approximately 2 years, including a 28-day screening period, up to twelve 8-week cycles of treatment, a 135-day clinical follow-up period, and up to 2-5 years of follow-up for survival (beginning from the first dose of study drug). If subjects progress during the clinical follow-up prior or the survival follow-up period, could further receive therapy with BMS-986016 alone or in combination therapy (Re-challenge) as long as they meet eligibility criteria and the risk:benefit ratio is considered favorable by the Investigator and the Medical Monitor. The original dose and schedule and protocol rules would apply accordingly. Subjects will not be re-challenged a second time. The total

duration of the study is expected to be approximately 7 years from the time of the first visit of the first subject to the required survival follow-up of the last subject enrolled.

Number of Subjects: Approximately up to 370 subjects may be dosed (up to approximately 100 subjects during dose escalation and approximately 270 subjects in cohort expansion).

Study Population: Male and female subjects with histologic or cytologic confirmation of advanced, non-resectable, or metastatic solid tumors and measurable disease who meet all eligibility criteria will be eligible to participate in the study. Unless otherwise stated in the criteria, subjects must be naive to prior immuno oncology agents (IOs) such as, but not limited to, anti-CTLA-4, and anti-PD-1, or anti-PD-L1 ; anti-PD- L2, anti-KIR, anti-CD137, and/or anti-OX40 antibodies.

Dose Escalation-Monotherapy (Part A): Subjects with any solid tumor type (with the exception of primary central nervous system [CNS] tumors or with CNS metastases as the only site of active disease) are eligible to enroll. Subjects must not have prior exposure to IOs.

Dose Expansion-Monotherapy (Part A1): Subjects with 1) NSCLC with prior anti-PD1 or PDL1 therapy allowed; 2) Subjects with renal cell carcinoma with prior anti-PD1 or PDL1 therapy allowed.

Dose Escalation- Sequential Infusion (Part B): Subjects with any solid tumor type (with the exception of primary CNS tumors or with CNS metastases as the only site of active disease) were eligible to enroll in the first two cohorts. Subjects naive to IOs, subjects with melanoma progressing while on- or after anti-CTLA-4 and/or anti-PD-1/ anti-PD-L1 antibody therapy and subjects with non-small cell lung cancer progressing while on- anti-PD-1 or anti-PD-L1 antibody therapy as their most recent are allowed (full criteria described in [Section 3.3.1](#)) were also eligible in the first 2 cohorts.

For subsequent cohorts, eligible tumor types (and all subtypes) will include: 1) NSCLC 1st line; 2) NSCLC whose disease progresses while-on therapy with anti-PD-1 or anti-PD-L1 antibody therapy; 3) melanoma 1st line; 4) melanoma progressing while-on or after receiving anti-CTLA-4 and/or anti-PD-1/ anti-PDL-1 antibody therapies; 5) renal cell carcinoma, naive to IOs; 6) other tumors naive to immuno-oncology agents including head and neck, gastric, hepatocellular, cervical, ovarian, bladder and colorectal cancers.

Cohort Expansion - Sequential Infusion (Part C): Tumor types include: 1) melanoma 1st line; 2) renal cell carcinoma naive to IO; 3) squamous cell carcinoma head and neck naive to IO; 4) NSCLC 1st/2nd line naive to IO; 5) NSCLC whose disease progressed while-on or after therapy with anti-PD-1 or anti-PD-L1 antibody as most recent therapy; 6) gastric cancer naive to IO; 7) hepatocellular cancer naive to IO; and 8) melanoma previously progressed on anti-PD-1/ anti-PDL-1 antibody alone or anti-PD-1/ anti-PDL-1 antibody in combination with anti-CTLA-4 antibody therapy.

Men who are sexually active with WOCBP must also use contraceptive method(s) based on the information in [Appendix 1](#). Men who are sexually active with WOCBP must follow instructions for birth control for a total of 33 weeks after their last dose of investigational drug (a period of 90 days plus the time required for the investigational drug to undergo 5 half-lives [i.e., 225 days or 33 weeks]).

Study Assessments:

- **Safety Outcome Measures:** Safety assessments will be based on medical review of AE reports and the results of vital sign measurements, ECGs, physical examinations, and clinical laboratory tests. AEs will be assessed continuously during the study and for 135 days after the last treatment. AEs will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA) and reviewed for potential significance and importance. Both AEs and laboratory tests will be graded using the NCI CTCAE v4.0.
- **Efficacy Measures:** Disease assessment using computed tomography (CT) and/or magnetic resonance imaging (MRI), as appropriate, will be performed at baseline and every 8 weeks during the treatment period (i.e. twelve 8-week cycles) after first dose of study medication. Tumor responses will be determined by investigator for subjects with adequate data as defined by RECIST v1.1. For selected disease cohorts in Part C, tumor responses

will also be determined by blinded independent central review committee (BICR) using RECIST v1.1. Pharmacokinetic Measures: Serial serum samples will be collected from all subjects at specified timepoints to evaluate concentrations of BMS-986016 and nivolumab. PK parameters such as C_{max}, C_{trough}, T_{max}, AUC(TAU), CLT, and AI will be derived from serum concentration versus time data. Sparse serum samples will be collected from subjects in Parts B and C to evaluate concentrations of nivolumab.

- Immunogenicity Measures: Serum samples to evaluate development of positive anti-drug antibody (ADA) response to BMS-986016 and nivolumab will be collected at specified timepoints.
- Biomarker Measures: The sample collection and biomarker assessment strategy is designed to address mechanisms of action, pharmacodynamic changes associated with BMS-986016, and the potential identification of predictive safety and efficacy biomarkers associated with BMS-986016, and to evaluate potential mechanisms of resistance to BMS-986016 and nivolumab. To address these key questions, peripheral blood, serum, and biopsy samples will be collected prior to and during study drug treatment during this study.

Statistical Considerations: Sample Size:

Dose Escalation (Parts A and B)

Sample size at each dose depends on observed toxicity and cannot be precisely determined. Parts A and B will have 3 to 9 subjects in each cohort.

Cohort Expansion (Part C)

The objective of this expansion in combination with nivolumab is to support further clinical testing by demonstrating adequate safety and tolerability as well as favorable risk/benefit by assessing preliminary efficacy measured by objective response rate (ORR) and other clinically relevant efficacy measures such as duration of response and disease control rate. However, the sample size is strictly based on efficacy, specifically based on the target ORR relative to historic ORR.

Disease-, as well as prior IO therapy-, restricted cohorts will be investigated in the Part C cohort expansion: NSCLC progressing on IO therapy; Melanoma progressing on anti-PD-1/anti-PD-L1; RCC naive to IO therapies; NSCLC 1st/2nd line naive to IO therapies; Melanoma 1st line; SCCHN naive to IO therapies; Gastric cancer naive to IO therapies; and HCC naive to IO therapies. The NSCLC progressing on IO therapy cohort will be analyzed as a whole and as two separate sub-groups, refractory and relapsed, as defined in [Section 3.3.1](#). All disease cohorts will be handled independently and there will be no multiplicity adjustment.

A multi-stage design will be used as a guide for each expansion cohort in order to decide whether the treatment of BMS-986016 in combination with nivolumab warrants more extensive development. At first, a 2-stage design with a reasonable false positive rate (eg, FPR < 10%) and false negative rate (eg, FNR < 10%) will be used for the decision making based on assumptions of true (target) and historic/standard-of-care response rate for each cohort. The assumed historic and target response rates may change over time and may need to be adjusted by the time of response data from this study are available. Using a 2-stage design provides an option to stop early for futility as well as a signal of preliminary antitumor activity for strong-go early on. Enrollment may continue into stage 2 while the planned number of subjects for stage 1 are followed for efficacy evaluable tumor assessments. There will be no stopping of a disease cohort for efficacy, although early plan for the next stage of clinical development may be initiated.

The ORRs considered to be of clinical value for further expansion of selected populations, sample size, and operational characteristics of using a 2-stage design, as an example are provided in [Table 3](#), although this is not for statistical hypothesis testing.

Once there is preliminary evidence of the treatment effect that may represent substantial improvement over available therapies, sufficient additional subjects will be treated to demonstrate a substantial and clinically meaningful effect in ORR that is supported by duration of the effect. The total sample size at this stage will be determined based on the

ability to produce a CI which would exclude an ORR of the historic response and to provide sufficient information for a reliable understanding of the safety profile. With 90 to 120 subjects in total, this design yields a less than 5% of 2-sided Type I error rate and at least 80% power depending on tumor type with specified historic/SOC and target rates. Table 4 summarizes the 95% exact CI for various observed ORRs with sample sizes of 90, 100, and 120.

Table 3: Example of a Two-stage Design Characteristics

Cohort	Historic/ Target rate (%)	Stage	Cum sample size	Conclude inefficacy if R ^a	Conclude efficacy If R	PET ^b for futility (%)	PEE ^c for efficacy (%)
Gastric IO naive							
HCC IO naive	10/30	1	15	≤ 1	≥ 4	55	70
Melanoma progressed on anti-PD- 1/PD-L1		2	26	≤ 5	≥ 6		
RCC IO naive	25/50	1	11	≤ 2	≥ 6	46	50
		2	26	≤ 9	≥ 10		
NSCLC IO refractory	5/20	1	12	0	≥ 3	54	44
NSCLC IO relapsed		2	37	≤ 3	≥ 4		
NSCLC 1/2L, IO naive	20/45	1	14	≤ 3	≥ 7	70	45
		2	25	≤ 7	≥ 8		
Melanoma 1L	40/65	1	13	≤ 5	≥ 10	57	28
		2	28	≤ 14	≥ 15		
SCCHN IO naive	20/40	1	20	≤ 4	≥ 8	63	58
		2	36	≤ 10	≥ 11		

^a R is the cumulative number of responses at the end of stage

^b probability of early termination

^c probability of early expansion

Table 4: Observed ORR with Exact 95% CI

Sample Size	Number of Responses	ORR	95% Exact CI
90	18	20%	[12.3%, 29.8%]
	27	30%	[20.8%, 40.6%]
	32	36%	[25.7%, 46.4%]
	37	41%	[30.8%, 52.0%]
	46	51%	[40.4%, 61.8%]

Table 4: Observed ORR with Exact 95% CI

Sample Size	Number of Responses	ORR	95% Exact CI
100	20	20%	[12.7%, 29.2%]
	30	30%	[21.2%, 40.0%]
	35	35%	[25.7%, 45.2%]
	40	40%	[30.3%, 50.3%]
	50	50%	[39.8%, 60.2%]
120	24	20%	[13.3%, 28.3%]
	36	30%	[22.0%, 39.0%]
	42	35%	[26.5%, 44.2%]
	48	40%	[31.2%, 49.3%]
	60	50%	[40.7%, 59.3%]

Cohort Expansion- Monotherapy (Part A1)

A sample size of 6 subjects per cohort allows for estimation of the proportion of subjects with objective response (i.e., CR + PR) within a cohort such that the maximum distance between the estimated rate and either limit of the exact 2-sided 95% Clopper-Pearson confidence interval is 47.5%.

A sample size of 12 subjects per cohort allows for estimation of the proportion of subjects with objective response (i.e., CR + PR) within a cohort such that the maximum distance between the estimated rate and either limit of the exact 2-sided 95% Clopper-Pearson confidence interval is 32.2%.

Endpoints:**Primary Endpoint:**

- The primary endpoint of this Phase 1/2a study is safety as measured by the rate of AEs, serious adverse events (SAEs), deaths, and laboratory abnormalities, assessed during treatment and for up to for 135 days after the last treatment. All subjects who receive at least one dose of BMS-986016 or nivolumab will be analyzed for safety.
- Objective response rate (ORR), disease control rate (DCR), and duration of response (DOR) by BICR using RECIST v1.1, where applicable, in selected disease cohorts in Part C will be the co-primary endpoints.

Secondary Endpoints:

- Efficacy:** The BOR, ORR, DCR, DOR, and PFS rates at pre-specified timepoints by investigator using RECIST v1.1 will be the secondary evaluation.
- Pharmacokinetics:** Select BMS-986016 PK parameters, such as C_{max}, C_{trough}, T_{max}, AUC (TAU), CLT, and AI, will be assessed from concentration-time data during Cycle 1 and Cycle 3.
- Immunogenicity:** The proportion of subjects who develop specific ADA to either BMS-986016 or nivolumab will be measured during treatment and for up to 135 days after their last treatment in post-treatment follow-up.
- ECG:** In Parts A and B, QTc will be assessed by a central reader for ECG collected at follow-up visit 1, as well as on Day 1 of Cycle 1 and Cycle 3 at the pre-dose and 4-hour post-dose time points.

Exploratory Endpoints:

- Biomarkers:** Biomarker endpoints from peripheral blood may include, but not limited to, measures such as levels of soluble factors, as well characterization by immunophenotyping, at each scheduled timepoint. Biomarker endpoints from tumor biopsies may include but will not be limited to measures such as level of

immune cell infiltration, somatic mutational load, expression of IFN response genes, functional status and diversity of T cell receptor repertoire, and expression of lymphocyte activation gene 3 (LAG-3), major histocompatibility complex (MHC) class II, PD-1, and PD-L1.

- **Pharmacokinetics:** PK parameters will include nivolumab concentration-time data at select trough (C_{trough}) and end-of-infusion (EOI) timepoints based on measurements collected for up to 135 days during the post-treatment follow-up.
- **Efficacy:** Landmark overall survival will be an exploratory efficacy endpoint in subjects treated with BMS-986016 alone and in combination with nivolumab.

Analyses:

Unless otherwise specified, data from Part A (monotherapy-dose escalation) and Part A1 (monotherapy-dose expansion) will be presented separately from data collected in Parts B and C (sequential combination therapy). Safety data from dose-escalation phase will be summarized by dose and across all doses. Safety data from dose-expansion phase will be summarized for each disease cohort and overall by dose and across doses. Efficacy data from dose-expansion phase will be summarized for each disease cohort by dose and across doses. Efficacy data from Parts dose-escalation phase will be summarized by dose and listed by tumor type.

Safety: All subjects who receive study drug therapy will be included in the analysis of safety endpoints. All recorded AEs will be listed and tabulated by system organ class, preferred term, relationship to study drug, and treatment and coded according to the most current version of MedDRA. Vital signs and clinical laboratory test results will be listed and summarized by treatment. Any significant physical examination findings and results of clinical laboratory tests will be listed. Any ECG abnormalities identified by the Investigator will be listed. In Parts A and B, ECG will be assessed by a central reader at specific timepoints. All ECG data analyses including summaries of each ECG parameters, frequency distributions of subjects' maximum values/changes, and scatter plots will be performed following the current practice of ECG data analysis. Concentration-response analysis may be performed using mixed effect model, if appropriate. The details of ECG data analysis will be provided in statistical analysis plan.

Pharmacokinetics: PK parameters for BMS-986016 will be calculated using noncompartmental analyses. Summary statistics will be tabulated for the PK parameters of BMS-986016 by treatment and study day/cycle. To describe the association of these parameters with dose of BMS-986016, scatter plots of C_{max} and AUC (TAU) versus dose may be provided for each day measured. Dose proportionality of BMS-986016 when administered alone or co-administered with nivolumab may also be assessed based on a power model. Nivolumab EOI and trough (C_{trough}) concentrations will be tabulated by treatment using summary statistics.

Immunogenicity Analyses: A listing will be provided for all available immunogenicity data. For each drug, the number and percent of subjects who meet specified endpoint definitions will be summarized; specifically, those with an ADA-positive sample at baseline, those who meet the definition of being ADA-positive, those who are persistently ADA-positive. To examine the potential relationship between immunogenicity and safety, a table summarizing the frequency and type of AEs of special interest may be explored by immunogenicity status. In addition, potential relationships between immunogenicity and efficacy and/or PK may also be explored.

Efficacy Analyses:

Individual BOR, DOR, and PFS will be determined based on RECIST v1.1 criteria. BOR outcomes will be summarized using frequency tables. Time to event distribution (eg. PFS and DOR) will be estimated using Kaplan-Meier (K-M) method. When appropriate, the median along with 95% CI will be provided using Brookmeyer and Crowley methodology (using log-log transformation for constructing the confidence intervals). Rates at fixed timepoints (e.g. PFSR 24 weeks) will be derived from the K-M estimate and corresponding confidence interval will be derived based on Greenwood formula. Confidence intervals for binomial proportions will be derived using the Clopper-Pearson method.

Biomarker Analyses: The pharmacodynamic effect in subjects who undergo biopsy will be assessed using summary statistics and plots. As an example, the correlation of TIL changes and tumor marker expression with measures of peripheral blood markers may be explored graphically and using appropriate modeling approaches based on data availability. Associations between biomarker measures from peripheral blood or tumor biopsy and clinical outcomes may also be explored graphically and further assessed as needed by methods such as, but not limited to, logistic regression and characterized by appropriate statistics.

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1 INTRODUCTION AND STUDY RATIONALE

Patients with metastatic or refractory solid tumors have very poor prognosis.¹ Despite advances in multimodal therapy, increases in overall survival in this patient population have been limited. To address this unmet medical need, compounds that have novel mechanisms of action will be evaluated in clinical studies with the goal of achieving better response rates and improved overall survival.

The use of immunotherapy in the treatment of cancer is based on the premise that tumors evade the endogenous immune response by being recognized as self, and not non-self. Tumors develop immune resistance using different mechanisms; the goal of immunotherapy is to counteract these resistance mechanisms, allowing the endogenous immune system to reject tumors. The recent success of immune-modulating agents in patients with refractory solid tumors has provided proof-of-concept of the efficacy of immune system activation as a therapeutic modality. Specifically, patients with metastatic melanoma had an increase in overall survival when treated with the anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) antibody, ipilimumab.² Moreover, the same patient population treated with the combination of ipilimumab and an anti-PD-1 antibody (nivolumab) achieved an unprecedented 53% response rate and prolonged responses.³ These data suggest that combination therapy with immune-modulating agents may achieve more robust and prolonged responses than single-agent therapy in select cancer types and deserves to be further explored.

1.1 Study Rationale

1.1.1 Rationale for Nivolumab Therapy

Programmed cell death 1 (PD-1) is a cell surface signaling receptor that plays a critical role in the regulation of T cell activation and tolerance.⁴ It is a type I transmembrane protein and together with BTLA, CTLA-4, ICOS, and CD28, make up the CD28 family of T cell co-stimulatory receptors. PD-1 is primarily expressed on activated T cells, B cells, and myeloid cells.⁵ It is also expressed on natural killer (NK) cells.⁶ Binding of PD-1 by its ligands PD-L1 and PD-L2, results in phosphorylation of the tyrosine residue in the proximal intracellular immune receptor tyrosine inhibitory domain, followed by recruitment of the phosphatase SHP-2, eventually resulting in down-regulation of T cell activation. One important role of PD-1 is to limit the activity of T cells in peripheral tissues at the time of an inflammatory response to infection, thus limiting the development of autoimmunity.⁷ Evidence of this negative regulatory role comes from the finding that PD-1-deficient mice develop lupus-like autoimmune diseases including arthritis and nephritis, along with cardiomyopathy.^{8,9} In the tumor setting, the consequence is the development of immune resistance within the tumor microenvironment.

PD-1 is highly expressed on tumor-infiltrating lymphocytes, and its ligands are upregulated on the cell surface of many different tumors.¹⁰ Multiple murine cancer models have demonstrated that binding of ligand to PD-1 results in immune evasion. In addition, blockade of this interaction

results in antitumor activity. These findings provided the rationale for testing PD-1 pathway blockade in clinical trials.

Nivolumab is a fully human monoclonal antibody that binds to PD-1 with nanomolar affinity and a high degree of specificity, thus precluding binding of PD-1 to its ligands PD-L1 and PD-L2.¹¹ Nivolumab does not bind other related family members, such as BTLA, CTLA-4, ICOS, or CD28. Results from clinical trials have demonstrated complete response (CR), partial response (PR), and mixed response in patients with advanced solid tumors treated with nivolumab monotherapy, including all tumor types chosen for expansion in this study: NSCLC, melanoma, and renal cell carcinoma (RCC), hepatocellular carcinoma (HCC), squamous cell cancer of the head and neck (SCCHN), and gastric cancer. (Section 1.4.2.6).

1.1.2 LAG-3 and T Cell Exhaustion

Lymphocyte activation gene-3 (LAG-3; CD223) is also a type I transmembrane protein that is expressed on the cell surface of activated CD4⁺ and CD8⁺ T cells and subsets of NK and dendritic cells.^{12,13} LAG-3 is closely related to CD4, which is a co-receptor for T helper cell activation. Both molecules have 4 extracellular Ig-like domains and require binding to their ligand, major histocompatibility complex (MHC) class II, for their functional activity. In contrast to CD4, LAG-3 is only expressed on the cell surface of activated T cells and its cleavage from the cell surface terminates LAG-3 signaling. LAG-3 can also be found as a soluble protein but it does not bind to MHC class II and its function is unknown.

It has been reported that LAG-3 plays an important role in promoting regulatory T cell (Treg) activity and in negatively regulating T cell activation and proliferation.¹⁴ Both natural and induced Treg express increased LAG-3, which is required for their maximal suppressive function.^{15,16} Furthermore, ectopic expression of LAG-3 on CD4⁺ effector T cells reduced their proliferative capacity and conferred on them regulatory potential against third party T cells.¹⁶ Recent studies have also shown that high LAG-3 expression on exhausted lymphocytic choriomeningitis virus (LCMV)-specific CD8⁺ T cells contributes to their unresponsive state and limits CD8⁺ T cell antitumor responses.^{17,18} In fact, LAG-3 maintained tolerance to self and tumor antigens via direct effects on CD8⁺ T cells in 2 murine models.¹⁸

Immune tolerance observed in the setting of tumor development and tumor recurrence, however, seems to be mediated by the co-expression of various T cell negative regulatory receptors, not solely from LAG-3. Data from chronic viral infection models,^{17,18,19} knock-out mice,^{20,21,22} tumor recurrence models,²³ and, to a more limited extent, human cancer patients,^{23,24,25} support a model wherein T cells that are continuously exposed to antigen become progressively inactivated through a process termed “exhaustion.” Exhausted T cells are characterized by the expression of T cell negative regulatory receptors, predominantly CTLA-4, PD-1, and LAG-3, whose action is to limit the cell’s ability to proliferate, produce cytokines, and kill target cells and/or to increase Treg activity. However, the timing and sequence of expression of these molecules in the development and recurrence of tumors have not been fully characterized.

It is hypothesized that CTLA-4 acts as the dominant off-switch for tolerance, but it is the strong synergy between the PD-1 and LAG-3 inhibitory pathways that seems to mediate tolerance to both self and tumor antigens.^{20,21,23} Whereas CTLA-4 knockout (KO) mice die prematurely from multiorgan inflammation,²⁶ PD-1 and LAG-3 single knockout mice present minimal immunopathologic sequelae.²¹ In contrast, dual knock-out mice (LAG3-/-PD1-/-) abrogates self-tolerance with resultant autoimmune infiltrates in multiple organs and even lethality.^{20,21} These dual knock-out mice also show markedly increased survival from and clearance of multiple transplantable tumors.²⁰

Conversely, extensive co-expression of PD-1 and LAG-3 on tumor-infiltrating CD4⁺ and CD8⁺ T cells has been shown in distinct transplantable tumors and samples from melanoma, RCC, head and neck, NSCLC and ovarian cancer patients.^{23,27,29,31,35,36,40} Blockade of PD-1/PD-L1 interactions has been successfully used to restore antitumor immunity in preclinical and clinical studies. But the simultaneous blockade of PD-1 and LAG-3 pathways on T cells may exert an even more robust antitumoral immunity in naive as well as in recurrent tumors due to the possibility of reversing LAG-3-mediated T cell exhaustion. In 2 syngeneic mice models, for example, dual anti-LAG-3/anti-PD-1 antibody therapy is able to cure most mice of established tumors that are largely resistant to single antibody treatment.²⁰ Furthermore, recurrent tumors from a melanoma mouse model with increased Treg cell numbers and increased expression of checkpoint inhibitors PD-1, LAG-3, TIGIT, and TIM-3, can be controlled by depletion of Tregs (via FoxP3-DTR) plus the administration of anti-PD-L1 antibody. But more importantly, tumor regression of these recurrent tumors can also be accomplished with the combination of anti-PD-L1 plus anti-LAG-3 antibodies (C9B7W mAb) which also increases T cell activity.²³

Given the literature supporting synergistic activity of nivolumab and anti-LAG-3 antibody in viral models, it is hypothesized that this combination could have antitumor effects in virally-related cancers, including human papilloma virus (HPV)-related tumors such as HPV+ head and neck cancer (HNC). Recent evidence has shown a role of immune inhibitory receptors (e.g., PD-1/PD-L1) in the adaptive immune resistance seen in HNCs associated with HPV. In these cancers with high lymphocytic infiltration, there is PD-1 expression on the majority of CD8⁺ tumor infiltrating lymphocytes (TILs) and PD-L1 expression on both tumor cells and tumor-associated macrophages.²⁸ In a recent analysis, 33% to 47% of head and neck tumors showed a T cell-inflamed phenotype (TCIP) similar to melanoma, based on a gene expression signature. Interestingly, 75% of HPV (+) tumors showed a TCIP compared to 23% of HPV(-) tumors.²⁹ Furthermore, various checkpoint molecules were universally co-expressed in these TCIP tumors including PD1, CTLA4, LAG3, PDL-2, and IDO, as shown in gene expression analysis. Altogether these data support a role for the PD-1:PD-L1 pathway in T cell exhaustion leading to both persistence of HPV infection and malignant progression in HNC patients. It is then possible that LAG-3 may also play a role in virally induced T cell exhaustion in these patients. Gastric cancer is another exploratory tumor suitable for T cell-directed therapy based on preliminary objective responses observed in patients treated with anti-PD-L1 antibody therapy.³⁰ In addition, LAG-3 expression $\geq 1\%$ by immunohistochemistry has been documented in $\sim 35\%$ of gastric cancer

samples.³¹ A subtype of gastric cancer is also associated with Epstein-Barr virus (EBV) infection.³² This subtype is characterized by massive lymphocyte infiltration, better prognosis than EBV-negative tumors, and worldwide distribution, particularly in Asia. So, similar to HNC, the expression of checkpoint inhibitors may be leading to the persistence of EBV infection and/or malignant progression of these tumors which could be halted by T cell-directed therapy.

Hepatocellular carcinoma is another virally-associated tumor suitable for combination therapy with BMS-986016 and nivolumab. On one hand, it has been shown that LAG-3 is selectively up-regulated on tumor infiltrating CD8+ T cells and that HBV specific CD8+ TILs have an impaired effector function in subjects with HCC³³. Furthermore, T-cell directed therapy with anti-CTLA-4 antibody (tremelimumab; NCT01008358)³⁴ or with nivolumab in HCC subjects has displayed an acceptable safety profile as well as antitumor and antiviral activity in clinical studies. In a Phase I trial,³⁵ nivolumab produced durable responses across all dose levels and HCC cohorts (ORR 19%), with a favorable 12-month OS rate of 62%, regardless of the underlying viral status.

Checkpoint molecules are also key immunomodulators in RCC, particularly PD1 and LAG 3. By IHC, it has been documented that LAG-3 expression $\geq 1\%$ is found in ~60% of RCC samples. Flow cytometry has demonstrated that PD-1 and LAG-3 were expressed by a significantly higher percentage of CD8+ TILs as compared with PBMCs obtained from RCC patients or healthy individuals.³⁶ Also, subjects with RCC primary tumors and lung metastases associated with extensive CD8+ T cell infiltrate were correlated with poor prognosis only if they had high expression of LAG-3 and PDL-2.³⁷ Finally, nivolumab produced durable responses across all doses (ORR 29%), with a favorable 3-year OS rate of 52%.³⁸

Finally, the efficacy and improved overall survival obtained with nivolumab in second-line treatment of squamous non-small cell lung cancer (NSCLC) has led to its recent approval in the US.³⁹ Nivolumab has also demonstrated a significant overall survival (OS) benefit in non-squamous tumors in the CheckMate 057 trial.⁴⁰ So considering that approximately 47% of the immune infiltrate in NSCLC is PD-L1 positive and that these tumors also express other immune checkpoints such as LAG-3, TIM3, B7-H3, B7-H4, and CTLA-4⁴¹, it is possible that dual blockade could improve the outcomes already seen with nivolumab single agent in these subjects.

Altogether, these data argue strongly that dual blockade of the PD-1 and LAG-3 pathways could be a promising combinatorial strategy for multiple malignancies.

1.1.3 Rationale for Anti-LAG-3 Antibody (BMS-986016) Therapy

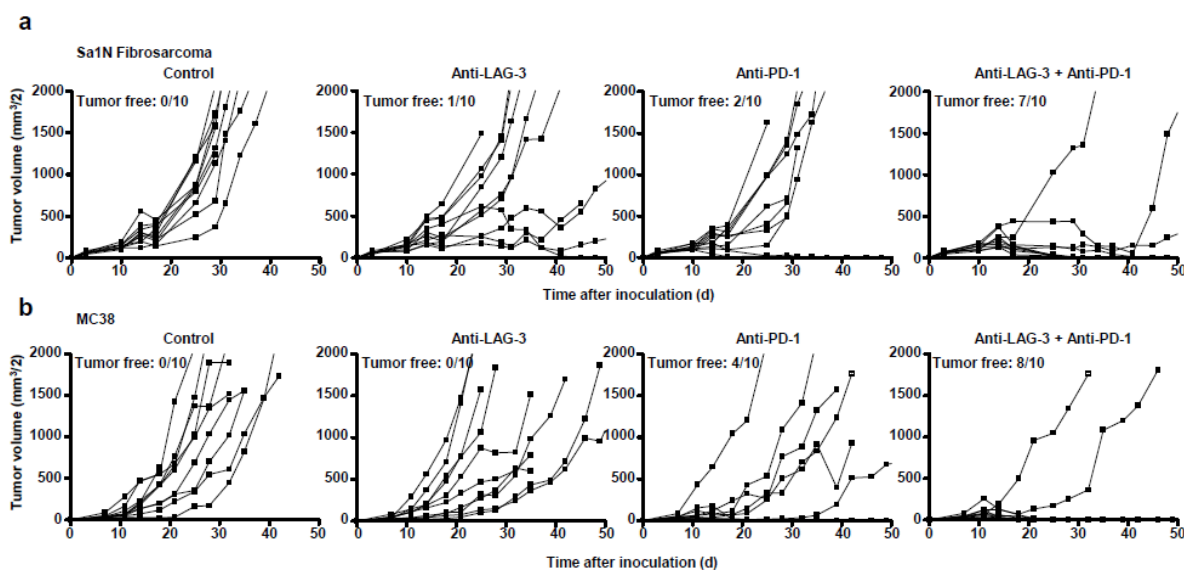
BMS-986016 is a fully human antibody specific for human LAG-3 that was isolated from immunized transgenic mice expressing human immunoglobulin genes. It is expressed as an IgG4 isotype antibody that includes a stabilizing hinge mutation (S228P) for attenuated Fc receptor binding in order to reduce or eliminate the possibility of antibody- or complement-mediated target cell killing. BMS-986016 binds to a defined epitope on LAG-3 with high affinity (K_d , 0.25-0.5 nM) and specificity and potently blocks the interaction of LAG-3 with its ligand, MHC class II (IC_{50} , 0.7 nM). The antibody exhibits potent in vitro functional activity in reversing LAG-

3-mediated inhibition of an antigen-specific murine T cell hybridoma overexpressing human LAG-3 (IC₅₀, 1 nM). In addition, BMS-986016 enhances activation of human T cells in superantigen stimulation assays when added alone or in combination with nivolumab (anti-PD-1 antibody).

1.1.4 Preclinical Studies utilizing Murine Anti-PD-1 and Anti-LAG-3 Antibodies

The importance of LAG-3 as an immunotherapy target was validated in murine in vivo models using 2 surrogate antibodies specific for mouse LAG-3. These studies evaluated tumor growth inhibition in syngeneic tumor models (Sa1N fibrosarcoma and MC38 colon adenocarcinoma) and monitored acceleration of autoimmunity in the non-obese diabetic (NOD) model. Anti-LAG-3 antibody administration resulted in both overall tumor growth inhibition and an increase in the number of tumor-free (TF) mice in those treatment groups (Figure 1.1.4-1). Anti-LAG-3 antibody administered in combination with anti-PD-1 antibody provided enhanced antitumor activity above the activity of either agent alone. For example, in multiple Sa1N tumor models, anti-LAG-3 antibody resulted in 20%–30% TF mice compared to control and anti-PD-1 antibody-treated mice (0%–10% TF mice), while the combination of anti-LAG-3 and anti-PD-1 antibodies resulted in 60%–90% TF mice. In the MC38 model, anti-LAG-3 antibody showed modest tumor growth inhibition alone but when administered in combination with anti-PD-1 antibody, resulted in enhanced antitumor activity above that observed for anti-PD-1 antibody alone (80% vs. 40% TF mice, respectively).

Figure 1.1.4-1: Antitumor Activity of Anti-LAG-3 and Anti-PD-1 Antibodies in Murine Models



1.1.5 Summary

Combined inhibition of T cell checkpoint molecules, such as CTLA-4, PD-1, and LAG-3, in preclinical models provides synergistic improvement in T cell activity, control of virus replication, and tumor inhibition in animal models. These observations led to the discovery of one of the key signature molecules associated with T cell exhaustion, the negative T cell regulator, LAG-3, and to the development of the antagonistic LAG-3 antibody, BMS-986016.

An initial evaluation of the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics will be conducted with an escalation arm of BMS-986016 monotherapy. It is proposed that this antibody should be considered for the treatment of multiple malignancies in combination with nivolumab (an anti-PD-1 antibody) as a T cell-core therapy with the aim to: 1) increase the number, type, and duration of responses in tumors known to respond to T cell checkpoint inhibitors; 2) rescue an adaptive response where patients are refractory to T cell checkpoint inhibitors and have progressed clinically; and/or 3) enhance the antitumor immunity in malignancies associated with chronic viral infections (e.g., HPV, EBV, HCV, HBV, etc).

1.1.6 Rationale for Dose Selection

CA224020 currently consists of 4 parts. Part A and Part B consist of a 3 + 3 + 3 dose escalation design with BMS-986016 administered as a single agent (Part A) or in combination as with nivolumab as sequential infusion (Part B) in subjects with advanced solid tumors. Part C consists of expansion cohorts of approximately 25-40 subjects each in disease-restricted populations (and further expansion of up to approximately 90-120 subjects in selected cohorts based upon safety and efficacy profiles), with BMS-986016 administered in combination with nivolumab as sequential infusions. Part A1 consists of expansion cohorts of approximately 6-12 subjects in each disease-restricted population, with BMS-986016 monotherapy.

1.1.6.1 Rationale for Flat Dosing

Therapeutic monoclonal antibodies doses have been routinely calculated on a body size basis with a perception that this approach may reduce intersubject variability in drug exposure compared with a flat dose approach. However, recent analyses of marketed and experimental monoclonal antibodies have demonstrated that body weight-based dosing did not always offer advantages over flat dosing in reducing exposure variability.^{42,43} Since the magnitude of the impact of body weight on the human PK of BMS-986016 is not yet determined and it is unknown if body size-based dosing would increase or decrease intersubject variability, this study will utilize a flat dose escalation and expansion since it is the simpler of the 2 approaches and may result in fewer dosing errors. The impact of body weight on the PK of nivolumab is small and the dose-response relationship is relatively shallow near the 3-mg/kg dose level, indicating that nivolumab can also be administered as a flat dose in combination with BMS-986016 in this study.

Flat doses for this study have been normalized for an average 80-kg adult cancer patient. A dataset from the nivolumab program used for preliminary population pharmacokinetics (PPK) contained 325 subjects with a median weight of 81 kg. This value aligns well with a study by Bai et al. which

found a median weight of 78 kg in 2519 adult patients with rheumatoid arthritis, breast cancer, colorectal cancer, non-small cell lung cancer (NSCLC), ovarian cancer, and non-Hodgkin's lymphoma.⁴²

1.1.6.2 Part A — BMS-986016 Dose

The first-in-human dose selected for this study is based on all available nonclinical data.

To balance the potential for pharmacologic activity and reasonable safety in this cancer patient population, a dose of 20 mg (0.25 mg/kg) was selected as the starting dose in monotherapy (Arm A). This dose is less than 1/10 of the human equivalent of the NOAEL (636 mg; 8.0 mg/kg) and is below the HED after a linear adjustment of the NOAEL target exposure for the highest affinity difference estimate of 265-fold (24 mg; 0.30 mg/kg) between activated human and cynomolgus T cells. No additional safety factor was added to the affinity-adjusted calculation because a linear adjustment is expected to be a conservative approach. Based on the model from the mouse efficacy data, this dose has the potential to have antitumor activity in humans. The calculated safety multiple for the 20-mg (0.25 mg/kg) dose is 315-fold based on the NOAEL of 100 mg/kg/week in the repeat-dose monkey study without accounting for affinity differences. In addition, a staggered dosing (sentinel subject) approach will be used in the first dose cohort as described in [Section 3.1.1.1](#). The top dose of 800 mg (10 mg/kg) is projected to have the potential for 71% to 179% TGI from the most sensitive model in mouse.

1.1.6.3 Part B — BMS-986016 Dose

The starting doses for Part B were selected based on all nonclinical data available from studies of the combination and BMS-986016 monotherapy and on emerging clinical safety and pharmacokinetic data from Part A monotherapy. In the repeated dose GLP toxicology study, a dose of 100 mg/kg/week of BMS-986016 + 50 mg/kg/week nivolumab was considered the severely toxic dose in 10% of the animals (STD10; refer to [Section 1.4.1.2](#)). The same approach to identifying human equivalent doses as described for monotherapy was used. Using a linear adjustment of the STD10 for a 265-fold affinity difference results in a dose of 20 mg (~0.3 mg/kg).

Pharmacokinetic data from Part A monotherapy suggested that subjects treated at 20 mg BMS-986016 (flat dose) have significant lower exposure compare to exposure associated with toxicity in the GLP- toxicology study with 100 mg/kg/week of BMS-986016 + 50 mg/kg/week nivolumab in cynos. Furthermore, BMS-986016 monotherapy was well tolerated in subjects treated with up to 800 mg BMS-986016 (flat dose) in Part A. The only high-grade related toxicity was an asymptomatic, self-limited, G3 lipase elevation in one subject treated at 20 mg flat dose. Therefore, the proposed starting dose for BMS-986016 in combination with nivolumab in Part B was 20 mg (~0.3 mg/kg) given every 2 weeks (Q2W). This dose cohort was initiated after the decision was made to escalate to the third dose cohort in Part A (monotherapy) in accordance with the dose escalation rules. Delaying initiation of the first dose cohort in Part B until after evaluation of the first 2 cohorts in Part A (i.e. up to 80 mg flat dose) provided additional clinical safety data with single-agent BMS-986016 at doses 4-fold higher than the 20-mg dose prior to administration of the combination. At no point will the dose of BMS-986016 administered in combination with nivolumab (Part B) exceed doses of BMS-986016 that have been demonstrated previously to be

safe on the monotherapy dose escalation arm (Part A). In addition, a staggered dosing (sentinel subject) approach will be used in the first dose cohort as described in [Section 3.1.1.2](#).

While the majority of assessments in this study have been and will be conducted using Q2W dosing, a Q4W dosing regimens will also be assessed in this study. Specifically, extending the dosing interval to Q4W provides numerous benefits to patients, including increased flexibility between clinical visits compared to Q2W.

Based on preliminary population PK simulation, the BMS-986016 doses of 160 and 320 mg Q4W are predicted to provide equivalent exposure corresponding to doses of 80 mg and 160 mg Q2W, respectively. BMS-986016 monotherapy doses up to 800 mg Q2W have been well tolerated but the safety of a higher nivolumab dose (>240 mg) in combination with BMS-986016 (up to 240 mg) is not yet established. Thus, the initial Q4W dose level would test the safety of the lower dose of BMS-986016 at 160 mg in combination with nivolumab (see [Table 3.1.1.2-1](#)).

1.1.6.4 Parts B, C — Nivolumab and Combination Dosing - Sequential infusion

As mentioned previously, a dose of 100 mg/kg/week of BMS-986016 + 50 mg/kg/week nivolumab was considered the STD10. Known human nivolumab PK parameters were used to calculate the HED. The same approach to identifying human equivalent doses as described for monotherapy was used. With an added 10-fold safety factor, the MRSD based on the STD10 is 320 mg (~4 mg/kg) in humans. The starting nivolumab dose for subjects in Part B is 80 mg (1 mg/kg) Q2W. All subsequent cohorts are planned to administer 240 mg of nivolumab Q2W, which is equivalent to the well tolerated global nivolumab monotherapy Phase 3 dose 3 mg/kg Q2W.¹¹ Most recently, the nivolumab dosage regimen was modified to a flat 240 mg Q2W as monotherapy for melanoma, NSCLC, and RCC in the US.¹¹ [USPI (Appendix 1)]

For the Q4W regimen in combination with BMS-986016, a starting dose cohort with 480 mg nivolumab was selected based on equivalence to the approved 240 mg Q2W nivolumab dosing. Based on pharmacokinetic modeling of nivolumab exposures, the 480 mg Q4W will provide a steady state average concentration similar to 240 mg Q2W. The simulated exposure (median and 95th prediction interval) across body weight range (35 - 160 kg) are also predicted to be maintained below the corresponding observed highest exposure experienced following nivolumab, wherein 10 mg/kg (or 800 mg) Q2W was well tolerated and no MTD was identified (clinical study CA209003). In addition, the exposure-response relationship for safety is flat. Thus, a slight increase in the steady state maximum concentration is not expected to increase the safety risk of nivolumab.

The dosing and schedule for subjects in Part C will be agreed upon by Investigators and the Sponsor based upon dosing shown to be safe in Part B. In Part B and Part C, the sequential infusion of both drugs will start with nivolumab administration first followed by infusion of BMS-986016. Based upon review of the available safety, pharmacokinetic, and peripheral trough receptor occupancy (RO) data, Part C expansions commenced at combination dosing of 80 mg BMS-

986016 and 240 mg nivolumab Q2W (see [section 1.4.1.4.2](#)) of this protocol and the BMS-986016 IB.³¹

1.2 Research Hypothesis

It is anticipated that anti-LAG-3 antibody (BMS-986016), administered as a single agent or in combination with anti-PD-1 antibody (BMS-936558, nivolumab), 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 Objectives

The primary objective is to determine the safety, tolerability, dose-limiting toxicities (DLTs), and maximum tolerated dose (MTD) of BMS-986016 administered alone and in combination with nivolumab in subjects with advanced solid tumors.

The co-primary objective in Dose Expansion Part C is to investigate the preliminary efficacy of BMS-986016 in combination with nivolumab as measured by objective response rate, disease control rate and duration of response.

1.3.2 Secondary Objectives

The secondary objectives are:

- To characterize the pharmacokinetics (PK) of BMS-986016 administered alone and in combination with nivolumab.
- To investigate the preliminary objective response rate (ORR) and/ or disease control rate (DCR) of BMS-986016 administered alone and in combination with nivolumab in subjects with advanced solid tumors in Parts A and B, Dose Escalation.
- To characterize the immunogenicity of BMS-986016 administered alone and in combination with nivolumab.
- In Parts A, and B, to assess the effect of BMS-986016 administered alone and in combination with nivolumab on QTc.

1.3.3 Exploratory Objectives

Exploratory objectives are:

- To evaluate safety and tolerability of combination therapy using sequential infusion therapy.
- To assess the pharmacodynamic effects of BMS-986016 alone and in combination with nivolumab based on select biomarkers in the peripheral blood and tumor biopsy specimens.
- To characterize T cell function during both BMS-986016 monotherapy and combination therapy with BMS-986016 and nivolumab.
- To assess the 1-year and 2-year landmark overall survival (OS) in subjects treated with BMS-986016 alone and in combination with nivolumab.

- To explore exposure-response relationships in subjects treated with BMS-986016 as monotherapy or in combination with nivolumab.
- To investigate the relationship between clinical efficacy and peripheral and tumor biomarkers.

1.4 Product Development Background

Information for nivolumab (BMS-936558, anti-PD-1 antibody) and BMS-986016 (anti-LAG-3 antibody) is provided in the sections below; additional details are provided in the respective Investigator Brochures.

1.4.1 BMS-986016 (anti-LAG-3 Antibody)

1.4.1.1 Nonclinical Pharmacology

The ability of BMS-986016 to bind recombinant human LAG-3 antigen was determined using Biacore and enzyme-linked immunosorbent assay (ELISA). Binding to human and primate LAG-3+ transfectants and to activated human or primate T cells was measured using flow cytometric and Scatchard analyses. BMS-986016 binds to human LAG-3 with high affinity (K_d , 0.12-0.5 nM), and inhibits the binding of LAG-3 to cells expressing its ligand, MHC class II (IC_{50} , 0.67 nM). BMS-986016 binds to cynomolgus LAG-3 on transfected CHO cells and on activated cynomolgus T cells with a lower affinity (EC_{50} , 21.5-34.3 nM) than to activated human T cells. A high concentration of BMS-986016, in the absence of secondary co-stimulation, elicits no measurable cytokine response from cultured human peripheral blood cells nor does the drug mediate measurable antibody-dependent or complement-dependent killing of target cells. BMS-986016 promotes the activation of an antigen-specific mouse T cell hybridoma expressing human LAG-3 in co-culture with an MHC class II-positive antigen-presenting cell. In addition, BMS-986016 enhances activation of human T cells in superantigen stimulation assays when added alone or in combination with nivolumab (anti-PD-1 antibody). Detailed information can be found in the current version of the BMS-986016 IB.³¹

1.4.1.2 Toxicity

The nonclinical toxicology package for BMS-986016 consists of the following studies:

- 1) Four-Week Intermittent (QW) Intravenous Exploratory Combination Pharmacodynamic and Toxicity Study in Cynomolgus Monkeys with Anti-LAG3.1 Antibody (a precursor of the anti-LAG3.5 antibody) and Nivolumab.
- 2) GLP-Compliant Four-Week Intravenous Combination Toxicity Study in Cynomolgus Monkeys with a 6-Week Recovery with BMS-986016 and Nivolumab.

The key results were as follows:

- Single-agent BMS-986016 administered at up to 100 mg/kg/week did not result in adverse changes.
- Combined administration of BMS-986016 and nivolumab (100 and 50 mg/kg/week, respectively) resulted in moribundity of 1 male out of 9 monkeys on study Day 29. From Days 26 to 29, this monkey presented with elevated body temperature, shivers, red or clear

nasal discharge, fecal changes (unformed, scant or absent feces), decreased feeding behavior, mild dehydration, sneezing, decreased activity, and hunched posture. After 2 days of veterinary care and antibiotic treatment, this animal did not show any improvement and was euthanized on Day 29 for poor clinical condition. There were no remarkable gross necropsy findings. Histopathological findings in this monkey included: slight lymphoplasmacytic inflammation of the choroid plexus; minimal to moderate lymphohistiocytic inflammation of the vasculature of the brain parenchyma, meninges, spinal cord (cervical and lumbar); and minimal to moderate mixed cell inflammation of the epididymes, seminal vesicles and testes. Clinical pathology changes indicated decreases in red blood cell count, hemoglobin concentration and hematocrit whose cause was unclear, and an increase in fibrinogen correlating with the inflammation observed in the central nervous system (CNS) and male reproductive tract.

- Additional histopathological findings upon combination administration of BMS-986016 and nivolumab (100 and 50 mg/kg/week, respectively) were limited to minimal to slight non-reversible lymphoplasmacytic inflammation of the choroid plexus in the brain in 7 of 8 remaining monkeys, and minimal lymphohistiocytic inflammation of the vasculature of the brain parenchyma in 1 of 8 remaining monkeys, whose reversibility could not be assessed.
 - NOAEL for single-agent BMS-986016 was considered to be 100 mg/kg/week (mean AUC[0-168h] = 474,000 µg·h/mL); NOAEL for single-agent nivolumab was considered to be 50 mg/kg/week (mean AUC[0-168h] = 193,000 µg·h/mL); NOAEL for combination of BMS-986016 and nivolumab was not determined.
 - However, the combination therapy was generally well tolerated and clinical signs of toxicity were observed in only 1 of 9 monkeys (approximately 10%). Therefore, 100/50 mg/kg/week BMS-986016/nivolumab (mean BMS-986016 AUC[0-168h] = 514,000 µg·h/mL; mean nivolumab AUC[0-168h] = 182,000 µg·h/mL) was considered the STD10.
 - The doses administered (100 mg/kg BMS-986016 and 50 mg/kg nivolumab) are ≥ 10 times higher than the maximum doses proposed for the current study.
- 3) GLP-Compliant Tissue Cross Reactivity Study in Human and Select Cynomolgus Monkey Tissues with BMS-986016.
- Positive staining with BMS-986016-FITC was observed in the plasma membrane or plasma membrane granules of mononuclear leukocytes of most human tissues, including lymphoid tissues and hematopoietic cells of the bone marrow. In addition, staining with BMS-986016-FITC was observed in the cytoplasm of the human pituitary endocrine cell epithelium. Although BMS-986016 is not expected to have access to the cytoplasmic compartment in vivo and the repeat-dose toxicology studies in monkeys showed no effects on the pituitary gland, these findings may be of clinical significance and will be monitored.
 - In Vitro Cytokine Release and Lymphocyte Activation Assessment with BMS-986016 using Human Peripheral Blood Mononuclear Cells.
 - BMS-986016 did not induce cytokine release when presented to human PBMCs regardless of concentration, donor, or incubation time. The levels of cytokines observed were either at or near the assay lower limits of quantification with no evidence of dose-dependence or pattern across donors (IL-1β, IL-2, IL-5, IL-10, IL-12p70, and IFN-γ) or were generally

overlapping with cytokine levels from PBMCs incubated with negative controls (IL-6, IL-8, TNF- α).

- Consistent with the lack of cytokine release, there was no evidence that BMS-986016 induced T or NK cell activation, as measured by surface expression of CD25 and CD69. Expression levels of these markers on T and NK cells following stimulation with BMS-986016 were similar to those observed upon stimulation with negative controls.
- Overall, these data indicate that BMS-986016 does not possess agonistic potential to induce either T or NK cellular activation or cytokine release.

Refer to the BMS-986016 Investigator's brochure v 4.0, 2016 for additional information regarding nonclinical toxicity of BMS-986016.

1.4.1.3 Nonclinical Metabolism and Pharmacokinetics

In accordance with regulatory guidelines for biotechnology-derived pharmaceuticals,⁴⁴ no metabolism studies with BMS-986016 have been conducted in animals. The expected in vivo degradation of monoclonal antibodies (mAbs) is to small peptides and amino acids via biochemical pathways that are independent of cytochrome P450 enzymes.

BMS-986016 demonstrated favorable PK properties in cynomolgus monkeys. From both single-dose and repeat-dose IV PK studies, BMS-986016 decayed bi-exponentially and the exposure was approximately dose-proportional. The systemic clearance (CL_{TP}) ranges from 0.12 to 0.22 mL/h/kg and a terminal half-life (T_{1/2}) 133 to 414 hours. The volume of distribution at steady state (V_{ss}) was 62 to 72 mL/kg, suggesting limited distribution outside the plasma. Anti-BMS-986016 antibodies were detected in some monkeys but the presence of anti-BMS-986016 antibodies appeared to have no impact on BMS-986016 exposure.

1.4.1.4 Clinical Pharmacology and Safety

1.4.1.4.1 Clinical Pharmacology

An interim determination of BMS-986016 multiple dose PK in solid tumor patients was carried out using all available serum concentrations data from 19 subjects in monotherapy and 25 subjects in combination with nivolumab. In general, the C_{max} and area under the concentration versus time curve over the dosing interval (AUC_{TAU}) values over the first dosing interval increased approximately equal to the increment in the BMS-986016 dose. The PK of BMS-986016 and nivolumab was not altered when given in combination. BMS-986016 concentration-time data were reasonably described by population PK model with linear, 2-compartment, zero-order IV infusion model with first-order elimination. The population PK model will be used to understand the source of variability in BMS-986016 PK and effect of intrinsic and extrinsic factors.

The immunogenicity of BMS-986016 was assessed when administered as monotherapy and in combination with nivolumab. Nivolumab immunogenicity was also assessed when administered in combination with BMS-986016.

None of samples were tested positive for anti-drug antibodies (ADA) of 12 subjects who were treated with BMS-986016 monotherapy. Of the 12 subjects who were treated with BMS-986016 in combination with nivolumab and were evaluable for the presence of anti-BMS-986016

antibodies, 4 (33%) subjects tested positive. However, titer appeared to be low across all samples. Anti-nivolumab antibodies were detected in 1 out of 9 ADA evaluable subjects receiving BMS-986016 in combination with nivolumab. The impact of immunogenicity on PK will be further evaluated using population PK approach.

1.4.1.4.2 Clinical Safety- Monotherapy (Part A) versus Combination Therapy (Part B) in CA224020

Adverse Events

A database lock was performed on Study CA224-020 on 29-Jun-2016. As of the clinical cutoff date (29-Jun-2016), 51 subjects have been treated in Study CA224-020 (22 in monotherapy and 29 in combination therapy [28 in Part B and 1 in Part C]). In Parts A and A1, which comprised the escalation phase (Part A, n = 17) and monotherapy expansion (Part A1, n = 5), 22 subjects with advanced solid tumors were treated with 20 mg (5 subjects), 80 mg (4 subjects), 240 mg (4 subjects), and 800 mg (9 subjects) BMS-986016. Thirteen of the 17 subjects in Part A were evaluable in the DLT period of 8 weeks. BMS-986016 single agent has had an acceptable safety profile at all tested doses in Part A (ie, 20, 80, 240 and 800 mg, flat dose). Of the 22 subjects treated with BMS-986016 monotherapy, 20 (90.9%) experienced at least 1 event. The most frequently reported AEs in these subjects were malignant neoplasm progression (50.0%); fatigue (45.5%); and nausea (36.4%); vomiting, decreased appetite, dizziness (22.7% each); and headache, pyrexia, arthralgia, back pain, cough, and anemia (18.2% each). Drug-related AEs were reported in 13 (59.1%) subjects with the most frequently reported being fatigue (27.3%); decreased appetite (13.6%); and headache, pruritus, nausea, dry mouth, arthralgia, myalgia, and maculo-papular rash (9.1% each). All these drug-related AEs were Grade 1 or 2. The only Grade 3 related AEs were a transient serum lipase elevation, which went back to normal values at the next dose of BMS-986016, and a Grade 3 related AE of maculopapular rash, which required dosing interruption, improved to Grade 1 within 7 days, and resolved within 14 days with topical steroid treatment. The MTD was not reached with up to 800 mg BMS-986016 q2w. The reported AEs in subjects during escalation monotherapy in Study CA224-020 are summarized in Table 5.5.1-1 of the BMS-986016 IB.

In Part B, which comprised the dose-escalation phase for BMS-986016 and nivolumab combination therapy, 28 subjects with advanced solid tumors were treated in 4 cohorts: Cohort 1: 20 mg BMS-986016 and 80 mg nivolumab (7 subjects); Cohort 2: 20 mg BMS-986016 and 240 mg nivolumab (9 subjects); Cohort 3: 80 mg BMS-986016 and 240 mg nivolumab (8 subjects), and Cohort 4: 240 mg BMS-986016 and 240 mg nivolumab (4 subjects). In combination therapy (Parts B [N = 28] and C [N = 1]), BMS-986016 with nivolumab has already demonstrated an acceptable safety profile at 3 of the 4 dose levels tested. The fourth dose level (240 mg BMS-986016/240 mg nivolumab) continues to be evaluated. Of the 29 subjects treated with BMS-986016 and nivolumab (Parts B [N = 28] and C [N = 1]), 28 (96.6%) subjects experienced at least 1 event. The most frequently reported AEs in these subjects were malignant neoplasm progression (41.4%); fatigue and nausea (34.5% each); decreased appetite (31.0%); constipation, diarrhea, and vomiting (27.6% each); abdominal pain and dyspnea (24.1% each). Drug-related AEs were reported in 18 (62.1%) subjects, with the most frequently reported being

fatigue (20.7%); nausea and rash (10.3% each); and amylase increased, diarrhea, dry mouth, hypothyroidism, infusion-related reaction, and lipase increased (6.9% each). Grade 3 drug-related AE included dyspnea, mucosal inflammation, dehydration, and amylase increased (1 subject each). Grade 4 drug-related AEs included ventricular fibrillation, lipase increased, and myocarditis (1 subject each). Grade 3 mucosal inflammation (20 mg BMS-986016/80 mg nivolumab), Grade 4 ventricular fibrillation (20 mg BMS-986016/240 mg nivolumab), Grade 4 elevated lipase (80 mg BMS-986016/240 mg nivolumab), and Grade 4 myocarditis (240 mg BMS-986016/240 mg nivolumab) were considered DLTs and led to discontinuation. The reported AEs in subjects during combination therapy in Study CA224-020 are summarized in Table 5.5.1-2 of the BMS-986016 IB. Since the clinical cutoff date the myocarditis case at the 240mg BMS-986016/240mg nivolumab dose became grade 5 as the subject died due to sequelae of myocarditis.

Serious Adverse Events

As of 29-Jun-2016 at least 1 SAE, regardless of causality, has been reported in 14 of the 22 subjects (63.6%) treated with BMS-986016 monotherapy. The reported SAEs were malignant neoplasm progression (50%); diarrhea (9.1%); and abdominal pain, fatigue, pain, sialoadenitis, urinary tract infection, intracranial mass, spinal cord compression, spinal cord hematoma, tachycardia, hepatic failure, liver function test increased, urethral obstruction, pneumonitis, pneumocystis jirovecii pneumonia, and vocal cord paralysis (1 subject each, 4.5%). There was only 1 drug-related SAE of Grade 2 pneumonitis reported in monotherapy.

At least 1 SAE, regardless of causality, has been reported in 21 of the 28 subjects (75%) treated with BMS-986016 and nivolumab in Part B. The reported SAEs were malignant neoplasm progression (42.9%); abdominal pain (10.7%); gastrointestinal hemorrhage (7.1%); and device occlusion, mucosal inflammation, ventricular fibrillation, dyspnea, anal incontinence, arthralgia, ascites, biliary tract infection, confusional state, constipation, duodenal obstruction, fracture, lung abscess, myocarditis, nausea, vomiting, nervous system disorder, pleural effusion, and urticaria (1 subject each, 3.6%).

Drug-related SAEs were reported in 4 of the 28 subjects treated with BMS-986016 and nivolumab in Part B. These included Grade 3 mucosal inflammation, Grade 3 dyspnea, Grade 4 ventricular fibrillation, and Grade 4 myocarditis (1 subject each).

Narratives of each of the drug related AEs are included in the BMS-986016 IB. The two cardiovascular drug-related AE narratives are iterated here:

- Grade 4 ventricular fibrillation occurred in a [REDACTED] with [REDACTED] cancer 12 days after receiving the third dose of therapy with 20 mg BMS-986016 and 240 mg nivolumab. The event occurred spontaneously while the subject [REDACTED] and CPR was administered by paramedics for 10 minutes. At assessment, there was no evidence of coronary artery abnormality, MI, myocarditis or pulmonary embolism. The peri-infusional Holter recording on Cycle 1 Day 1 did not show arrhythmia. Ingestion of [REDACTED] history of smoking, hypertension, use of clorfeniramine and caffeine and prior episode of loss of consciousness were potential contributing factors for the event and suggestive of pre-existing cardiac problem/arrhythmia, however, in the absence of a clearly identified

cause, a contribution from BMS-986016 and nivolumab could not be entirely excluded. Thus, this event was considered as a drug-related SAE and DLT and was reported as a SUSAR. The subject fully recovered, was discontinued from study therapy, and subsequently had an AICD implanted without report of cardiac event recurrence.

- A [REDACTED] with metastatic chemotherapy refractory thymoma presented with dyspnea and weakness on Cycle 1 Day 35, approximately 1 week after [REDACTED] third (every-2-week) dose of combined 240 mg BMS-986016 and 240 mg nivolumab. The subject had a history of coronary artery disease with prior coronary artery bypass graft approximately 10 years prior to the current event and MI approximately 1 year prior to the current event requiring placement of 2 stents, as well as prior chest irradiation. The subject was initially found to have third degree heart block with an elevated troponin level so there was initial concern for MI. Coronary catheterization showed the coronary anatomy was without significant change with patent grafts. Echocardiogram revealed a left ventricular ejection fraction of 45%. Given the presentation, continued symptoms of congestive heart failure, and the concern for possible myocarditis, the subject was started on steroids on third day of hospitalization. Subsequent cardiac magnetic resonance imaging revealed patchy septal late gadolinium enhancement suggestive of myocarditis and a worsening of [REDACTED] left ventricular ejection fraction (LVEF) to 15%. Active diffuse lymphocytic myocarditis was confirmed with endomyocardial biopsy followed by a 5-day course of anti-thymocyte globulin. The subject had only partial recovery of cardiac function while requiring a permanent pacemaker in the setting of prolonged hospitalization, prolonged high-dose steroid treatment, and ongoing severe decrease in overall functional status. After the clinical cut-off date the subject died (grade 5) due to sequelae of the myocarditis.

Infusion Reactions

During monotherapy, an infusion-related reaction (Grade 2) was reported in 1 subject. The infusion-related reaction is described below.

A subject with colorectal cancer reported infusion-related reaction (Grade 2) at the 240-mg dose level. The subject tolerated [REDACTED] first dose without any difficulties. On Cycle 1 Day 15 (second dose), the subject developed stabbing back pain and facial flushing after receiving 8.5 mL of the infusion. The event recurred on Cycle 1 Day 29 after 10 minutes of infusion, and again on Cycle 1 Day 43. In each case, these reactions were manageable and reversible with subsequent completion of the infusions following infusion-reaction treatment guidelines in the protocol.

With combined therapy of BMS-986016 and nivolumab, 2 infusion-related reactions (both Grade 2) were reported by 2 subjects. These infusion-related reactions are described in detail in the BMS-986016 IB and both occurred during the nivolumab infusion, which precedes the BMS-986016 infusion, and were manageable following infusion-reaction treatment guidelines in the protocol.

Adverse Events Leading to Discontinuation

As of 29-Jun-2016, at least 1 AE leading to discontinuation has been reported in 3 of 22 subjects (13.6%) treated with monotherapy (Parts A and A1). The AEs leading to discontinuation were: 1) One subject treated with 20 mg BMS-986016 monotherapy had a Grade 3 increased liver function tests on Cycle 1 Day 58 which was not related to treatment, 2) One subject treated with 240 mg BMS-986016 monotherapy had persistent drug-related grade 2 exertional dyspnea and wheezing, and 3) One subject treated with 800 mg BMS-986016 NSCLC discontinued study drug after recurrent drug-related Grade 2 pneumonitis. Further details are provided in the BMS-986016 IB.

As of 29-Jun-2016, at least 1 AE leading to discontinuation has been reported in 4 of 29 subjects (13.8%) treated with combination therapy. The AEs leading to discontinuation are described as: 1) Grade 3 drug-related mucosal inflammation, which occurred after the second dose of combination therapy with 20 mg BMS-986016/80 mg nivolumab, 2) Grade 4 ventricular fibrillation, which occurred after the third dose of combination therapy with 20 mg BMS-986016/240 mg nivolumab (see narrative above under Serious Adverse Events), 3) Grade 4 drug-related elevated lipase which was asymptomatic and without evidence of pancreatitis. The protocol has since been amended to allow continued treatment when such elevations decrease to at least grade 3, 4) Grade 4 drug-related myocarditis, which occurred after the third dose of combination therapy with 240 mg BMS-986016/240 mg nivolumab (see narrative above under Serious Adverse Events).

Deaths

As of 29-Jun-2016, of the 22 subjects treated with BMS-986016 monotherapy, 13 subjects (59.1%) died during the course of the study. Deaths were reported at 20 mg (5 subjects), 80 mg (3 subjects), 240 mg (2 subjects), and 800 mg (3 subjects) dose levels. All deaths in monotherapy have been due to disease progression and were not considered related to study drug. Of the 28 subjects treated with BMS-986016 and nivolumab in combination therapy, 15 subjects (53.6%) died during the course of the study. Deaths were reported at 20 mg BMS-986016/80 mg nivolumab (6 subjects), 20 mg BMS-986016/240 mg nivolumab (5 subjects), 80 mg BMS-986016/240 mg nivolumab (3 subjects), and 240 mg BMS-986016/240 mg nivolumab (1 subject) combination dose levels. At the time of the clinical cut-off date, all deaths in combination therapy have been due to disease progression and were not considered related to study drug. Since the clinical cut-off date one drug-related death (grade 5 myocarditis observed at the 240mg BMS-986016/240mg nivolumab) has occurred.

1.4.1.4.3 Clinical Efficacy- Monotherapy (Part A) versus Combination Therapy (Part B): CA224020 Study

Efficacy is currently being evaluated for Part A, Part B, Part A1, and Part C of the study.

1.4.2 Nivolumab (BMS-936558, anti-PD-1 Antibody)

1.4.2.1 Nonclinical Pharmacology

Nivolumab is a fully human, IgG4 (kappa) isotype monoclonal antibody that binds to PD-1 with nanomolar affinity (K_d, 3.06 nM) and a high degree of specificity, thus precluding binding to its ligands PD-L1 and PD-L2. Nivolumab does not bind to other related family members, such as BTLA, CTLA-4, ICOS, or CD28. Nonclinical testing of nivolumab demonstrated that binding to PD-1 results in enhanced T cell proliferation and release of interferon-gamma (IFN-gamma) in vitro. Additional details are provided in the current version of the nivolumab (BMS-936558) Investigator Brochure.¹¹

1.4.2.2 Toxicity

Toxicology studies in cynomolgus monkeys revealed that nivolumab was well tolerated at doses up to 50 mg/kg given twice weekly for 27 doses. Drug-related findings were limited to a reversible decrease in triiodothyronine (T3) by 28%, without concomitant abnormalities in other markers of thyroid function. Additional details are provided in the current version of the nivolumab (BMS-936558) Investigator Brochure.¹¹

Preliminary new nonclinical safety findings of adverse pregnancy outcomes and infant losses in the absence of overt maternal toxicity have been reported.⁴⁵ The findings of increased late-stage pregnancy loss and early infant deaths/euthanasia in nivolumab-exposed pregnant monkeys suggest a potential risk to human pregnancy if there is continued treatment with nivolumab during pregnancy.

1.4.2.3 Nonclinical Metabolism and Pharmacokinetics

Please see the nivolumab (BMS-936558) Investigator Brochure for current data.¹¹

1.4.2.4 Clinical Safety

Nivolumab has been studied in over 8,600 subjects and is widely approved in multiple indications. Extensive details on the safety profile of nivolumab are available in the Investigator Brochure, and will not be repeated herein.

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

The safety profile of nivolumab in combination with ipilimumab was consistent with the mechanisms of action of nivolumab and ipilimumab. The nature of the AEs was similar to that observed with either agent used as monotherapy; however, both frequency and severity of most AEs were increased with the combination. A dose of 3 mg/kg nivolumab/3 mg/kg ipilimumab exceeded the MTD, and both 1 mg/kg nivolumab/3-mg/kg ipilimumab and 3 mg/kg nivolumab/1 mg/kg ipilimumab were identified as the MTD. Across all studies conducted to date, drug-related

AEs have included pulmonary toxicity, renal toxicity (including acute renal failure), endocrine abnormalities, GI toxicity, dermatologic toxicity (including rash), and hepatotoxicity.

A pattern of immune-related adverse events has been defined, for which management algorithms have been developed; these are provided in [Appendix 1](#). Most high-grade events were manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in these algorithms. For additional material, see the nivolumab Investigator Brochure ¹¹.

Additional details on the safety profile of nivolumab, including results from other clinical studies, are also available in the nivolumab IB. ¹¹

1.4.2.5 Clinical Pharmacokinetics

Single-dose PK of nivolumab was evaluated in 39 subjects with multiple tumor types in CA209001 in the dose range of 0.3 to 10 mg/kg. The median T_{max} across dose levels ranged from 1.6 to 3.1 hours with individual values ranging from 0.9 to 7 hours. The PK of nivolumab was linear in the range of 0.3 to 10 mg/kg with dose-proportional increase in C_{max} and AUC(INF); low to moderate intersubject variability was observed at each dose level (i.e., coefficient of variation [CV] ranging from 16 to 45%). Geometric mean clearance (CLT) after a single IV dose ranged from 0.13 to 0.19 mL/h/kg, while mean volume of distribution (V_z) varied between 83 to 113 mL/kg across doses. The mean terminal T-HALF of nivolumab was 17 to 25 days, consistent with half-life of endogenous IgG4, indicating that the elimination mechanism of nivolumab may be similar to IgG4. Both elimination and distribution of nivolumab appeared to be independent of dose within the dose range studied. In a multiple dose study of multiple tumor types (CA209003), available data from 128 subjects, mean T-HALF was 21 - 24 hours and median T-max ranged from 0.6 to 3.3 across dose levels, which aligns with the single dose data. Additional details are provided in the current version of the nivolumab (BMS-936558) IB. ¹¹

1.4.2.6 Clinical Activity

Nivolumab has demonstrated clinical activity in subjects with a variety of malignancies including melanoma, NSCLC, and renal cell carcinoma as described in the nivolumab investigative brochure (IB) ¹¹ appendices [USPI (Appendix 1) and SmPC (Appendix 2)], and in the following additional studies also detailed in section 5.4 of the nivolumab IB:

- SCCHN (Nivolumab IB Section 5.4.5) CA209141: completed Phase 3, randomized, open-label study of nivolumab vs investigator's choice therapy in recurrent or metastatic platinum-refractory SCCHN.
- Gastric Cancer (Nivolumab IB Section 5.4.7) CA209032: ongoing Phase 1/2, open-label study of nivolumab monotherapy or nivolumab combined with ipilimumab in subjects with advanced or metastatic solid tumors, including gastric cancer
- Hepatocellular Carcinoma (Nivolumab IB Section 5.4.9) CA209040: ongoing Phase 1/2, open-label study of nivolumab in subjects with advanced hepatocellular carcinoma

1.5 Overall Risk/Benefit Assessment

Subjects who have advanced solid tumors have poor prognosis and few curative options. Nivolumab has demonstrated clinical activity in subjects with advanced NSCLC, RCC, melanoma, cHL, SCCHN, and other tumors. Treatment related adverse events (AEs) include those associated with autoimmune activation, such as pneumonitis, thyroiditis, hepatitis, nephrotoxicity, adrenal insufficiency, and less commonly neurotoxicity and myocarditis.

In the nonclinical GLP toxicology study, lymphoplasmacytic infiltration in the choroid plexus (and spinal cord) was reported at the highest doses of anti-PD-1 antibody (3/6 animals) and the anti-LAG-3 + anti-PD-1 antibody combination (5/6). These are nonspecific histopathology changes, without clinical manifestations in all but one of the animals treated with combination therapy, which have been observed in other studies with antibodies and small molecules in monkeys. However, lymphoplasmacytic inflammation of the choroid plexus could manifest in human subjects as aseptic meningitis or encephalitis. Thus, increased safety precautions have been instituted in this study to exclude subjects with chronic neurologic disease or recent history of encephalitis or meningitis, as well as mandated neurologist evaluation in the setting of any grade 2 neurologic adverse events and site personnel training in treatment of immune-mediated neurologic toxicities. As of a clinical cut-off date of Oct. 7 2016 there were two BMS-986016 drug-related cases of grade 3 aseptic meningitis. One case occurred in a subject with melanoma after 3 doses of combined 240 mg BMS and 240 mg nivolumab and the other occurred in a Hodgkin's lymphoma subject (treated in the CA224022 study) after 14 doses of 800 mg BMS-986016 monotherapy. Both cases presented with a new headache and either associated nausea and/or photophobia but without focal neurologic deficits or imaging findings. Each responded promptly to steroids. The subject with melanoma had recurrence of symptoms while on a steroid taper that responded to repeated high dose therapy with eventual resolution while being followed off therapy with a confirmed partial tumor response. The Hodgkin's lymphoma subject was re-challenged with 800 mg BMS-986016 monotherapy without meningitis recurrence. These cases have not altered the overall risk benefit profile of BMS-986016.

Therapy with BMS-986016 and nivolumab is investigational and it is possible that a higher incidence of immune mediated-adverse events may occur with the combination of 2 antibodies targeting T cells. As of 29-Jun-2016, four serious adverse events (SAE), Grade 3 mucositis, Grade 3 dyspnea, Grade 4 ventricular fibrillation, and Grade 4 myocarditis were reported in combination therapy, Part B. Whether the mucositis or dyspnea events could be considered irAEs or not, cannot be defined at this time and close monitoring of additional events is ongoing. The immune-related myocarditis event prompted closer monitoring of subjects with ECGs and troponins, as well as tighter eligibility criteria regarding baseline ejection fraction and history of cardiovascular disease. Unanticipated side effects events may also occur, like the Grade 4 ventricular fibrillation that was also reported in combination therapy, Part B. There were several confounding factors in this case but, in the absence of a clear etiology, the event was considered treatment-related. Adverse events and SAEs will continue to be reviewed expeditiously by the Medical Monitor, investigators and the Pharmacovigilance group to monitor safety.

There is risk associated with tumor biopsies, including bleeding, infection, and pain. While there is no direct benefit to subjects who undergo these procedures, there is a potential that data generated from these samples will guide the further development of these compounds and may be of direct benefit for others with advanced solid tumors.

The potential direct benefit to subjects who participate in the CA224020 study is that both single-agent and combined therapy with these investigational agents may result in a greater proportion of subjects with stabilization of disease, objective response, or increased duration of response than those observed with nivolumab monotherapy. It is also possible that combination therapy may reverse LAG-3-mediated T cell exhaustion and achieve responses in 1) tumor types known to be unresponsive to nivolumab; 2) tumors refractory to anti-CTLA4 and anti-PD-1 or anti-PD-L1 antibody therapy; and/or 3) virally-associated tumors. In fact, multiple RECIST1.1 defined partial responses have been observed with BMS-986016 monotherapy and in combination with nivolumab, both in the immunotherapy naive, as well as the anti-PD-1 resistant setting. Thus, the potential for direct benefit in subjects with few if any alternative treatment options warrants continued evaluation of the combination in the Phase 1/2a clinical setting, including evaluating potential response rates in specific tumor and prior anti-PD-1 defined expansion cohorts at combination doses shown to be tolerated.

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 United States 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 approval/favorable opinion by Institutional Review Board/Independent Ethics Committee (IRB/IEC) and regulatory authorities according to applicable local regulations prior to initiation of the study.

All potential serious breaches must be reported to Bristol-Myers Squibb (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 (e.g., 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 Investigator Brochure 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 (e.g., 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 to subjects, their legally acceptable representatives 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 (i.e., Global or Local) sample informed consent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

- Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
- Allow time necessary for subject or 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 informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.
- If informed consent is initially given by a 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 informed consent form (ICF) and, in the US, the subjects' signed Health Insurance Portability and Accountability Act (HIPAA) Authorization.

The consent form 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-986016 administered as a single agent and in combination with nivolumab to subjects with advanced solid tumors. **Part A and Part B** consist of a 3 + 3 + 3 dose escalation design with BMS-986016 administered as a single agent (Part A) or in combination with nivolumab (Part B) as sequential infusions in subjects with advanced solid tumors. Treatment in Part B will be initiated upon the decision to escalate to the third dose cohort in Part A (in accordance with dose escalation rules); subsequently, escalation in the 2 parts will proceed in parallel. At no point will the dose of BMS-986016 administered in combination with nivolumab (Part B) exceed doses of BMS-986016 that have been demonstrated previously to be safe on the monotherapy dose escalation arm (Part A).

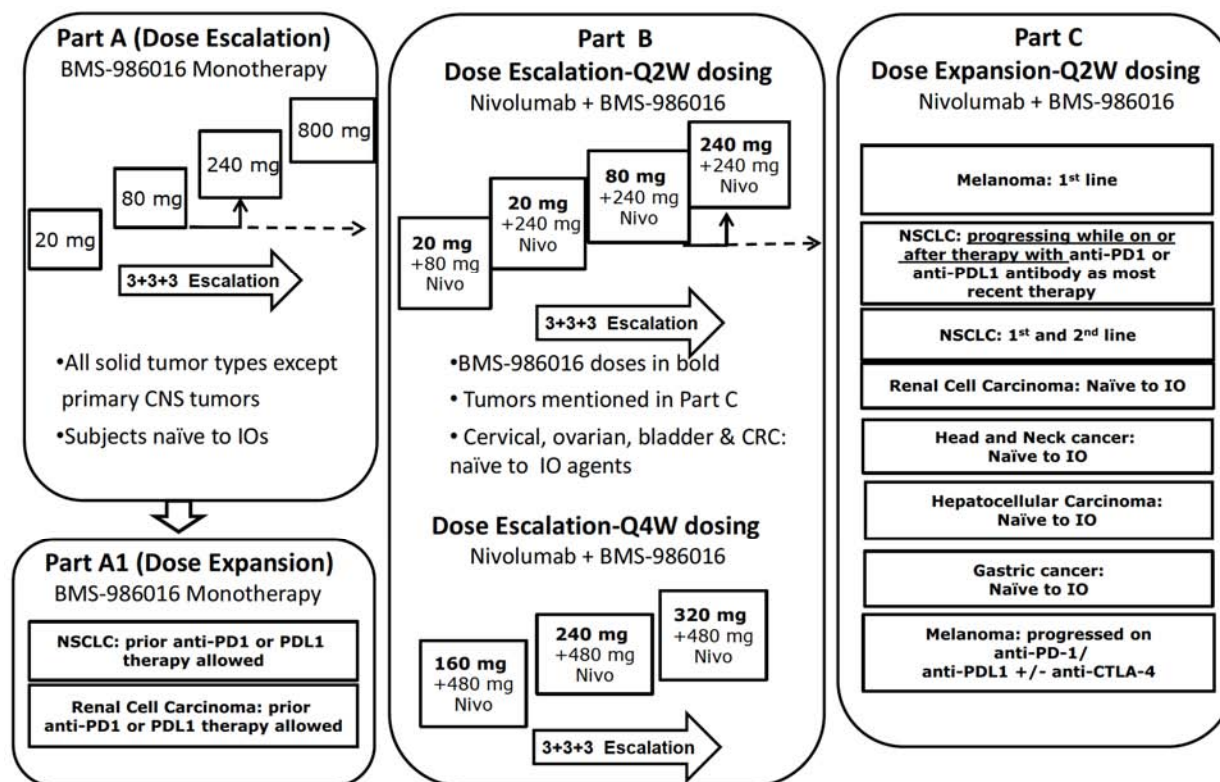
Part A1 consists of cohort expansion with BMS-986016 monotherapy in 2 disease-restricted cohorts of approximately 6-12 subjects each. Treatment in Part A1 will be initiated at the maximum administered dose (MAD) determined in Part A (i.e., 800 mg). The dose selected for Part A1 will not exceed the MAD in Part A, but dose selection may change according to assessment of other data including toxicities and PK and pharmacodynamic data from Parts A and A1. Subjects in Part A1 who progress on monotherapy may crossover to combination therapy with nivolumab and BMS-986016 as long as they meet eligibility criteria and the risk:benefit ratio is considered favorable by the Investigator and the Medical Monitor. Subjects will receive combination therapy in sequential infusion at the doses that have been declared safe in dose escalation or dose expansion parts at the time of cross-over. The original protocol rules will apply accordingly. Combination therapy may thus be administered for up to 12 additional eight week cycles according to the protocol rules. Collection of archival tissue (baseline) and tumor biopsies (baseline and on-therapy) will be optional for subjects crossing-over and PK and biomarker monitoring will be limited ([Sections 5.5](#) and [5.7](#)).

Part C consists of cohort expansion in disease-restricted cohorts using a multi-stage approach, treated with sequential infusion of nivolumab and BMS-986016. Cohorts deemed futile ([Section 8.1.2](#)) at Stage 1 will be discontinued. Cohorts deemed promising may be expanded further up to 90 to 120 subjects in total after careful evaluation of all available data including the totality of efficacy, safety profile, and PK/PD. Otherwise, additional subjects may be treated to collect more data during Stage 2 in order to make decision for further expansion. The doses and schedule selected for Part C will not exceed the Part B MTD or MAD, and specific doses selected may

incorporate assessment of other data including toxicities, PK and pharmacodynamic data from Parts A and B. Subjects who crossed over to combination therapy in Part A1 and subsequently have an objective response will not be considered in the decision making for Part C. Subjects in Part C cannot crossover to Part A1 either.

A schematic of the study is provided in [Figure 3.1-1](#).

Figure 3.1-1: CA224020 Study Schematic



Sequential = sequential administration of nivolumab first followed by BMS-986016 infusion within 30 minutes of completing nivolumab's.

IO = immuno-oncology agents (such as, but not limited to, anti-CTLA-4, anti-PD-1, anti-PD-L1, anti-PD-L2, anti-KIR, anti-CD137, and/or anti-OX40 antibodies).

Subjects will complete up to 4 periods of the study: **Screening** (up to 28 days), **Treatment** (up to a maximum of twelve 8-week cycles of study therapy), **Clinical Follow-up** (135 days), and **Survival Follow-up** (up to 2 years following the first dose of study drug. Additional survival follow-up may continue for up to 5 years from the first dose. Two independent periods, **Cross-Over** and **Re-challenge**, may be conducted in selected cases at progression. The **Treatment Period** consists of up to twelve 8-week treatment cycles. Each treatment cycle is comprised of 4 doses of either BMS-986016 alone (Parts A and A1) or in combination with nivolumab (Parts B and C), administered on Days 1, 15, 29, and 43 of each treatment cycle. In Part B, every 4 week dosing, BMS-986016 and nivolumab will be administered on Days 1 and 29 of each treatment cycle. In Parts B and C when both study drugs are given as sequential infusion, nivolumab will be given first followed by BMS-986016 between 15 and 30 minutes of completing the infusion of nivolumab. Tumor response will be evaluated using RECIST v1.1. Subjects will be allowed to continue study therapy until the occurrence of either: (1) confirmed complete response (CR), (2) completion of the maximum number of twelve 8-week cycles, (3) progressive disease (PD), (4) clinical deterioration, and/or (5) meeting other criteria for discontinuation ([Section 3.5](#)). Treatment

beyond progression may be allowed in select subjects with initial RECIST v1.1-defined PD who are receiving clinical benefit as assessed by the Investigator, tolerating treatment, and meeting other criteria specified in [Section 4.3.4](#). Subjects who discontinue treatment will enter a 135-day **Clinical Follow-up** period.

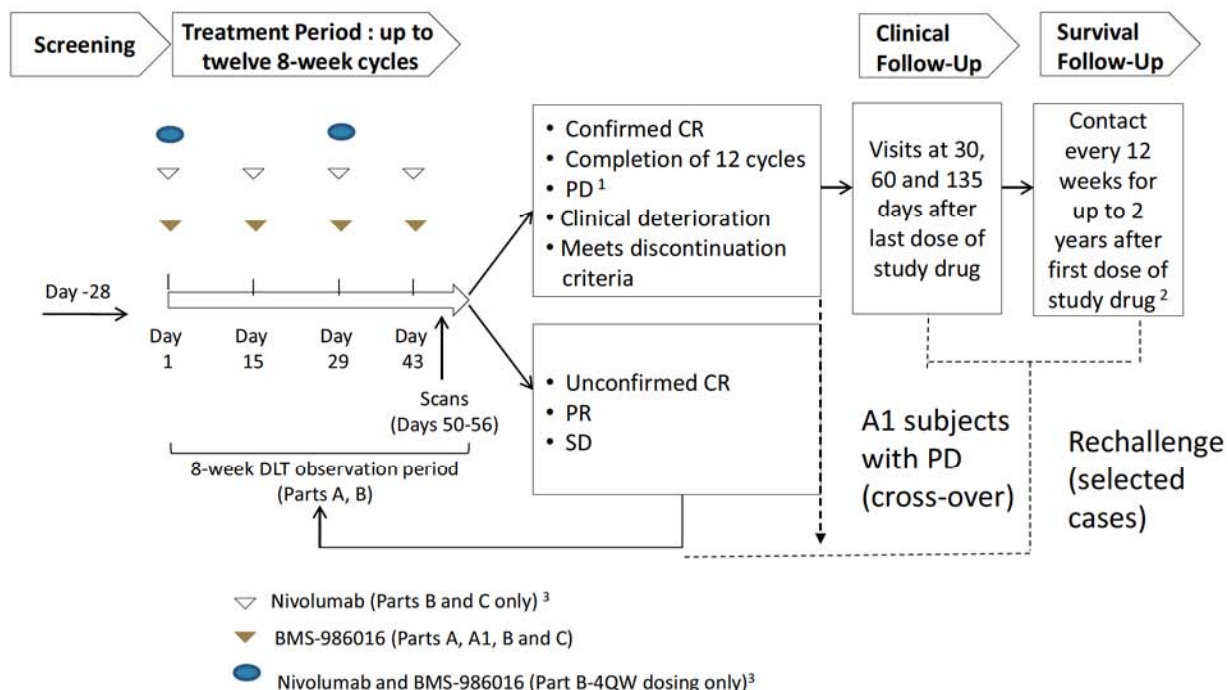
After completion of the Clinical Follow-up period, subjects enter the **Survival Follow-up** period. During this period, clinic visits or telephone contact every 12 weeks will be performed to assess survival status. Diagnostic imaging must be performed every 12 weeks until progression in subjects who discontinue due to CR, and in subjects with PR or SD at the end of Cycle 12. The duration of this period is up to 2 years following the first dose of study drug, however, additional survival follow-up may continue for up to 5 years from the first dose.

If subjects progress during the clinical follow-up period or the survival follow-up period, they could further receive therapy with BMS-986016 alone or in combination therapy (**Re-challenge period**) as long as the risk:benefit ratio is considered favorable by the Investigator and the Medical Monitor and eligibility criteria is met ([Section 3.1.2.4](#)). The original dose and schedule and protocol rules would apply accordingly. Thus, subjects could receive therapy for up to 12 additional eight-week cycles. Subjects will not be re-challenged a second time. Collection of archival tissue (baseline) and tumor biopsies (baseline and on-treatment) will be optional for subjects enrolled for re-challenge. PK and biomarker monitoring will be limited ([Sections 5.5](#) and [5.7](#)).

Also, subjects receiving therapy with BMS-986016 alone in expansion Part A1, may Cross-Over to combination therapy at confirmed progression ([Section 3.1.2.1](#)).

A study schematic is provided in [Figure 3.1-2](#).

Figure 3.1-2: Detailed Study Schematic



¹ Treatment beyond progression may be considered in select subjects as described in [Section 4.3.4](#).

² Diagnostic imaging must be performed every 12 weeks until progression in subjects who discontinue due to CR and in subjects with PR at the end of Cycle 12.

³ For treatment visits in Parts B and C where BMS-986016 and nivolumab are administered sequentially, nivolumab will be administered first followed by BMS-986016 within 15 to 30 minutes after completion of the nivolumab infusion.

Assessments including physical examinations, vital sign measurements, 12-lead ECG, and clinical laboratory evaluations will be performed at selected times throughout the dosing interval. Subjects will be closely monitored for AEs throughout the study. Blood samples will be collected for up to 4 hours following the start of study drug administration for PK analysis.

Subjects will be allowed to continue on therapy for up to twelve 8-week cycles or until confirmed CR, PD, clinical deterioration, or meeting criteria for discontinuation. Subjects may be on study for a total of up to approximately 2-4 years, including a 28-day screening period, up to twelve 8-week cycles of treatment, a 135-day clinical follow-up period, and up to 2 years of follow-up for survival (beginning from the first dose of study drug). Additional survival follow-up may continue for up to 5 years from the first dose. Additional OS analysis may be conducted periodically until end of study. The study will end once survival follow-up has concluded. The total duration of the study is expected to be approximately 7 years from the time of the first visit of the first subject to the required survival follow-up of the last subject enrolled.

3.1.1 Dose Escalation

3.1.1.1 Part A- Monotherapy

In Part A, a 3 + 3 + 3 design will be used to assess the safety of BMS-986016 given as single agent. A fourth subject may be enrolled at the beginning of a dose escalation cohort following agreement between the Investigator and the Sponsor/Medical Monitor, if subject is able to start the first day of dosing within approximately one week of the third subject in the same dose escalation cohort.

The dosages during dose escalation are provided in [Figure 3.1-1](#) and [Table 3.1.1.1-1](#).

Three subjects (or 4, if applicable) will initially be treated in each dose cohort; in Dose Cohort 1, each of the first 3 subjects (or 4, if applicable) will be designated as sentinel subjects and will begin treatment at least 5 days apart. Subjects in subsequent cohorts will not be required to observe the 5-day interval between treatment start dates.

Dose escalation in Part A will proceed as follows:

- If 0 of the first 3 (or 4, if applicable) subjects experiences a DLT within the DLT evaluation interval, a new cohort of 3 subjects will be treated at the next higher dose level.
- If 1 of 3 (or 4, if applicable) subjects experiences a DLT within the DLT evaluation interval, that cohort will be expanded to 6 subjects (or 7, if applicable).
- If 2 of 6 (or 7, if applicable) subjects experience a DLT within the DLT evaluation interval, that cohort will be expanded to 9 subjects.
- If ≥ 2 of 3 (or 4, if applicable), ≥ 3 of 6 (or 7, if applicable), or ≥ 3 of 9 subjects experience DLTs within a dose cohort during the DLT evaluation interval, then that dose level will be determined to have exceeded the MTD.

Table 3.1.1.1-1: Dose Escalation and Dose Expansion Schedules for Part A and Part A1 BMS-986016 Monotherapy

Part A Dose Escalation Cohort Number	Total Subjects	BMS-986016 Dose (IV; mg)
1	n = approximately 3-9	20
2	n = approximately 3-9	80
3	n = approximately 3-9	240
4	n = approximately 3-9	800
Total	N=approximately 12-36	
Part A1 Dose Expansion Cohorts		
NSCLC prior anti-PD1 or PDL1 therapy allowed ^a	n = approximately 6-12	800
Renal Cell Carcinoma: prior anti-PD1 or PDL1 therapy allowed ^a	n = approximately 6-12	800
Total	N = approximately 12-24	

^a see [Section 3.3](#) for detailed eligibility criteria

Prior to declaring the MTD (or MAD), and in consultation with Investigators, the Sponsor has the option to expand any cohort previously established to be safe in order to obtain additional experience or to investigate dose levels intermediate to those defined in the protocol. Dose escalation rules (cohort size, DLT evaluation interval, cohort expansion criteria, etc.) will apply to these expanded or additional cohorts. A maximum of 9 subjects will be enrolled in any additional or expanded dose cohorts.

No within-subject dose escalations will be permitted. If a dose level is found to exceed the MTD subjects enrolled in that dose level may be treated at a lower dose following consultation and agreement between Investigators and the Sponsor.

3.1.1.2 Part B- Sequential Infusion

Treatment in Part B will be initiated after the decision is made to escalate to the third dose cohort in Part A (in accordance with dose escalation rules). Subsequently, escalation in the 2 parts will proceed in parallel. At no point will the dose of BMS-986016 administered in combination with nivolumab (Part B) exceed doses of BMS-986016 that have been demonstrated previously to be safe on the monotherapy dose escalation arm (Part A). Treatment assignments for subjects eligible for both Part A and Part B will alternate between the 2 parts, with consecutively treated subjects assigned to different parts through interactive voice response system (IVRS) whenever possible. If there are no openings available in the part to which the subject would be assigned by this algorithm, then the subject will be assigned to the next open cohort or part.

As in Part A, a 3 + 3 + 3 design will also be used in Part B to assess the safety of BMS-986016 given in combination with nivolumab as a sequential infusion. A fourth subject may be enrolled at the beginning of a dose escalation cohort following agreement between the Investigator and the Sponsor/Medical Monitor, if subject is able to start the first day of dosing within approximately one week of the third subject in the same dose escalation cohort. The potential dose levels evaluated during dose escalation are provided in Table 3.1.1.2-1. Intermediate and lower dose levels may be assessed following agreement between the Investigator and the Sponsor/Medical Monitor based upon ongoing review of safety data.

Table 3.1.1.2-1: Dose Escalation Schedule for Part B — BMS-986016 in Combination with Nivolumab every 2 week dosing

Dose Cohort Number	Total Subjects	BMS-986016 Dose (IV; mg)	Nivolumab Dose (IV; mg)
1	n = approximately 3-9	20	80
2	n = approximately 3-9	20	240
3	n = approximately 3-9	80	240
Intermediate	n = approximately 3-9	160	240
4	n = approximately 3-9	240	240
Dose Escalation Schedule for Part B — BMS-986016 in Combination with Nivolumab <u>every 4 week dosing</u>			
1	n = approximately 3-9	160	480
2	n = approximately 3-9	240	480
3	n = approximately 3-9	320	480
Total	N = approximately 24-72		

Three subjects (or 4, if applicable) will be treated initially in each dose cohort; in Dose Cohort 1, each of the first 3 subjects (or 4, if applicable), designated as sentinel subjects, will begin treatment at least 5 days apart. Subjects in subsequent cohorts will not be required to observe the 5-day interval between treatment start dates.

Dose escalation in Part B will proceed as described for Part A. If the MTD is exceeded in Dose Cohort 2, the potential subsequent cohort will be treated with 80 mg of BMS-986016 and 80 mg of nivolumab. If this dose combination is found to be safe, following consultation and agreement between Investigators and the Sponsor, escalation may proceed at the previously defined BMS-986016 doses, maintaining the nivolumab dose at 80 mg, or an intermediate dose level. Testing of the Q2W and Q4W dosing schedules can proceed concurrently with independent escalation decisions based upon review of the current total safety experience and following consultation and agreement between Investigators and the Sponsor.

Prior to declaring the MTD (or MAD), and in consultation with Investigators, the Sponsor has the option to expand any cohort previously established to be safe in order to obtain additional

experience or to investigate dose levels intermediate to those defined in the protocol. Dose escalation rules (cohort size, DLT evaluation interval, cohort expansion criteria, etc.) will apply to these expanded or additional cohorts. A maximum of 9 subjects will be enrolled in any additional or expanded dose cohorts.

No within-subject dose escalations will be permitted. If a dose level is found to exceed the MTD, subjects enrolled in that dose level may be reduced to a lower dose following consultation and agreement between Investigators and the Sponsor.

3.1.2 Cohort Expansion

3.1.2.1 Cohort Expansion (Part A1)- Monotherapy

The purpose of cohort expansion is to gather additional safety, tolerability, preliminary efficacy, PK, and pharmacodynamic information of BMS-986016 monotherapy. The doses selected for Part A1 will not exceed the MTD or MAD in Part A, but may incorporate assessment of other data including toxicities and PK and pharmacodynamic data from Part A. Doses to be considered may include doses intermediate to those evaluated in Part A, if recommended by the Investigators and the Sponsor. Two expansion cohorts will be restricted to the tumor types listed in [Table 3.1.1.1-1](#).

Subjects with progressive disease in Part A1 may cross over to combination therapy with sequential infusion of nivolumab and BMS-986016 if the following criteria are met: 1) Subject has confirmed disease progression (investigator-assessed RECIST 1.1-defined progression confirmed at least 4 weeks after the initial tumor assessment showing progression; 2) Subject has not experienced BMS-986016 related adverse events leading to permanent discontinuation; 3) Subject is not continuing to derive any clinical benefit from BMS-986016 single agent therapy as assessed by the investigator; 4) The individual case has been discussed with the medical monitor prior to cross over; 5) At least an 8 week period in between the last dose of monotherapy and the first dose of combination therapy. Subjects crossing over to combination therapy will start treatment at Cycle 1 Day 1 as described for subjects in Part C. Subjects who crossover will receive combination therapy in sequential infusion at the doses that have been declared safe in dose escalation and/ or dose expansion parts at the time of cross-over. The original protocol rules will apply accordingly. Combination therapy may thus be administered for up to 12 additional eight week cycles according to the protocol rules. Subjects who crossed over and subsequently have an objective response in combination therapy will not be considered in the decision making for Part C. Subjects in Part C cannot crossover to Part A1.

Collection of archival tissue (baseline) and tumor biopsies (baseline and on-therapy) will be optional in subjects crossing-over and PK and biomarker monitoring will be limited ([Sections 5.5 and 5.7](#))

3.1.2.2 Cohort Expansion (Part C) - Sequential Infusion

The purpose of cohort expansion is to gather additional safety, tolerability, preliminary efficacy, PK, and pharmacodynamic information in subjects treated with sequential infusion of nivolumab

followed by administration of BMS-986016. The initial doses selected for specific Part C cohorts will not exceed the MTD (or MAD if no MTD is determined) in Part B, but may incorporate consideration of other data including (but not necessarily limited to) toxicities, PK and pharmacodynamic data from Parts A and B and can be chosen while additional Part B dose escalation cohorts continue to be explored. Part C expansion cohort doses to be considered will include those doses shown to be safe in Part B (or intermediate to those doses) as recommended by the Investigators and the Sponsor. Dosing of subsequent patients within an expansion cohort, or between cohorts, can be increased (if deemed safe in Part B) or decreased (based upon ongoing reviews of the totality of the safety data), all to be decided in agreement between the Investigators and the Sponsor. There will be no dose adjustments for individual subjects. Expansion cohorts in Part C will be restricted to six tumor types in eight cohorts ([Section 3.1](#)). Efficacy analyses in all cohorts will be guided by a multi-stage evaluation approach. Cohorts deemed futile at Stage 1 will be discontinued while those deemed promising may be expanded up to 90 to 120 subjects in total after careful evaluation of all available data including the totality of efficacy, safety profile, and PK/PD ([Section 8.1.2](#)). Otherwise, additional subjects may be treated to collect more data during Stage 2 in order to make a decision for further expansion. Enrollment to Stage 2 or further expansion in a given cohort can continue even if the other cohorts are still in Stage 1. Subjects who crossed over to combination therapy in Part A1 and subsequently have an objective response will not be considered in the decision making for Part C. Subjects in Part C cannot crossover to Part A1 either.

3.1.2.3 All Cohort Expansion Parts (A1 and C)

Continuous evaluation of toxicity events in the cohort expansions will be performed throughout enrollment in the expansion cohorts. Safety conference calls with the BMS Medical Monitor, investigators and representatives of the sponsor are being held regularly during the escalation and expansion parts. In addition, separate BMS medical safety teams (MST) routinely review safety signals across the BMS-986016 and nivolumab programs. If, at any time, the aggregate rate of treatment-related toxicities meeting DLT criteria exceeds 33% across all subjects treated in any of these cohort expansions Parts, the findings will be discussed and further enrollment must be interrupted in that particular cohort and others. Depending on the nature and grade of the toxicity and after assessing the risk:benefit ratio, a new dose(s) for all cohorts may be initiated at a previously tested lower dose level or at a dose level intermediate to previously tested lower dose levels.

3.1.2.4 Re-challenge in Dose Escalation (Parts A and B) and Cohort Expansion Parts (A1 and C)

If subjects progress during the clinical follow-up period or the survival follow-up period, they could further receive therapy with BMS-986016 alone or in combination therapy (**Re-challenge**) as long as the risk:benefit ratio is considered favorable by the Investigator and the Medical Monitor and the following eligibility criteria are met: 1) Subject has confirmed disease progression (investigator-assessed RECIST 1.1-defined progression confirmed at least 4 weeks after the initial tumor assessment showing progression; 2) Subject has not experienced BMS-986016 related adverse events leading to permanent discontinuation. The original dose and schedule of therapy

and protocol rules will apply. Thus subjects could receive therapy for up to 12 additional eight-week cycles. Collection of archival tissue (baseline) and tumor biopsies (baseline and on-therapy) will be optional for subjects crossing-over and PK and biomarker monitoring will be limited (Sections 5.5 and 5.7)

Subjects who are re-challenged and who subsequently have an objective response will not be included in the primary analysis of efficacy. Responses to re-challenge will be evaluated in a separate analysis. Subjects will not be re-challenged a second time.

3.1.3 Dose-Limiting Toxicities

BMS-986016 has the potential to augment the frequency and severity of previously described AEs associated with nivolumab, or to produce new toxicities. For the purpose of guiding decisions regarding dose escalation in Parts A and B, dose-limiting toxicity (DLT) will be determined based on the incidence, intensity, and duration of AEs that are related to study drug and that occur within 56 days (8 weeks) of initiation of study drug (i.e., the DLT evaluation interval, through the completion of Cycle 1). The severity of AEs will be graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.0.

For the purpose of subject management, potential DLTs that occur at any time, whether during dose escalation (Parts A and B) or cohort expansion (Parts A1 and C) will result in all study drug(s) being held pending evaluation of the event's relatedness to study drug, severity, and duration, and in accordance with Section 4.3.2. Subjects must meet criteria for re-treatment prior to re-initiation of study treatment (see Section 4.3.3).

Hepatic, non-hematologic, and hematologic DLTs are defined separately as outlined below.

Hepatic DLT

Any of the following drug-related events will be considered a hepatic DLT (non HCC subjects):

- ALT or AST $> 8 \times$ ULN, regardless of duration, or
- ALT or AST $> 5 \times$ and $\leq 8 \times$ ULN, that fails to return to \leq Grade 1 within 2 weeks despite medical intervention, or
- Total bilirubin $> 5 \times$ ULN, or
- Potential drug-induced liver injury (DILI) event (Section 6.6)

For subjects with HCC, hepatic DLT criteria differ due to intrinsic involvement of the liver. In addition, for subjects with hepatitis B or hepatitis C, it is possible that virological breakthrough may occur, leading to temporary hepatic abnormalities. In these cases, subjects who regain virologic control may be allowed to resume study therapy after agreement between the Investigator and Sponsor.

Any of the following events will be considered a hepatic DLT for subjects with HCC:

- ALT or AST $> 15 \times$ ULN, regardless of duration
- ALT or AST $> 10 \times$ ULN for greater than 2 weeks

- Total bilirubin $> 8 \times$ ULN regardless of duration for subjects with elevated bilirubin at study entry or $> 5 \times$ ULN for subjects with normal bilirubin at study entry
- Potential drug-induced liver injury (DILI) event for HCC ([Section 6.6](#))

Non-Hematologic DLT

Any of the following drug-related events will be considered a non-hematologic DLT:

- Grade 2 immune related-eye pain or reduction in visual acuity that requires systemic treatment, or
- Grade 2 eye pain or reduction in visual acuity that does not respond to topical therapy and that does not improve to Grade 1 within 2 weeks of initiation of topical therapy, or
- \geq Grade 3 non-hepatic or non-hematologic toxicity with the exceptions noted below

The following Grade 3 or 4 non-hematologic events **will not** be considered DLTs:

- Grade 3 electrolyte abnormality (and grade 4 hyperglycemia) that lasts < 72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical intervention
- Grade 3 or 4 increase in amylase and/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 \leq Grade 1 either spontaneously or with conventional medical intervention
- Grade 3 diarrhea that lasts < 72 hours, does not result in hospitalization, and resolves to \leq 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 endocrinopathy that is well controlled by hormone replacement
- Grade 3 tumor flare (defined as pain, irritation, or rash that localizes to sites of known or suspected tumor)
- Grade 3 fatigue for less than 7 days
- Grade 3 rash meeting the following criteria: 1) improves to grade 1 within 2 weeks, 2) does not limit self-care, and 3) is not associated with infection.
- Grade 3 troponin not associated with any other sign of cardiac toxicity (as determined by a cardiac evaluation)

Definition of Hematologic DLT

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

- Grade 4 febrile neutropenia of any duration
- Grade 4 neutropenia that lasts > 5 days
- Grade 4 thrombocytopenia

- Grade 4 anemia
- Grade 3 thrombocytopenia associated with clinically significant bleeding
- Grade 3 febrile neutropenia that lasts > 48 hours
- Grade 3 hemolysis

In the event that study drug cannot be administered at a scheduled visit during the DLT evaluation interval, it must be administered as soon as possible. Subjects may be dosed no less than 12 days from the previous dose during Q2W cycles and no more than 3 days from scheduled dose. If an infusion cannot be administered at a scheduled visit, it should be administered as soon as possible. Subsequent dosing visits will follow every 2 weeks after the delayed dose. A dose given more than 3 days after the intended dose date will be considered a delay. A maximum delay of 6 weeks between doses is allowed. Longer delays may be allowed following discussion with the Medical Monitor. For Q4W dosing cycles, subjects may be dosed within a +/- 3 day window. For the purpose of making decisions on dose escalation from a safety perspective, subjects will be considered evaluable if they have received 3 out of the 4 scheduled BMS-986016 doses in Part A (or 3 out of 4 scheduled BMS-986016 and nivolumab doses in Part B) through the 8 week observation period, only if the one missed dose was secondary to progressive disease or non-medical reasons. Unevaluable subjects may be replaced at the same dose level.

3.2 Post Study Access to Therapy

At the end of the study, BMS will not continue to supply study drug to subjects or 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) The subject must sign and date the IRB/IEC approved written informed consent form prior to the performance of any study-related procedures that are not considered part of standard of care.
- b) Consent for tumor biopsy samples
 - i) Parts A and B Dose Escalation:
 - (1) Subject must consent and will be required to undergo a **MANDATORY** pre-treatment biopsy; therefore, subjects must have a lesion located such that the specimen can be obtained at acceptable clinical risk as judged by the Investigator. The acquisition of existing formalin-fixed paraffin-embedded (FFPE) tumor tissue, either a block or unstained slides, for performance of correlative studies should also

be collected if available. Subjects unable to provide a pre-treatment tumor biopsy or do not have accessible lesions are not eligible.

ii) Parts A1 and C Cohort Expansion:

- (1) All subjects in Part C will be required to undergo MANDATORY pre-treatment biopsy; therefore, subjects must have a lesion located such that the specimen can be obtained at acceptable clinical risk as judged by the Investigator. Subjects who do not meet these criteria are not eligible; however, subjects whose screening biopsy yields inadequate tissue quantity or quality will not be ineligible on this basis alone. The acquisition of existing formalin-fixed paraffin-embedded (FFPE) tumor tissue, either a block or unstained slides, for performance of correlative studies should also be collected if available. Subjects unable to provide a pre-treatment tumor biopsy or do not have accessible lesions are not eligible.

- (2) Not applicable per Protocol Amendment 011.

iii) If there is only one measurable lesion, and a fine-needle biopsy is done (instead of excisional), the lesion may be used as measurable lesion. If there are more than one measurable lesions, the lesion being biopsied should not be a target lesion.

2) Target Population

a) Subjects must have histologic or cytologic confirmation of an incurable solid malignancy that is advanced (metastatic and/or unresectable):

i) Part A: Dose Escalation: BMS-986016 monotherapy

- (1) All solid tumor histologies will be permitted except for subjects with primary CNS tumors
- (2) Only subjects without prior exposure to immuno-oncology (IO) agents such as, but not limited to, anti-CTLA-4, anti-PD-1, anti-PDL-1, anti-PD-L2, anti-KIR, anti-CD137, or anti-OX40 antibodies, are allowed.
- (3) Subjects must have received, and then progressed or been intolerant to, at least one standard treatment regimen in the advanced or metastatic setting, if such a therapy exists.

ii) Parts B: Dose Escalation: BMS-986016 + nivolumab

- (1) Selected solid tumor histologies naive to immuno-oncology (IO) agents such as, but not limited to, anti-CTLA-4, anti-PD-1, anti-PDL-1, anti-PD-L2, anti-KIR, anti-CD137, or anti-OX40 antibodies, will be permitted except for subjects with primary CNS tumors. Selected tumor types (and all subtypes) include melanoma 1st line, RCC, NSCLC 1st, 2nd, or 3rd line, head and neck (any histology), gastric (includes gastro-esophageal junction) cancer, hepatocellular, cervical, ovarian, bladder and colo-rectal cancers.

- (2) Not applicable per Protocol Amendment 02

- (3) NSCLC subjects progressing while on or after therapy with anti-PD-1 or anti-PD-L1 antibody (for Part B this does not need to be the most recent therapy)
 - (a) Not applicable per Protocol Amendment 02
 - (b) Cannot have had therapy discontinued due to serious and/or life-threatening anti-PD-1 or anti-PD-L1 antibody-related toxicity (e.g., dose-limiting toxicity in prior study) per Investigator's assessment in consultation with the BMS Medical Monitor.
 - (c) Not applicable per Protocol Amendment 02
 - (d) Cannot have had prior exposure to other IOs, such as, but not limited to, anti-PD-L2, anti-KIR, anti-CD137, or anti-OX40 antibodies. Prior anti-CTLA-4 antibody therapy is allowed.
- (4) Melanoma subjects whose disease is progressing while on or after receiving anti-CTLA-4 and/or anti-PD-1 / anti-PDL-1 antibody therapies
 - (a) Anti-CTLA-4 and/or anti-PD-1 or anti-PDL-1 antibody therapies could have been received in sequential or combination regimens, as well as in combination with BRAF and/or MEK inhibitors.
 - (b) Last dose of antibody therapy must have been received ≥ 30 days of first dose of study medication
 - (c) Cannot have had therapy discontinued due to serious and/or life-threatening antibody-related toxicity (e.g., dose-limiting toxicity in prior study) per Investigator's assessment in consultation with the BMS Medical Monitor.
 - (d) Cannot have had prior exposure to any IOs other than anti-CTLA-4 and/or anti-PD-1 /anti-PDL-1 antibody therapy. Prior IL-2 and IFN therapy is allowed.
- (5) Subjects must have received, and then progressed or been intolerant to, at least one standard treatment regimen or refused standard therapy in the advanced or metastatic setting, if such a therapy exists; except for NSCLC and melanoma, where treatment as 1st line therapy is allowed.
 - (a) For first line NSCLC subjects: The drug regimen with the highest likelihood of benefit with toxicity deemed acceptable to both the physician and the patient should be given as initial therapy for advanced lung cancer. EGFR or ALK genetic aberrations must be documented (if possible) - and if positive, subjects must be offered targeted therapy if appropriate and available. Otherwise subjects should be offered chemotherapy if appropriate and available. Patients may refuse these standard treatments. The reason for why a subject does not receive standard first line metastatic therapy must be documented.
 - (b) For first line melanoma subjects: Some prior neoadjuvant and adjuvant treatments are allowed (including cytokines, interferon, and anti-CTLA-4), but

other are NOT (including, but not limited to, anti-PD-1, anti-PD-L1, anti-PD-L2, anti-KIR, anti-CD137, or anti-OX40 antibodies). For first line NSCLC subjects: Prior adjuvant or neoadjuvant chemotherapy, or definitive chemoradiation is permitted as long as the last administration of the prior regimen occurred at least 6 months prior to enrollment; while prior IO therapies are not allowed.

iii) Part C Cohort Expansion- sequential dosing

(1) The following groups will be enrolled:

(a) Melanoma – First line:

- (i) Untreated, histologically confirmed unresectable Stage III or Stage IV melanoma, as per AJCC staging system.
- (ii) Both BRAF V600 wild-type and mutant melanomas are allowed and mutation status must be documented.
- (iii) Prior adjuvant or neoadjuvant melanoma therapy is permitted if it was completed at least 6 weeks prior to enrollment and all related adverse events have either returned to baseline or stabilized. Note that adjuvant or neoadjuvant cytokine (IL-2 or IFN) therapy is allowed but other IO therapies such as, but not limited to, anti-CTLA-4, anti-PD-1, anti-PD-L1, anti-PD-L2, anti-KIR, anti-CD137, or anti-OX40 antibodies, are not allowed.
- (iv) Uveal melanoma subjects are not eligible

(b) Renal cell carcinoma - naive to IOs.

- (i) Histology must have a clear-cell component.
- (ii) Subjects must have received at least one, but not more than two, prior anti-angiogenic therapy regimens (including, but not limited to, sunitinib, sorafenib, pazopanib, axitinib, tivozanib, everolimus, temsirolimus, and bevacizumab) in the advanced or metastatic setting.
- (iii) No more than three total previous regimens of systemic therapy are allowed, including cytokines (IL-2 or IFN), vaccine therapy, and cytotoxic chemotherapy drugs, and disease progression during or after the last treatment regimen and within 6 months before study enrollment.
- (iv) Subjects cannot have had prior exposure to non-cytokine IO therapies such as, but not limited to, anti-CTLA-4, anti-PD-1, anti-PD-L1, anti-PD-L2, anti-KIR, anti-CD137, or anti-OX40 antibodies.

(c) Non-small cell lung cancer (NSCLC) naive to IOs: First, second, or third line

(i) First Line:

- a. Subjects with histologically confirmed Stage IIIB, IV, or recurrent NSCLC⁴⁶, squamous or nonsquamous histology, with no prior systemic anticancer therapy (including EGFR and ALK inhibitors) given as primary therapy for advanced or metastatic disease.
- b. Prior adjuvant treatments (except IO therapies) are allowed as long as there was a six month interval between last adjuvant treatment dose and diagnosis of advanced disease. Prior definitive chemoradiation for locally advanced disease is also permitted as long as the last administration of chemotherapy or radiotherapy (which ever was given last) occurred at least 6 months prior to enrollment.
- c. NOTE: The drug regimen with the highest likelihood of benefit with toxicity deemed acceptable to both the physician and the patient should be given as initial therapy for advanced lung cancer. EGFR or ALK genetic aberrations must be documented (if possible) - and if positive, subjects must be offered targeted therapy if appropriate and available. Otherwise subjects should be offered chemotherapy if appropriate and available. Patients may refuse these standard treatments. The reason for why a subject does not receive standard first line metastatic therapy must be documented.

(ii) Second or Third line:

- a. Subjects with histologically or cytologically-documented locally advanced non-squamous cell NSCLC who present with Stage IIIB/Stage IV or recurrent or progressive disease following multi-modality therapy (radiation therapy, surgical resection or definitive chemoradiation therapy for locally advanced disease).
- b. Subjects who will receive study therapy as second line of treatment:

Subjects must have experienced disease recurrence or progression during or after one prior platinum doublet-based chemotherapy regimen for advanced or metastatic disease.

First line therapy is defined as therapy used to treat advanced disease. Each subsequent line of therapy is preceded by disease progression. A switch of an agent within a regimen in order to manage toxicity does not define the start of a new line of therapy. Subjects must have received at least 2 cycles of platinum doublet based chemotherapy before discontinuation for toxicity.

Experimental therapies when given as separate regimen are considered as separate line of therapy.

Maintenance therapy following platinum doublet-based chemotherapy is not considered as a separate regimen of therapy and could comprise

continuation of one or more of the agents used in the first-line therapy regimen or switch to another non cross-resistant agent. The initiation of maintenance therapy requires the lack of progressive disease with front-line therapy.

Treatment given for locally advanced disease is not considered as a line of therapy for advanced disease. Subjects with recurrent disease > 6 months after platinum-containing adjuvant, neoadjuvant or definitive chemoradiation therapy given for locally advanced disease, who also subsequently progressed during or after a platinum doublet-based regimen given to treat the recurrence, are eligible.

Subjects who received platinum-containing adjuvant, neoadjuvant or definitive chemoradiation therapy given for locally advanced disease, and developed recurrent (local or metastatic) disease within 6 months of completing therapy are eligible.

Adjuvant or neoadjuvant platinum-doublet chemotherapy (after surgery and/or radiation therapy) followed by recurrent or metastatic disease within 6 months of completing therapy is considered as first line therapy for advanced disease.

- c. Subjects who will receive study therapy as third line of treatment must have experienced disease recurrence or progression during or after a separate EGFR or ALK tyrosine kinase inhibitor (TKI) regimen in addition to one prior platinum doublet-based chemotherapy regimen (regardless of order of administration)

Subjects who received an EGFR TKI (erlotinib, gefitinib or experimental) in addition to a platinum-based chemotherapy must have a tumor with a known activating EGFR mutation.

Subjects with a tumor with EGFR wild-type or unknown EGFR mutation status who received an EGFR TKI after failure of a prior platinum-based chemotherapy are excluded.

Subjects who received an ALK inhibitor (crizotinib or experimental) in addition to a platinum-based chemotherapy must have a tumor with a known ALK translocation.

- (d) NSCLC subjects progressing while on or after therapy with anti-PD-1 or anti-PD-L1 antibody as most recent therapy.

- (i) Squamous or nonsquamous histology.
 - (ii) This cohort includes two separate subgroups, 1) primary refractory disease: defined as those subjects that progressed within the first 12 weeks of the prior

anti-PD-1 or anti-PD-L1 antibody therapy, and 2) relapsed disease: defined as those subjects that do not meet the criterion for primary refractory disease.

(iii) Subjects should not have discontinued antibody therapy due to serious and/or life-threatening toxicity (e.g., dose-limiting toxicity in prior study) per Investigator's assessment in consultation with the BMS Medical Monitor.

(iv) These subjects cannot have had prior exposure to any other IOs such as, but not limited to, anti-PD-L2, anti-KIR, anti-CD137, or anti-OX40 antibodies. Prior anti-CTLA-4 antibody therapy is allowed.

(e) Head and Neck cancer – naive to IOs.

(i) Histology restricted to squamous cell carcinoma (SCCHN), from any of the following primary sites only: oral cavity, oropharynx, hypopharynx and larynx

(ii) Subjects are eligible regardless of HPV status.

(iii) Tumor progression on or after platinum therapy in the adjuvant (ie, with radiation after surgery), primary (ie, with radiation), recurrent, or metastatic setting.

(iv) Subjects cannot have had prior exposure to IO therapies such as, but not limited to, anti-CTLA-4, anti-PD-1, anti-PD-L1, anti-PD-L2, anti-KIR, anti-CD137, or anti-OX40 antibodies.

(f) Not applicable per Protocol Amendment 04

(g) Melanoma - previously progressed on anti-PD-1/ anti-PDL-1 antibody therapy

(i) Prior anti-PD-1/anti-PDL-1 antibody alone or in any combination with anti-CTLA-4 antibody therapy, BRAF and/or MEK inhibitors are allowed.

(ii) Subjects should not have discontinued antibody therapy due to serious and/or life-threatening toxicity (e.g., dose-limiting toxicity in prior study) per Investigator's assessment in consultation with the BMS Medical Monitor.

(iii) Subjects cannot have had prior exposure to IOs therapies including, but not limited to anti-PD-L2, anti-KIR, anti-CD137, or anti-OX40 antibodies. IO therapies including, but not limited to, anti-CTLA-4, anti-PD-1, anti-PDL-1 antibody therapies or IL-2 and IFN cytokine therapies are allowed.

(iv) Prior adjuvant or neoadjuvant therapy with cytokines (IL-2 or IFN) or anti-CTLA-4 antibodies is allowed.

(v) Uveal melanoma subjects are not eligible

(h) Gastric adenocarcinoma (includes gastro-esophageal junction) - naive to IOs.

(i) HER2(+) and HER2(-) subjects will be allowed

- (ii) Subjects cannot have had prior exposure to IO therapies such as, but not limited to, anti-CTLA-4, anti-PD-1, anti-PD-L1, anti-PD-L2, anti-KIR, anti-CD137, or anti-OX40 antibodies.
- (i) Hepatocellular carcinoma - naive to IOs.
 - (i) Child-Pugh score of 6 points or less, i.e., Child-Pugh A
 - (ii) Without history of encephalopathy, clinically significant ascites (within one year of enrollment), or clinically significant variceal bleeding (within 6 months of enrollment)
 - (iii) Subjects with or without viral infection (uninfected, HCV-infected, and HBV-infected) are eligible
 - (iv) Disease not amenable for management with curative intent by surgery or local therapeutic measures.
 - (v) Subjects with radiological diagnosis may be enrolled for screening in the study but histological confirmation is mandatory prior to initiation of study therapy.
 - (vi) Subjects with chronic HBV infection must have a HBV DNA viral load < 100 IU/mL at screening. In addition, they must be on antiviral therapy per regional standard of care guidelines prior to initiation of study therapy. If not on antiviral therapy at screening, then the subject must initiate treatment per regional standard of care guidelines at the time of consent. All subjects enrolled in the HBV cohort must continue antiviral therapy for the duration of the study. Both HBeAg positive and negative subjects will be included. Subjects with hepatitis B infection must not have co-infection with hepatitis C or hepatitis D (must obtain hepatitis D antibody testing).
 - (vii) Subjects cannot have had prior exposure to IO therapies such as, but not limited to, anti-CTLA-4, anti-PD-1, anti-PD-L1, anti-PD-L2, anti-KIR, anti-CD137, or anti-OX40 antibodies.
 - (viii) Fibrolamellar and sarcomatoid histologies are not eligible
- (2) Prior lines of therapy (applies to all Part C subjects except those treated as first line NSCLC and first line melanoma): Subjects must have received, and then progressed or been intolerant to, at least one standard treatment regimen in the advanced or metastatic setting, if such a therapy exists or refused standard treatment (refusal must be documented). Number of maximum allowed prior systemic treatment regimens in the advanced or metastatic setting based on cohort: NSCLC progressing on prior IO = 3 lines, unless targetable EGFR or ALK genomic tumor aberrations, then 4 lines are allowed; Melanoma progressing on prior IO = 3 lines, unless targetable BRAF V600 mutation, then 4 lines are allowed; Gastric = no limit; Head and Neck = 2 prior lines; HCC = no limit. For RCC and NSCLC IO naive cohorts see criteria in individual cohort eligibility sections above.

iv) Part A1 Cohort Expansion- Monotherapy

(1) The following groups will be enrolled:

- (a) NSCLC - subjects whose disease progressed while on or after therapy with anti-PD-1 or anti-PD-L1 antibody (for Part B this does not need to be the most recent therapy) Subjects should have not discontinued antibody therapy due to serious and/or life-threatening toxicity (e.g., dose-limiting toxicity in prior study) per Investigator's assessment in consultation with the BMS Medical Monitor. These subjects cannot have had prior exposure to any other IOs such as, but not limited to, anti-PD-L2, anti-KIR, anti-CD137, or anti-OX40 antibodies. Prior anti-CTLA-4 antibody therapy is allowed.
- (b) Renal cell carcinoma - Subjects must have received at least one prior anti-angiogenic therapy regimen (including, but not limited to, sunitinib, sorafenib, pazopanib, axitinib, tivozanib, everolimus, temsirolimus, and bevacizumab) in the advanced or metastatic setting. Subjects whose disease progressed while-on or after therapy with an anti-PD-1 or anti-PD-L1 antibody are allowed. Subject should have not discontinued antibody therapy due to serious and/or life-threatening toxicity (e.g., dose-limiting toxicity in prior study) per Investigator's assessment in consultation with the BMS Medical Monitor. These subjects cannot have had prior exposure to any other IOs such as, but not limited to, anti-PD-L2, anti-KIR, anti-CD137, or anti-OX40 antibodies. Prior anti-CTLA-4 antibody therapy is allowed.

(2) Subjects must have received, and then progressed or been intolerant to, at least one standard treatment regimen or refuse standard therapy in the advanced or metastatic setting, if such a therapy exists.

- b) In subjects with prior treatment regimens, the following are not considered separate lines of treatment: addition of a compound to an ongoing regimen, restarting the same regimen after a drug holiday, or switching from IV to oral therapy. In addition, a switch of an agent within a regimen in order to manage toxicity does not define the start of a new line of therapy. Maintenance therapy is not considered as a separate regimen of therapy and could comprise continuation of one or more of the agents used in the effective treatment regimen or switch to another non cross-resistant agent. The initiation of maintenance therapy requires the lack of progressive disease with the effective treatment regimen.
- c) Presence of at least one lesion with measurable disease as defined by RECIST v1.1 criteria for response assessment. 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 prior to the time of informed consent and can be measured accurately.

- d) ECOG status of 0 or 1. For RCC subjects ONLY: Karnofsky Performance Score (KPS) \geq 70% ([Appendix 3](#))
- e) Life expectancy of \geq 12 weeks at the time of informed consent per Investigator assessment.
- f) Adequate organ function as defined by the following:
 - i) White blood cells (WBCs) \geq 2000/ μ L (stable off any growth factor within 4 weeks of first study drug administration)
 - ii) Neutrophils \geq 1500/ μ L (stable off any growth factor within 4 weeks of first study drug administration)
 - iii) Platelets \geq 100 (\geq 60 for HCC) $\times 10^3$ / μ L (transfusion to achieve this level is not permitted within 2 weeks of first study drug administration)
 - iv) Hemoglobin \geq 8.5 g/dL (transfusion to achieve this level is not permitted within 2 weeks of first study drug administration)
 - v) Creatinine $< 1.5 \times$ ULN or creatinine clearance \geq 40mL/min (Cockcroft-Gault formula)
 - vi) ALT and AST $\leq 3 \times$ ULN ($\leq 5 \times$ ULN for HCC)
 - vii) Lipase and amylase $< 1.5 \times$ ULN
 - viii) Total bilirubin $\leq 1.5 \times$ ULN (except subjects with Gilbert's Syndrome who must have normal direct bilirubin) [3 mg/dL for HCC]
 - ix) Normal thyroid function, or stable on hormone supplementation per investigator assessment
 - x) Albumin \geq 2.8 g/dl
 - xi) Cardiac Troponin T (cTnT) or I (cTnI) $\leq 2 \times$ institutional ULN. Subjects with cTnT or cTnI levels between > 1 to $2 \times$ ULN will be permitted if repeat levels within 24 hours are ≤ 1 ULN
 - (1) If cTnT or cTnI levels are >1 ULN at 24 hours, the subject may undergo a cardiac evaluation and be considered for treatment, following a discussion with the BMS Medical Monitor or designee.
- g) Ability to comply with treatment, PK, and pharmacodynamic sample collection and required study follow-up.
- h) Subject re-enrollment: This study permits the re-enrollment of a subject that has discontinued the study as a pre-treatment failure (i.e., subject has not been randomized / has not been treated). If re-enrolled, the subject must be re-consented.
- i) LVEF assessment with documented LVEF \geq 50% by either TTE or MUGA (TTE preferred test) within 6 months from first study drug administration

3) Age and Reproductive Status

- a) Men and women, ages \geq 18 years at the time of informed consent

- b) WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with BMS-986016 plus 5 half-lives of BMS-986016 (135 days) plus 30 days (duration of ovulatory cycle) for a total of 165 days (24 weeks) after completion of treatment.
- c) 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 study drug.
- d) Women must not be breastfeeding.
- e) Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with BMS-986016 plus 5 half-lives of BMS-986016 (135 days) plus 90 days (duration of sperm turnover) for a total of 225 days (33 weeks) after completion of treatment.

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 WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% per year when used consistently and correctly.

At a minimum, subjects must agree to the use of 2 methods of contraception, with one method being highly effective and the other being either highly effective or less effective as listed in [Appendix 1](#).

- f) WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However, WOCBP who abstain from heterosexual activity on a continuous basis must still undergo pregnancy testing as described in this protocol.

3.3.2 Exclusion Criteria

1) Target Disease Exceptions

- a) Subjects with known or suspected CNS metastases or with the CNS as the only site of active disease are excluded with the following exceptions:
 - i) Subjects with controlled brain metastases will be allowed to enroll. Controlled brain metastases are defined as those with no radiographic progression for at least 4 weeks after radiation and/or surgical treatment at the time of consent. Subjects must have been off of steroids for at least 2 weeks prior to informed consent, and have no new or progressive neurological signs and symptoms.
 - ii) Subjects with signs or symptoms of brain metastases are not eligible unless brain metastases are ruled out by computed tomography (CT) or magnetic resonance imaging (MRI).
- b) Participation in any prior clinical study with nivolumab, including subjects in comparator arms, in which overall survival is listed as the primary or co-primary endpoint and which has not completed analysis based on the primary endpoint.

2) Medical History and Concurrent Diseases

- a) Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast.
- b) Subjects with an active, known or suspected autoimmune disease. Subjects with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
- c) 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 subject or could adversely affect the ability of the subject to comply with or tolerate study.
- d) Requirement for daily supplemental oxygen
- e) Uncontrolled or significant cardiovascular disease including, but not limited to, any of the following:
 - i) Myocardial infarction (MI) or stroke/transient ischemic attack (TIA) within the 6 months prior to consent
 - ii) Uncontrolled angina within the 3 months prior to consent
 - iii) Any history of clinically significant arrhythmias (such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes)
 - iv) QTc prolongation > 480 msec
 - v) History of other clinically significant cardiovascular disease (i.e., cardiomyopathy, congestive heart failure with New York Heart Association [NYHA] functional classification III-IV, pericarditis, significant pericardial effusion, significant coronary stent occlusion, deep venous thrombosis, etc)
 - vi) Cardiovascular disease-related requirement for daily supplemental oxygen
 - vii) History of two or more MIs OR two or more coronary revascularization procedures
 - viii) Subjects with history of myocarditis, regardless of etiology
- f) A confirmed history of encephalitis, meningitis, or uncontrolled seizures in the year prior to informed consent
- g) Positive blood screen for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)
- h) History of any chronic hepatitis (except for subjects with HCC) as evidenced by:
 - i) Positive test for hepatitis A antibody (HepA IgM). Note: history of resolved hepatitis A virus infection is not an exclusion criterion.
 - ii) Positive test for hepatitis B surface antigen (HBsAg) and/or hepatitis B core antigen
 - iii) Positive test for qualitative hepatitis C viral load (by PCR)
- i) Evidence of active infection that requires systemic antibacterial, antiviral, or antifungal therapy ≤ 7 days prior to initiation of study drug therapy
- j) Any other significant acute or chronic medical illness

- k) Subjects who are unable to undergo venipuncture and/or tolerate venous access
- l) Any other sound medical, psychiatric, and/or social reason as determined by the Investigator.
- m) Any of the following procedures or medications:
 - i) Within 2 weeks prior to time of study treatment:
 - (1) Systemic or topical corticosteroids at immunosuppressive doses (> 10 mg/day of prednisone or equivalent). Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
 - (2) Palliative radiation or gamma knife radiosurgery
 - (3) Not Applicable per Protocol Amendment 02
 - ii) Within 4 weeks prior to study drug administration:
 - (1) Any investigational cytotoxic drug. Exposure to any non-cytotoxic drug within 4 weeks or 5 half-lives (whichever is shorter) is prohibited. If 5 half-lives is shorter than 4 weeks, agreement with Sponsor/Medical Monitor is mandatory.
 - (2) Not applicable per Protocol Amendment 05.
 - (3) Non-oncology vaccines containing live virus
 - (4) Allergen hyposensitization therapy
 - (5) Growth factors, e.g., granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF), erythropoietin
 - (6) Major surgery
 - (7) Not applicable per Protocol Amendment 11
 - iii) Not applicable per Protocol Amendment 04
- n) Subjects with history of life-threatening toxicity related to prior immune therapy (eg. anti-CTLA-4 or anti-PD-1/PD-L1 treatment or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways) except those that are unlikely to re-occur with standard countermeasures (e.g., hormone replacement after endocrinopathy).

3) Allergies and Adverse Drug Reaction

- a) History of allergy to anti-PD-1 or anti-PD-L1 antibody therapy or to other monoclonal antibodies or related compounds or to any of their components (e.g., history of severe hypersensitivity reactions to drugs formulated with polysorbate 80).

4) Other Exclusion Criteria

- a) Prisoners or subjects who are involuntarily incarcerated
- b) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (e.g., infectious disease) illness

- c) Inability to comply with restrictions and prohibited activities and treatments as listed in Section 3.4

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) are defined as any female who have 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 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 judgement in checking serum FSH levels. If the serum FSH level is >40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal.

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

Other parenteral products may require washout periods as long as 6 months.

3.4 Concomitant Treatments

3.4.1 Prohibited and/or Restricted Treatments

The following medications are prohibited during the study:

- Immunosuppressive agents unless they are utilized to treat an AE or as specified in [Sections 3.4.3 and 3.4.4](#).
- Concurrent administration of any anticancer therapies (investigational or approved) with the exception of subjects in the survival period of the study
- Use of growth factors unless prior discussion and agreement with BMS Medical Monitor
- Use of allergen hyposensitization therapy
- Use of cannabis or other recreational drugs

Palliative radiotherapy is permitted only under certain conditions as described in Section 3.4.3.

3.4.2 Other Restrictions and Precautions

Any vaccination containing attenuated or inactivated virus may be permitted if clinically indicated. However, this must be discussed and documented with the BMS Medical Monitor **prior to administration** and may require a study drug washout period prior to and after administration of the vaccine. Inactivated influenza vaccination will be permitted on study without restriction.

It is the local imaging facility's responsibility to determine, based on subject attributes (e.g., 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. Specific to MRI, subjects with severe renal insufficiency (i.e., estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m²) are at increased risk of nephrogenic systemic fibrosis. MRI contrast should not be given to this subject population. 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). Immunosuppressive agents and the use of systemic corticosteroids are permitted in the context of treating AEs, prophylaxis prior to a diagnostic procedure (e.g. contrast MRI/CT scans) or as specified in [Section 3.4.4](#). A brief course of corticosteroids for prophylaxis (e.g., contrast dye allergy) is permitted after discussion with the BMS Medical Monitor.

Subjects may continue to receive HRT.

Palliative and supportive care for disease-related symptoms may be offered to all subjects on the trial; however, Investigators should consult with the BMS Medical Monitor prior to initiating palliative radiation in subjects who have not yet completed the DLT evaluation interval (Part A, and B).

The potential for overlapping toxicities with radiotherapy and BMS-986016 ± nivolumab is currently not known. Therefore, palliative radiotherapy is not recommended while receiving any of these drugs, alone or in combination. If palliative radiotherapy in short courses and for isolated fields is required to control symptoms not clearly related to disease progression, then drug administration should be withheld, if possible, for at least 1 week before radiation and for at least 1 week after its completion. Subjects should be closely monitored for any potential toxicity during and after receiving radiotherapy. Prior to resuming study drug treatment, radiotherapy-related AEs should resolve to ≤ Grade 1 or baseline and subjects must meet relevant eligibility criteria as determined by the BMS Medical Monitor in discussion with the Investigator. The BMS Medical

Monitor must be consulted prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks after the last dose.

Details of palliative radiotherapy should be documented in the source records and electronic case report form (eCRF). Details in the source records should include: dates of treatment, anatomical site, dose administered and fractionation schedule, and AEs. Symptoms requiring palliative radiotherapy should be evaluated for objective evidence of disease progression. Subjects receiving palliative radiation of target lesions will have the evaluation of ORR just prior to radiotherapy but such subjects will no longer be evaluable for determination of response subsequent to the date palliative radiation occurs.

For subjects who need to undergo elective surgery (not tumor-related) during the study, it is recommended to hold study drug(s) for at least 2 weeks before and 2 weeks after surgery, or until the subject recovers from the procedure, whichever is longer. Prior to resuming study drug treatment, surgically-related AEs should resolve to \leq Grade 1 or baseline and subjects must meet relevant eligibility criteria as determined by the BMS Medical Monitor in discussion with the Investigator. The BMS Medical Monitor must be consulted prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks after the last dose.

3.4.4 Treatment of BMS-986016 or Nivolumab-Related Infusion Reactions

Since BMS-986016 and nivolumab contain only human immunoglobulin protein sequences, they are unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the BMS Medical Monitor and reported as an SAE if it meets the criteria. Infusion reactions should be graded according to NCI CTCAE version 4.0 guidelines.

If a subject has an infusion reaction with nivolumab, the BMS-986016 infusion can be given (without prophylactic medications) if the infusion reaction resolves within 3 hours. For scheduling purposes after a nivolumab infusion reaction, the BMS-986016 infusion may be given the next day. Prophylactic pre-infusion medications should be given prior to all subsequent nivolumab infusions.

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 [e.g., 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 acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur, then no further study drug will be administered at that visit.

For future infusions, the following prophylactic premedications are recommended:

Diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg should be administered at least 30 minutes before study drug infusions. If necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent) may be used.

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

- Immediately discontinue infusion of study drug. Begin an IV infusion of normal saline and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous (SC) administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the Investigator is comfortable that the symptoms will not recur. All study drug(s) will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery of the symptoms.

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

Please refer to [Appendix 4](#) for a complete list of the Nivolumab Management Algorithms.

3.5 Discontinuation of Subjects from Treatment

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
- Pregnancy
- 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 (e.g., infectious disease) illness
- Inability to comply with protocol requirements
- Progressive disease (PD) (see also [Section 4.3.4](#) for details regarding continuing treatment beyond initial assessment of PD per RECIST)
- Complete Response (CR) (see [Section 3.1.2.4](#) for potential for re-challenge)
- Completion of the maximum number of twelve 8-week cycles (see [Section 3.1.2.4](#) for potential for re-challenge)
- Clinical deterioration as assessed by the investigator
- Adverse event meeting discontinuation criteria ([Section 4.3.5](#))

All subjects who discontinue investigational product should comply with protocol-specified follow-up procedures as outlined in [Section 5](#). 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 (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study treatment 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 case report form (CRF) page.

3.6 Post Treatment Study Follow up

In this study, overall survival is an exploratory endpoint of the study. Post-treatment study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study treatment must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with [Section 5](#) until death or the conclusion of the study.

3.6.1 Withdrawal of Consent

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

4 TREATMENTS

All protocol-specified investigational and non-investigational products are considered study drug.

4.1 Study Treatments

Product description and storage information is described in [Table 4.1-1](#). Preparation and administration instructions will be provided separately via site training materials.

For study drugs not provided by BMS and obtained commercially by the site, storage should be in accordance with the package insert, summary of product characteristics (SmPC), or similar documentation.

Table 4.1-1: Product Description and Dosage Form

Product Description and Dosage Form	Potency	Primary Packaging (Volume)/ Label Type	Secondary Packaging (Qty) /Label Type	Appearance	Storage Conditions (per label)
BMS-986016-01 ^a Injection, 110 mg/vial (11 mg/mL) BMS-986016-01 ^a Injection, 100 mg/vial (10 mg/mL)	11 mg/mL OR 10mg/mL	10 mL vial/open label	4 vials/carton/open label	A clear to slightly opalescent, colorless to pale yellow liquid. May contain particles	Store refrigerated, 2-8 °C (36-46 °F) Protect from light Protect from freezing
BMS-936558-01 ^b Nivolumab Injection, 100 mg/vial (10 mg/mL)	10 mg/mL	10 mL vial/open label	4 or 10 vials/carton/open label	Clear to opalescent, colorless to pale yellow liquid. May contain particles	Store refrigerated, 2-8 °C (36-46 °F) Protect from light Protect from freezing

^a Designated as BMS-986016 in the protocol

^b Nivolumab; designated as BMS-936558 in the protocol

4.1.1 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.

In this protocol, investigational products are: BMS-986016 and nivolumab (BMS-936558).

4.1.2 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.

In this protocol, non-investigational product(s) is/are: Not applicable for this study.

4.1.3 Handling 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.

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

For non-investigational product, if marketed product is utilized, it should be stored in accordance with the package insert, summary of product characteristics (SmPC), or similar.

For treatment visits in Part B and C where both BMS-986016 and nivolumab are administered, nivolumab will be administered first followed by BMS-986016 within 15 to 30 minutes after completion of the nivolumab infusion. The nivolumab infusion will be administered over approximately 30 minutes in all Part C cohorts. Further details regarding preparation and administration will be provided separately in site/pharmacy training materials.

4.2 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. The investigative site will call into the enrollment option of the IVRS 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 [REDACTED], e.g., [REDACTED]..... The patient identification number (PID) will ultimately comprise the site number and subject number. For example, if the first subject is enrolled at site [REDACTED], they will have a PID of [REDACTED]. Specific instructions for using IVRS will be provided to the investigational sites in a separate document.

Once it is determined that the subject meets the eligibility criteria, the investigative site will call the IVRS within 3 days prior to first study drug administration for the subject to be either:

- Assigned to a part (Parts A and B) and dose cohort in the dose escalation portion of the study
- Assigned to an expansion cohort in the cohort expansion portion (Part A1 and C) of the study

During dose escalation, all subjects will be assigned to Part A until the decision is made to escalate to the third dose cohort. Subsequently, treatment in Part B will be initiated and escalation in the 2 parts will occur in parallel. Treatment assignments for subjects eligible for both Part A and Part B will alternate between the 2 parts, with consecutively treated subjects assigned to different parts through IVRS whenever possible. If there are no openings available in the part to which the subject would be assigned by this algorithm, then the subject will be assigned to the next open part/cohort.

During dose escalation (Parts A and B), subjects who are not evaluable for DLT determination may be replaced. Replacement subjects will be assigned to the same part (Part A or Part B) and dose, but will be assigned a new subject number.

Treatment assignments for subjects eligible for both Part A1 and Part C will alternate between the 2 parts, with consecutively treated subjects assigned to different parts through IVRS whenever possible. If there are no openings available in the part to which the subject would be assigned by this algorithm, then the subject will be assigned to the next open part/cohort.

4.3 Selection and Timing of Dose for Each Subject

4.3.1 Guidelines for Dose Modification

4.3.1.1 Intrasubject Dose Escalation

Intrasubject dose escalation of BMS-986016 or nivolumab (BMS-936558) is not permitted in this study.

4.3.1.2 Dose Reductions

With the possible exception of subjects being treated at a dose level that is subsequently deemed to exceed the MTD, intrasubject dose reduction of BMS-986016 or nivolumab (BMS-936558) is not permitted.

4.3.2 Dose Delay Criteria

In some cases, the natural history of select AEs associated with immunotherapy can differ from and be more severe than AEs caused by other therapeutic classes. Early recognition and management may mitigate severe toxicity.

Guidance for Investigators is provided in the current BMS-986016 and BMS-936558 (nivolumab) Investigator's Brochures.^{11,31} Additionally, management algorithms have been developed to assist Investigators with select toxicities and can be found in the current BMS-936558 (nivolumab) Investigator's Brochure; toxicities for which management algorithms have been developed include:

- Pulmonary
- Gastrointestinal
- Hepatic
- Endocrine
- Renal
- Dermatologic
- Neurologic (see [Table 5.1-2](#) "Neurological Exam" for criteria for protocol-required neurologic exams)

Subjects who experience the following must have all study drug(s) held:

- Potential DLTs (per definition, are related to study drug) until DLT relatedness is defined.
- Select drug-related AEs and drug-related laboratory abnormalities:
 - \geq Grade 1 pneumonitis
 - \geq Single grade increase shift from baseline (at least to grade 2) of AST, ALT, and/or total bilirubin
 - \geq Grade 2 creatinine
 - \geq Grade 2 diarrhea or colitis
 - \geq Grade 2 neurological AE
 - Grade 4 amylase and/or lipase abnormalities regardless of symptoms or clinical manifestations
- AE, laboratory abnormality, or concurrent illness that, in the judgment of the Investigator, warrants delaying the dose of study drug.

Subjects may be dosed no less than 12 days from the previous dose during Q2W cycles and no more than 3 days from scheduled dose. If an infusion cannot be administered at a scheduled visit, it should be administered as soon as possible. Subsequent dosing visits will follow every 2 weeks after the delayed dose. A dose given more than 3 days after the intended dose date will be considered a delay. A maximum delay of 6 weeks between doses is allowed. Longer delays may be allowed following discussion with the Medical Monitor. Subjects who meet criteria listed in [Section 4.3.5](#) are required to permanently discontinue all study drug(s). All other subjects will be permitted to resume therapy with study drug(s) at the same dose level(s) following resolution of the AE as described in Section 4.3.3.

4.3.3 Criteria to Resume Treatment After Dose Delay

Subjects will be permitted to resume therapy at the same dose level(s) following resolution of the AE to \leq Grade 1 or to baseline within 6 weeks after last dose, with the exception of subjects who

meet criteria for permanent discontinuation as specified in [Section 4.3.5](#). Subjects who meet criteria for permanent discontinuation should receive no further study therapy. The following exceptions apply:

- If the toxicity resolves to \leq Grade 1 or baseline $>$ 6 weeks after last dose, but the subject does not otherwise meet the criteria for permanent discontinuation (see Section 4.3.5), and the Investigator believes that the subject is deriving clinical benefit, then the subject may be eligible to resume the study drug(s) following the approval of the BMS Medical Monitor.
- 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.
- Subjects with baseline Grade 1 AST, ALT, or total bilirubin who require dose delays for reasons other than a drug-related hepatic event may resume treatment in the presence of Grade 2 AST, ALT, or total bilirubin.
- Subjects who require dose delays for drug-related elevations in AST, ALT, or total bilirubin may resume treatment when these values have returned to their baseline CTCAE Grade or normal, provided the criteria for permanent discontinuation are not met.
- Subjects may resume treatment in the presence of Grade 2 fatigue.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment.

4.3.4 Treatment beyond Disease Progression

Accumulating evidence indicates that a subset of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of PD. Per RECIST v1.1, PD is defined as $\geq 20\%$ increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. In addition to the relative increase of 20%, the sum must also demonstrate an **absolute increase of at least 5 mm**. NOTE: Either the appearance of ≥ 1 new lesions or the unequivocal progression of existing non-target lesions is also considered progression. Subjects with initial RECIST v1.1-defined PD may be permitted to continue study therapy provided the following criteria are met:

- Subject is deriving clinical benefit as assessed by the Investigator
- Disease progression is not rapid as assessed by the Investigator
- Subject continues to meet relevant eligibility criteria as determined by the BMS Medical Monitor in discussion with the Investigator
- Subject tolerates study drug
- Subject has stable performance status

- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (e.g., CNS metastases)
- Subjects have provided written informed consent prior to receiving additional study drug

A follow-up scan should be performed at the next scheduled imaging evaluation 8 weeks later (but no sooner than 4 weeks) to determine whether there has been a decrease in the tumor size or continued PD. The assessment of clinical benefit should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment. If the Investigator feels that the subject continues to achieve clinical benefit by continuing treatment, the subject should remain on the study and continue to receive monitoring according to the Time and Events Schedule (Table 5.1-2). The decision to continue treatment should be discussed with the BMS Medical Monitor and documented in the study records.

For subjects who continue study therapy beyond initial RECIST v1.1-defined PD, further progression is defined as an additional 10% increase in tumor burden volume from time of initial PD assessment. This includes an increase in all target lesions and/or the development of new measurable lesions. Study therapy should be discontinued in any subject for whom these criteria are met and documented.

New lesions are considered measureable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). Any new lesion considered non-measureable at the time of initial progression may become measureable and therefore included in the tumor burden volume if the longest diameter increases to at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm).

4.3.5 Guidelines for Permanent Discontinuation

Subjects meeting any of the following criteria will be required to permanently discontinue all study drug(s) (BMS-986016 in Part A and Part A1; BMS-986016 and nivolumab [BMS-936558] in Parts B and C:

- Any Grade 2 drug-related uveitis, eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days or recurs, with the following exceptions for laboratory abnormalities, drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, infusion reactions, and endocrinopathies:
- Grade 3 drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
- Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation

- Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
- Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
- AST, ALT, or bilirubin abnormalities that meet DLT criteria ([section 3.1.3](#)) (In most cases of AST or ALT elevation meeting DLT criteria study drugs will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drugs, a discussion between the investigator and the BMS Medical Monitor/designee must occur).
- Elevated troponin that meets DLT criteria (section 3.1.3)
- Any Grade 4 drug-related adverse event or laboratory abnormality (including but not limited to creatinine, AST, ALT, or Total Bilirubin), except for the following events which do not require discontinuation:
 - Grade 4 neutropenia ≤ 7 days
 - Grade 4 lymphopenia or leukopenia
 - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis
 - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
 - Grade 4 drug-related endocrinopathy adverse events, such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS Medical Monitor.
- Any event that leads to delay in dosing lasting > 6 weeks from the previous dose requires discontinuation, with the following exceptions:
 - Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing delay lasting > 6 weeks from the previous dose, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.
 - Dosing delays lasting > 6 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS medical monitor. Prior to re-initiating treatment in a subject with a dosing delay lasting > 6 weeks, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is

delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.

- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing.

The consideration to re-initiate study therapy in selected cases at any time point after discontinuation could be made on a case-by-case basis after considering the overall benefit/risk profile and in consultation between the Investigator and the study Sponsor. The selected subjects will need to meet eligibility criteria. The original dose and schedule and protocol rules would apply accordingly ([Section 3.1.2.4](#)).

4.4 Blinding/Unblinding

Not applicable.

4.5 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-986016 and nivolumab (BMS-936558) administration in subjects' medical records and CRF.

4.6 Destruction and Return of Study Drug

4.6.1 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 may 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 (e.g., 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 (SOPs) 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, i.e., incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

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.

4.6.2 *Return of Study Drug*

If 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 a BMS designated site for destruction. The return of study drug will be arranged by the responsible BMS Study Monitor.

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.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Study assessments and procedures are presented in [Table 5.1-1](#), [Table 5.1-2](#), and [Table 5.1-3](#).

Table 5.1-1: Screening Procedural Outline (CA224020)

Procedure	Screening Visit (Day -28 to -1)	Day -14 to -1 Visit	Day -3 to -1 Visit	Notes
Eligibility Assessments				
Informed consent	X See Notes			A subject is considered enrolled only when an IRB/IEC-approved informed consent is signed and dated. Obtain subject number from IVRS.
Inclusion/exclusion criteria	X			
Medical history	X			May include more detailed medical history of risk factors for potential events such as pulmonary-related events. Include any toxicities or allergy related to previous treatments. Include any prior PDL1 results available.
Archived tumor tissue sample	X See Notes and Table 5.7-3			For all subjects: Study personnel should check that paraffin tissue block or FFPE unstained slides physically exists. If archived tumor tissue is unavailable, subject may still be eligible for treatment. See Laboratory Manual for delivery and processing indications. Slides/tissue block to be sent to central lab after performing specified tests locally (see “Laboratory tests” in this table below).
Fresh pre-treatment tumor biopsy	X See Notes and Table 5.7-3			For all subjects: Biopsy is MANDATORY. See Laboratory Manual for delivery and processing indications. Tumor tissue to be sent to central lab after performing specified tests locally (see “Laboratory tests” in this table below).
Safety Assessments				
Physical examination (PE)	X			If the screening PE is performed within 1 day of dosing on Cycle 1 Day 1, then a single exam may count as both the screening and pre-dose evaluation.
Performance status	X			ECOG Performance Status/ KPS for RCC subjects ONLY (Appendix 3)
Physical measurements	X			Includes height, weight.

Table 5.1-1: Screening Procedural Outline (CA224020)

Procedure	Screening Visit (Day -28 to -1)	Day -14 to -1 Visit	Day -3 to -1 Visit	Notes
Vital signs	X See Notes			Includes body temperature, seated blood pressure, and heart rate. Blood pressure and heart rate should be measured after the subject has been seated quietly for at least 5 minutes.
Oxygen saturation	X See Notes			Collected at rest and after mild exertion via pulse oximetry to establish baseline. If subject has oxygen saturation \leq 90%, consult BMS Medical Monitor prior to enrollment.
Electrocardiogram (ECG)	X			12-lead ECG

Table 5.1-1: Screening Procedural Outline (CA224020)

Procedure	Screening Visit (Day -28 to -1)	Day -14 to -1 Visit	Day -3 to -1 Visit	Notes
Chest radiograph	X			Posterior-anterior (PA) and lateral chest x-ray to establish baseline
Echocardiogram	X See Note			LVEF assessment with documented LVEF \geq 50% by either TTE or MUGA (TTE preferred test) within 6 months from first study drug administration
Laboratory tests	X See Notes			<p><u>Blood and Urine Tests:</u> To include hematology, serum chemistry, endocrine panel, serology, urinalysis, and CARDIAC TROPONIN LEVELS. See Section 5.3.1 for panel requirements. (Subjects with controlled hyperthyroidism must be negative for thyroglobulin and thyroid peroxidase antibodies and thyroid-stimulating immunoglobulin.) (Subjects with type 2 diabetes must have HbA1c to establish baseline.)</p> <p>If tests are performed within 3 days of dosing on C1D1, then C1D1 laboratories are not required.</p> <p><u>Tests on Tumor Tissue (see Section 5.3.1):</u></p> <ul style="list-style-type: none"> <u>For all Subjects:</u> Subjects with applicable tumor types must provide results of previous gene mutation testing. For colorectal cancer, EGFR, K-RAS and MSI mutation status, for gastric cancer, presence of Epstein-Barr virus (EBV) and HER-2, for melanoma BRAF mutation status, and NSCLC ALK, K-RAS and EGRF mutation status; otherwise, these tests will be performed locally. Test(s) will be requested at baseline but subjects can proceed to treatment prior to receipt of results. <u>Subjects in Part C with head and neck tumors:</u> Subjects must be tested for HPV status by p16 immunohistochemistry and/or HPV ISH. If testing has not been previously performed, testing must be performed locally to confirm HPV status. Not required for subjects in cohorts for cross-over and re-challenge

Table 5.1-1: Screening Procedural Outline (CA224020)

Procedure	Screening Visit (Day -28 to -1)	Day -14 to -1 Visit	Day -3 to -1 Visit	Notes
Pregnancy test (WOCBP)			X See Notes	Pregnancy test should be performed in all WOCBP prior to first study drug administration. Serum or urine pregnancy test (minimum sensitivity of urine pregnancy test of 25 IU/L of either total hCG or the beta fraction). If performed within 24 hours of dosing on C1D1, then C1D1 pregnancy test is not required.
Follicle-stimulating hormone (FSH)	X See Notes			If needed to document post-menopausal status as defined in Section 3.3.3 Not required at cross-over or re-challenge
Concomitant medications		X		Collected during the 2-week period prior to Cycle 1 Day 1
Assessment of signs and symptoms		X		Collected during the 2-week period prior to Cycle 1 Day 1
Adverse Event Reporting				
Monitor for serious adverse events	X			All SAEs must be collected from the date of subject's written consent
Efficacy Assessments				
Diagnostic Imaging	X See Notes			CT with contrast is the preferred modality (CT chest without contrast or MRI if CT is not feasible or appropriate given location of the disease). Assessment should include the chest/abdomen/pelvis at a minimum, and should include other anatomic regions as indicated based on the subject's tumor type and/or disease history. Imaging scans must be de-identified and archived in their native DICOM format as part of the subject study file.

Table 5.1-1: Screening Procedural Outline (CA224020)

Procedure	Screening Visit (Day -28 to -1)	Day -14 to -1 Visit	Day -3 to -1 Visit	Notes
Brain imaging	X See Notes			<u>Applicable Subjects:</u> Brain imaging (MRI) for subjects with history or symptoms of brain metastases who have not had brain imaging, within 30 days of anticipated first study drug administration. MRI of the brain should have been be done for all subjects treated on study as first line NSCLC or 1st line melanoma as part of their initial evaluation of advanced disease, and if not, it should be done during screening.
Bone Scan	X See Notes			As clinically indicated (i.e., subjects with history or symptoms of bone metastases), but bone scans will not be considered a modality for assessment for measurable disease.

Table 5.1-2: On-Treatment Procedural Outline

Procedure	Cycles 1-12					Notes
	Day 1 (± 2 days)	Day 15 (± 2 days)	Day 29 (± 2 days)	Day 43 (± 2 days)	Day 50 -56 ^a	
IVRS Assignment						
IVRS assignment	X See Notes					Cycle 1 only Once subject eligibility has been confirmed, IVRS assignment can be performed within 3 days prior to first study drug administration. (Discuss with Sponsor if institutional policies and procedures require additional lead-time.)
Safety Assessments	All assessments are to be performed / results are to be reviewed <u>PRIOR</u> to study drug dosing unless otherwise specified.					
Physical examination (PE)	X See Notes	X See Notes	X See Notes	X See Notes		On Day 1 of each cycle perform a complete PE. On subsequent treatment visits in each cycle perform a symptom-directed PE.
Neurological exam (NE)	See Notes					<u>Subjects in Parts B and C:</u> Obtain neurological exam (performed by a neurologist) in subjects who experience a study drug related ≥ Grade 2 neurological AE.
Performance status	X	X	X	X		ECOG score /KPS for RCC subjects ONLY (Appendix 3).
Weight	X	X	X	X		
Vital signs	X See Notes	X See Notes	X See Notes	X See Notes		Includes temperature, seated blood pressure, and heart rate. Blood pressure and heart rate should be measured after the subject has been seated quietly for at least 5 minutes. On Cycle 1 Day 1, vital signs will be obtained before the infusion and then every 15 minutes (± 5 minutes) until 60 minutes (120 minutes for subjects in the first dose cohort of Part B) after completion of the infusion. Vital signs on subsequent treatment visits will be collected before the

Table 5.1-2: On-Treatment Procedural Outline

Procedure	Cycles 1-12					Notes
	Day 1 (± 2 days)	Day 15 (± 2 days)	Day 29 (± 2 days)	Day 43 (± 2 days)	Day 50 -56 ^a	
						infusion and then every 30 minutes (± 10 minutes) until 60 minutes following completion of the infusion. If any vital sign is abnormal (based upon clinician assessment) at the final check, the subject must be observed further for a period of time, as clinically indicated.
12-lead electrocardiogram (ECG)	X See Notes	X See Notes	X See Notes	X See Notes		<p><u>Subjects enrolled in Part A and B:</u></p> <ul style="list-style-type: none"> • Cycle 1 Day 1 and Cycle 3 Day 1: 12-lead ECG collected per Holter monitor. Monitoring to begin prior to dosing and to continue through the collection of the 4 hour post-dose BMS-986016 PK sample. • 12-lead ECG to be performed pre-dose on Day 1 for ALL cycles using site's own ECG machine; results to be assessed prior to dosing. For Cycle 1 only, 12-lead ECG is also to be performed pre-dose on Day 15, Day 29 and Day 43. <p><u>Subjects enrolled in Part A1 and C:</u></p> <ul style="list-style-type: none"> • 12-lead ECG to be performed pre-dose on Day 1 of all cycles using site's own ECG machine; results to be assessed prior to dosing. For Cycle 1 only, 12-lead ECG is also to be performed pre-dose on Day 15, Day 29 and Day 43. <p><u>Subjects enrolled in Cohorts for Re-challenge or Cross-Over:</u></p> <ul style="list-style-type: none"> • 12-lead ECG to be performed pre-dose on Day 1 of all cycles using site's own ECG machine; results to be assessed prior to dosing
Chest radiograph						As clinically indicated

Table 5.1-2: On-Treatment Procedural Outline

Procedure	Cycles 1-12					Notes
	Day 1 (± 2 days)	Day 15 (± 2 days)	Day 29 (± 2 days)	Day 43 (± 2 days)	Day 50 -56 ^a	
Oxygen saturation	X See Notes	X See Notes	X See Notes	X See Notes		Collected at rest and after mild to moderate exertion via pulse oximetry. Oxygen levels will be used in combination with clinical signs and symptoms and radiographic images to evaluate pulmonary/respiratory status. Changes in O2 levels will not be used in isolation to document or diagnose pulmonary toxicity.
Laboratory tests	X See Notes	X See Notes	X See Notes	X See Notes		Labs are performed locally and may be collected within 3 days prior to dosing. To include serum chemistry, hematology, and urinalysis; see Section 5.3.1 for panel requirements. Serology tumor markers are to be performed on Day 1 of each cycle
Endocrine panel	X See Notes					Labs are performed locally and may be collected within 3 days prior to dosing. See Section 5.3.1 for panel requirements. Results must be reviewed by the Investigator or appropriate designee within 2 days following dose administration
Cardiac Troponin	See Notes C2 Day 1 ONLY	X See Notes	X See Notes	X See Notes		Labs are performed locally only for Cycle 1 Day 15, 29 and 43 and Cycle 2 Day 1 and may be collected within 3 days prior to dosing. Results must be reviewed by the Investigator or appropriate designee prior to dose administration. See Section 5.3.1 for requirements.
Pregnancy test (WOCBP)	X See Notes		X See Notes			A pregnancy test must be performed within 24 hours prior to administration of study drug. Serum or urine pregnancy test may be performed (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG) If results are positive hold all study drug and perform confirmatory testing. If pregnancy is confirmed, permanently

Table 5.1-2: On-Treatment Procedural Outline

Procedure	Cycles 1-12					Notes
	Day 1 (± 2 days)	Day 15 (± 2 days)	Day 29 (± 2 days)	Day 43 (± 2 days)	Day 50 -56 ^a	
						discontinue all study drug and immediately notify Sponsor per Section 6.4 .
Assess adequate contraceptive use	X See Notes		X See Notes			For WOCBP and male subjects able to reproduce and sexually active with WOCBP: Assess for continued use of acceptable methods of contraception; see Appendix 1
Adverse Event and ConMed Assessment						
Monitor for non-serious adverse events	X	X	X	X		
Monitor for serious adverse events	X	X	X	X		
ConMed assessment	X	X	X	X		
Sample Collection						
Pharmacokinetic (PK) assessments	See Section 5.5 and Table 5.5.1-1 and Table 5.5.1-2 Table 5.5.1-3 and Table 5.5.1-4 for Q4W dosing only.					Performed in all subjects
Immunogenicity assessments	See Table 5.5.1-1 and Table 5.5.1-2 .					Performed in all subjects

Table 5.1-2: On-Treatment Procedural Outline

Procedure	Cycles 1-12					Notes
	Day 1 (± 2 days)	Day 15 (± 2 days)	Day 29 (± 2 days)	Day 43 (± 2 days)	Day 50 -56 ^a	
Biomarker assessments	See Section 5.7 and Table 5.7-1 and Table 5.7-2 . See Notes					<p>Subjects in Part A and B: Performed in all subjects enrolled at each dose level. See Laboratory Manual for delivery and processing indications.</p> <p>Subjects in Part C: Biomarker collections are required in 48 subjects at US IION sites. Additional biomarker collections may be performed in additional subjects from any expansion cohort in Part C. See Laboratory Manual for delivery and processing indications.</p> <p>Subjects in Part A1: Mandatory in all subjects of each cohort for US IION sites. See Laboratory Manual for delivery and processing indications.</p>
On-treatment tumor biopsy			X See Notes			<p>Perform a one-time on-treatment biopsy during Cycle 1. Biopsy can be obtained anytime at pre-dose Day 23-31 and may be coordinated with protocol specified Day 29 visit.</p> <p>On treatment biopsies are required in 48 subjects at US IION sites. Additional on treatment biopsies may be performed in additional subjects from any expansion cohort in Part C. See Laboratory Manual for delivery and processing indications.</p>
OPTIONAL Post-progression (PD) tumor biopsy	See Notes See Table 5.7-3					OPTIONAL tumor biopsy for any subject; obtained upon confirmation of PD. See Laboratory Manual for delivery and processing indications (the latter may be local or centralized). Tumor tissue to be sent to central lab after performing specified tests locally (see “Laboratory tests” in this table below).
Efficacy Assessments						
Diagnostic imaging					X See Notes	<p>By methods used at baseline.</p> <p>Imaging scans must be de-identified and archived in their native DICOM format as part of the subject study file</p>

Table 5.1-2: On-Treatment Procedural Outline

Procedure	Cycles 1-12					Notes
	Day 1 (± 2 days)	Day 15 (± 2 days)	Day 29 (± 2 days)	Day 43 (± 2 days)	Day 50 -56 ^a	
Brain imaging					X See Notes	As clinically indicated
Bone scan					X See Notes	As clinically indicated
Serologic tumor markers	X See Notes					Labs performed locally for subjects with colorectal, gastric, germ cell, HCC, ovarian, or prostate cancer. See Section 5.3.1 .
Response assessment					X See Notes	Assessed by RECIST v1.1; see Appendix 2 . Assessment must be performed prior to initiating the next cycle of treatment.
Study Drug Administration	Details regarding preparation and administration are provided in site training materials.					
Parts A, A1, B and C: BMS-986016 administration	X	X	X	X		Use vials assigned per IVRS: approximately 60 minute infusion
Parts B and C: Nivolumab (BMS-936558) administration	X See Notes	X See Notes	X See Notes	X See Notes		Use vials assigned per IVRS. Nivolumab is administered ONLY for those subjects enrolled in Part B and Part C. Combination therapy with nivolumab and BMS-986016 will be administered as sequential infusions (Parts B and C). In Part C, nivolumab infusion will be administered over approximately 30 minutes.
Part B: Q4 week: Nivolumab BMS-936558 and BMS-986016 administration	X See Notes		X See Notes			Combination therapy with nivolumab and BMS-986016 will be administered as sequential infusions. The nivolumab infusion will be administered over approximately 30 minutes and BMS-986016 over approximately 60 minutes.

^a This visit is not a clinic visit. The purpose of this visit is for diagnostic imaging and subsequent evaluation of results by the Investigator (response assessment). Diagnostic imaging should occur during Day 50-56 and response assessment must be completed prior to initiating the next cycle of treatment.

Table 5.1-3: Follow-Up Procedural Outline (CA224020)

Procedure	Clinical Follow-Up			Survival Follow-Up	Notes
	FU 1 30 days ^a (± 5 days)	FU 2 60 days ^a (± 5 days)	FU 3 135 days ^a (+ 5 days)	Begins After Completion of Clinical Follow-Up Every 12 weeks (± 2 wks) until 2 yrs after FIRST dose of study drug	
Safety Assessments					
Physical examination (PE)	X	X	X		
Performance status	X	X	X		ECOG score/KPS for RCC subjects ONLY (Appendix 3)
Weight	X	X	X		
Vital signs	X See Notes	X See Notes	X See Notes		Includes body temperature, seated blood pressure, and heart rate. Blood pressure and heart rate should be measured after the subject has been seated quietly for at least 5 minutes.
12-lead electrocardiogram (ECG)	X See Notes				<u>Subjects enrolled in Part A, and B:</u> <ul style="list-style-type: none">12-lead ECG collected per Holter monitor, as well as an additional 12- lead ECG using site’s own ECG machine <u>Subjects enrolled in Parts C:</u> <ul style="list-style-type: none">12-lead ECG using site’s own ECG machine

Table 5.1-3: Follow-Up Procedural Outline (CA224020)

Procedure	Clinical Follow-Up			Survival Follow-Up	Notes
	FU 1 30 days ^a (± 5 days)	FU 2 60 days ^a (± 5 days)	FU 3 135 days ^a (+ 5 days)	Begins After Completion of Clinical Follow-Up Every 12 weeks (± 2 wks) until 2 yrs after FIRST dose of study drug	
Oxygen saturation	X See Notes	X See Notes	X See Notes		Collected at rest and after mild to moderate exertion via pulse oximetry. Oxygen levels will be used in combination with clinical signs and symptoms and radiographic images to evaluate pulmonary/respiratory status. Changes in O2 levels will not be used in isolation to document or diagnose pulmonary toxicity.
Laboratory tests	X See Notes		X See Notes		To include serum chemistry, hematology, endocrine panel and urinalysis; see Section 5.3.1 for panel requirements.
Pregnancy test (WOCBP)	X See Notes	X See Notes	X See Notes		Serum or urine pregnancy test may be performed (clinic urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG). Home pregnancy testing required on FU Days 90, 120, 150, and 165. If positive, perform confirmatory testing. If pregnancy is confirmed, immediately notify Sponsor per Section 6.4 .

Table 5.1-3: Follow-Up Procedural Outline (CA224020)

Procedure	Clinical Follow-Up			Survival Follow-Up	Notes
	FU 1 30 days ^a (± 5 days)	FU 2 60 days ^a (± 5 days)	FU 3 135 days ^a (+ 5 days)	Begins After Completion of Clinical Follow-Up Every 12 weeks (± 2 wks) until 2 yrs after FIRST dose of study drug	
Assess adequate contraceptive use	X See Notes	X See Notes	X See Notes		For WOCBP and male subjects able to reproduce and sexually active with WOCBP: Assess for continued use of acceptable methods of contraception; see Appendix 1
Adverse Event and ConMed Assessment					
Monitor for non-serious adverse events	X See Notes	X See Notes	X See Notes		Non-serious AEs will be collected starting with the first dose of study medication and through 135 days after discontinuation of dosing.
Monitor for serious adverse events	X See Notes	X See Notes	X See Notes		All SAEs must be collected starting at the time a subject signs informed consent and through 135 days after discontinuation of dosing.
ConMed assessment	X	X	X		
Sample Collection					
Pharmacokinetic (PK) assessments	X See Notes	X See Notes	X See Notes		See Table 5.5.1-1 and Table 5.5.1-2 See Table 5.5.1-3 and Table 5.5.1-4 for Q4W
Immunogenicity (ADA) assessments	X See Notes	X See Notes	X See Notes		See Table 5.5.1-1 and Table 5.5.1-2 See Table 5.5.1-3 and Table 5.5.1-4 for Q4W

Table 5.1-3: Follow-Up Procedural Outline (CA224020)

Procedure	Clinical Follow-Up			Survival Follow-Up	Notes
	FU 1 30 days ^a (± 5 days)	FU 2 60 days ^a (± 5 days)	FU 3 135 days ^a (+ 5 days)	Begins After Completion of Clinical Follow-Up Every 12 weeks (± 2 wks) until 2 yrs after FIRST dose of study drug	
Efficacy Assessments					
Diagnostic imaging	X See Notes		X See Notes		Diagnostic imaging required by method used at baseline; an unconfirmed PR, unconfirmed CR, or unconfirmed PD must be confirmed ≥ 4 weeks after initial assessment. Diagnostic imaging at FU3 must be performed in subjects who discontinue with CR, PR or SD
Serologic tumor markers	X See Notes				Labs performed locally for subjects with colorectal, gastric, germ cell, HCC, ovarian, or prostate cancer. See Section 5.3.1 .
Response assessment	X See Notes				Assessed by RECIST v1.1; see Appendix 2 .
Survival Status					
Assessment of subject survival status				X See Notes	Subject status will be assessed by either a clinic visit or telephone contact. The nature and start dates of any new anti-cancer therapies during this period will be recorded.
Diagnostic imaging				X See Notes	Required for subjects who discontinued study due to CR or PR only

^a After last dose of study drug

5.2 Study Materials

The following materials will be provided at study start:

- NCI CTCAE version 4.0
- BMS-986016 and BMS-936558 Investigator Brochures
- Pharmacy binder
- Laboratory manuals for collection and handling of blood (including PK, immunogenicity, and biomarkers) and tissue specimens
- Holter monitor, associated supplies, and manual
- IVRS manual
- Enrollment worksheets
- Serious Adverse Event forms
- Pregnancy surveillance forms

5.3 Safety Assessments

Adverse events will be assessed continuously during the study and for 135 days after the last treatment. Adverse events will be evaluated according to the NCI CTCAE version 4.0 and should be followed per requirements in [Sections 6.1.1](#) and [6.2.1](#). Adverse events will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA) and reviewed for potential significance and importance.

Protocol-specified assessments are described in [Table 5.1-1](#) (Screening Procedural Outline), [Table 5.1-2](#) (On-Treatment Procedural Outline), and [Table 5.1-3](#) (Follow-Up Procedural Outline).

5.3.1 Laboratory Test Assessments

A local laboratory will perform the analyses and will provide reference ranges for these tests.

Clinical laboratories will be assessed at the timepoints indicated in [Table 5.1-1](#) (Screening Procedural Outline), [Table 5.1-2](#) (On-Treatment Procedural Outline), and [Table 5.1-3](#) (Follow-Up Procedural Outline).

At screening, sites should collect samples during the timeframe indicated in [Table 5.1-1](#) and ensure that results required for eligibility are verified prior to registration. During treatment, unless otherwise indicated in [Table 5.1-2](#), results of clinical laboratory tests must be reviewed prior to dosing.

The following clinical laboratory tests will be performed:

Hematology

Hemoglobin

Hematocrit

Total leukocyte count, including differential

Platelet count

Serum Chemistry

Aspartate aminotransferase (AST)	Lipase
Alanine aminotransferase (ALT)	C-reactive protein (CRP)
Total bilirubin	Albumin
Alkaline phosphatase	Sodium
Lactate dehydrogenase (LDH)	Potassium
Creatinine	Chloride
Creatinine clearance ^a (screening only)	Bicarbonate
Blood urea nitrogen (BUN)	Calcium
Glucose	Magnesium
Amylase	Phosphorus
HbA1c (obtain during screening to establish baseline in subjects with type 2 diabetes, then as clinically indicated)	

^a Cockcroft-Gault formula

Endocrine Panel

Thyroid-stimulating hormone (TSH) with reflex to free T3 and free T4 as applicable
Subjects with controlled hyperthyroidism must be negative for thyroglobulin and thyroid peroxidase antibodies and thyroid stimulating immunoglobulin (screening only)

Urinalysis

Protein
Glucose
Blood
Leukocyte esterase

Microscopic examination of the sediment if blood, protein, or leukocyte esterase are positive on the dipstick

Serology (screening only)

Hepatitis A antibody (HepA IgM)

Hepatitis B surface antigen (HBsAg) and/or hepatitis B core antigen

Hepatitis D antibody (for HCC subjects only)

Test for quantitative hepatitis B viral load (by PCR) (for HCC subjects only)

Test for quantitative hepatitis C viral load (by PCR)

HIV-1, -2 antibody

Cardiac Troponin

T (cTnt) or I (cTnI)

For those subjects receiving on-going treatment with BMS-986016 and nivolumab, troponin elevations will require the subject to undergo a cardiac evaluation. Following this evaluation, determination of further treatment will be based on the discussion with the BMS Medical Monitor or designee.

Reproductive Analyses

Pregnancy test: serum or urine (minimum sensitivity of urine pregnancy test of 25 IU/L of either total human chorionic gonadotropin (hCG) or the beta fraction)

Home pregnancy test kits

Follicle-stimulating hormone (FSH; if needed to document post-menopausal status as defined in [Section 3.3.3](#))

Other Analyses

Various serologic tumor markers, gene mutation status, and additional analyses are required dependent upon the subject's tumor type as listed in [Table 5.3.1-1](#). With the exception of the serologic tumor markers, the assessments do not need to be performed if the lab results from previous testing are available to be submitted to the Sponsor.

Table 5.3.1-1: Biomarkers by Tumor Type - All cohorts except for subjects crossing-over or re-challenged				
Tumor Type	Matrix	Lab Test	Assessment	Timepoint
Colorectal	Blood	Serologic Tumor Marker	CEA ^a	Multiple
	Tumor Tissue	Gene Mutation Status	EGFR ^b K-RAS MSI ^c	Screening
Gastric	Blood	Serologic Tumor Marker	CEA ^a	Multiple
	Tumor Tissue	Gene Amplification Status	HER-2 ^d	Screening
	Tumor Tissue	Real Time qPCR ^e and/or EBER ISH ⁱ (ICH also allowed but not preferred)	EBV ^f	Screening
Germ Cell	Blood	Serologic Tumor Marker	βhCG ^g AFP ^h	Multiple
Head and Neck	Tumor Tissue	p16 IHC and/or HPV ISH ⁱ	HPV ^j	Screening
HCC	Blood	Quantitative PCR	HBV or HCV viral load ⁿ	Multiple
	Blood	Serologic Tumor Marker	AFP ^h	Multiple
Melanoma	Tumor Tissue	Gene Mutation Status	BRAF	Screening
NSCLC	Tumor Tissue	Gene Mutation Status	ALK ^k K-RAS EGFR ^b	Screening
Ovarian	Blood	Serologic Tumor Marker	CA125 ^l	Multiple
Prostate	Blood	Serologic Tumor Marker	PSA ^m	Multiple

^a CEA: carcinoembryonic antigen

^b EGFR: epidermal growth factor receptor

^c MSI: microsatellite instability

^d HER-2: human epidermal growth factor receptor 2 amplification status via IHC and/or ISH

^e Real time qPCR: real time quantitative polymerase chain reaction for BamH1-A Reading Frame-1(BARF1) gene

^f EBV: Epstein-Barr virus

^g βhCG: beta-human chorionic gonadotrophin

^h AFP: alpha-fetoprotein

ⁱ ISH: In Situ Hybridization

^j HPV: human papilloma virus

^k ALK: anaplastic lymphoma kinase

^l CA125: cancer antigen 125

^m PSA: prostate specific antigen

ⁿ HBV /HCV: Hepatitis C virus or hepatitis B virus load, depending on the underlying infection, if any

Additional measures including non–study-required laboratory tests should be performed as clinically indicated.

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 (e.g., provided electronically). If the units of a test result differ from those printed on the CRF, the recorded laboratory values must specify the correct units. Any abnormal laboratory test result considered clinically significant by the investigator must be recorded on the appropriate AE page of the CRF (see [Section 6.3](#)).

5.4 Efficacy Assessments

5.4.1 Imaging Assessment for the Study

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

Contrast-enhanced Computed Tomography (CT) scans acquired on dedicated CT equipment is preferred for this study. CT with contrast of the chest, abdomen and pelvis are to be performed for tumor assessments. CT scans should be acquired with 5mm slices with no intervening gap (contiguous). Should a subject have a contraindication for CT IV contrast, a non-contrast CT of the chest and a contrast enhanced MRI of the abdomen and pelvis may be obtained. MRI's should be acquired with slice thickness of 5 mm with no gap (contiguous). Every attempt should be made to image each subject using an identical acquisition protocol on the same scanner for all imaging time points.

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

Bone scans can be used to evaluate metastatic disease, if applicable.

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 Investigator as per standard medical/clinical judgment.

5.4.2 Efficacy Assessment for the Study

Efficacy will be evaluated in Parts A and B (dose escalation) as well as in Part A1 and C (cohort expansion). Changes in tumor measurements and tumor response at the time of each assessment will be determined by the Investigator based on RECIST v1.1 (see [Appendix 2](#)).⁴⁷ In addition, the longest diameter of any new measureable lesions will be captured at each timepoint.

The baseline assessment during the screening period requires CT chest, CT or MRI scans of the abdomen, and pelvis, and other anatomic regions as indicated by individual subject's tumor type and/or disease history. Subsequent timepoints require scans of the chest, abdomen, and pelvis, as well as other anatomic regions that were scanned at baseline based on the individual subject's tumor type and/or disease history. Scans of the brain are otherwise required as clinically indicated.

Individual subject's best overall response (BOR) will be determined as appropriate.

Tumor status will be assessed at baseline, during treatment (every 8 weeks) for up to twelve 8-week cycles of therapy. Tumor assessments will continue every 12 weeks until progression in: 1) subjects who discontinue due to CR, and 2) in subjects with PR at the end of Cycle 12. CT and MRI scans will be read and assessed locally per RECIST v1.1. All imaging scans must be de-identified and archived in their native Digital Imaging and Communications in Medicine (DICOM) format as part of the subject's study file. At the Sponsor's discretion, scans may be collected centrally to be reviewed by independent radiologists.

Efficacy assessment of subjects who have been re-challenged after achieving a response or stable disease will be conducted in a separate analysis. However, the best overall response in the first treatment may be considered in the study analysis. Subjects who cross-over from BMS-986016 monotherapy (Part A1) to combination therapy are not to be included in the analysis of any expansion cohorts with combination therapy.

5.4.3 Primary Efficacy Assessment

The best overall response (BOR) based on blinded independent central review assessment using RECIST v1.1 will be the primary assessment, where applicable, in selected cohorts in Part C..

5.4.4 Secondary Efficacy Assessments

The best overall response (BOR) will be assessed by investigator using RECIST v1.1.

5.4.5 Exploratory Efficacy Assessments

Overall survival (OS) will be assessed.

5.5 Pharmacokinetic Assessments

Serum samples for BMS-986016 and nivolumab PK and anti-drug antibody (ADA) assessments will be collected for all subjects.

5.5.1 Pharmacokinetics: Collection and Processing

A detailed schedule of PK and ADA evaluations is provided in Table 5.5.1-1 and Table 5.5.1-2 for Q2W dosing, and Table 5.5.1-3 and Table 5.5.1-4 for Q4W dosing. All timepoints are relative to the start of BMS-986016 study drug 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). Further details of sample collection, processing, and shipment will be provided in the laboratory procedures manual. On-treatment PK samples are intended to be drawn relative to actual dosing days, if a dose occurs on a different day within the cycle due to delays or minor schedule adjustments, PK samples should be adjusted accordingly.

Table 5.5.1-1: PK and ADA Sampling Schedule for BMS-986016 and Nivolumab for Dose Escalation Parts A and B Q2W dosing and Expansion Parts A1 and C (Approximately the first 6 subjects in each cohort only)

Study Day of Sample Collection	Event (Relative to BMS-986016)	Time (Relative To Start of BMS-986016 Infusion) Hour: Min	BMS-986016 PK Sample (All Subjects)	Nivolumab PK Sample (All subjects except Part A and A1)	BMS-986016 ADA Sample (All Subjects)	Nivolumab ADA Sample (All subjects except Part A and A1)
Cycle 1						
1	predose ^a	00:00	X	X	X	X
1	EOI ^b	01:00 ^b	X	X		
1		04:00	X			
2		24:00	X			
5 ^c		96:00	X			
8 ^d		168:00	X			
15	predose ^a	00:00	X	X	X	X
29	predose ^a	00:00	X	X	X	X
43	predose ^a	00:00	X	X	X	X
Cycle 2						
1	predose ^a	00:00	X	X	X	X
1	EOI ^b	01:00 ^b	X	X		
15	predose ^a	00:00	X	X		
Cycle 3						

Table 5.5.1-1: PK and ADA Sampling Schedule for BMS-986016 and Nivolumab for Dose Escalation Parts A and B Q2W dosing and Expansion Parts A1 and C (Approximately the first 6 subjects in each cohort only)

Study Day of Sample Collection	Event (Relative to BMS-986016)	Time (Relative To Start of BMS-986016 Infusion) Hour: Min	BMS-986016 PK Sample (All Subjects)	Nivolumab PK Sample (All subjects except Part A and A1)	BMS-986016 ADA Sample (All Subjects)	Nivolumab ADA Sample (All subjects except Part A and A1)
1	predose ^a	00:00	X	X	X	X
1	EOI ^b	01:00 ^b	X	X		
1		04:00	X			
2		24:00	X			
5 ^c		96:00	X			
8 ^d		168:00	X			
15	predose ^a	00:00	X	X		
Alternate Treatment Cycles (Cycles 5, 7, 9 and 11)						
1	predose ^a	00:00	X	X	X	X
End of Treatment and Follow-up Period						
30-Day FU ^e			X	X	X	X
60-Day FU ^e			X	X	X	X
135-Day FU ^e			X	X	X	X
Upon drug-related AE						
Upon occurrence of ≥ Grade 2 drug related pneumonitis or neurological AE			X	X	X	X

^a Predose: All predose samples for nivolumab and BMS-986016 should be taken prior to the start of nivolumab infusion.

^b EOI: End of Infusion. EOI samples for both nivolumab and BMS-986016 should be collected after the end of the BMS-986016 infusion. This sample should be taken immediately prior to stopping the infusion (preferably within 2 minutes prior to the end of infusion). If the end of infusion is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.

^c Day 5 sample may be taken during Days 3-5 of a cycle

- ^d Day 8 sample may be taken during Days 7-9 of a cycle
- ^e FU: Follow-Up

Table 5.5.1-2: PK and ADA Sampling Schedule for BMS-986016 and Nivolumab for Dose Expansion- Parts A1 and C Q2W dosing (after first 6 subjects) and for Cohorts with Cross-Over or Re-challenge

Study Day of Sample Collection	Event (Relative to BMS-986016)	Time (Relative To Start of BMS-986016 Infusion) Hour: Min	BMS-986016 PK Sample (All Subjects)	Nivolumab PK Sample (All subjects except Part A1)	BMS-986016 ADA Sample (All Subjects)	Nivolumab ADA Sample (All subjects except Part A1)
Cycle 1						
1	predose ^a	00:00	X	X	X	X
1	EOI ^b	01:00 ^b	X	X		
15	predose ^a	00:00	X	X	X	X
29	predose ^a	00:00	X	X	X	X
43	predose ^a	00:00	X	X		
Cycle 2						
1	predose ^a	00:00	X	X	X	X
1	EOI ^b	01:00 ^b	X	X		
Cycle 3						
1	predose ^a	00:00	X	X	X	X
1	EOI ^b	01:00 ^b	X	X		
Alternate Treatment Cycles (Cycles 5, 7, 9 and 11)						
1	predose ^a	00:00	X	X	X	X
End of Treatment and Follow-up Period						
30-Day FU ^c			X	X	X	X
60-Day FU ^c			X	X	X	X
135-Day FU ^c			X	X	X	X
Upon drug-related AE						
Upon occurrence of ≥ Grade 2 drug related pneumonitis or neurological AE			X	X	X	X

- ^a Predose: All predose samples for nivolumab and BMS-986016 should be taken prior to the start of nivolumab infusion.
- ^b EOI: End of Infusion. EOI samples for both nivolumab and BMS-986016 should be collected after the end of the BMS-986016 infusion. This sample should be taken immediately prior to stopping the infusion (preferably within 2 minutes prior to the end of infusion). If the end of infusion is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.
- ^c FU: Follow-Up

Table 5.5.1-3: PK and ADA Sampling Schedule for BMS-986016 and Nivolumab for Dose Escalation Parts B and Expansion Parts C (Approximately the first 6 subjects in each cohort only) with every 4 week regimen

Study Day of Sample Collection	Event (Relative to BMS-986016)	Time (Relative To Start of BMS-986016 Infusion) Hour: Min	BMS-986016 PK Sample	Nivolumab PK Sample	BMS-986016 ADA Sample	Nivolumab ADA Sample
Cycle 1						
1	predose ^a	00:00	X	X	X	X
1	EOI ^b	01:00 ^b	X	X		
1		04:00	X			
2		24:00	X			
5 ^c		96:00	X			
8 ^d		168:00	X			
15		336:00	X	X	X	X
29	predose ^a	00:00	X	X	X	X
Cycle 2						
1	predose ^a	00:00	X	X	X	X
1	EOI ^b	01:00 ^b	X	X		
29	predose ^a	00:00	X	X		
Cycle 3						
1	predose ^a	00:00	X	X	X	X
1	EOI ^b	01:00 ^b	X	X		
1		04:00	X			
2		24:00	X			
5 ^c		96:00	X			

Table 5.5.1-3: PK and ADA Sampling Schedule for BMS-986016 and Nivolumab for Dose Escalation Parts B and Expansion Parts C (Approximately the first 6 subjects in each cohort only) with every 4 week regimen

Study Day of Sample Collection	Event (Relative to BMS-986016)	Time (Relative To Start of BMS-986016 Infusion) Hour: Min	BMS-986016 PK Sample	Nivolumab PK Sample	BMS-986016 ADA Sample	Nivolumab ADA Sample
8 ^d		168:00	X			
15		336:00	X			
29	predose ^a	00:00	X	X		
Alternate Treatment Cycles (Cycles 5, 7, 9 and 11)						
1	predose ^a	00:00	X	X	X	X
End of Treatment and Follow-up Period						
30-Day FU ^e			X	X	X	X
60-Day FU ^e			X	X	X	X
135-Day FU ^e			X	X	X	X
Upon drug-related AE						
Upon occurrence of ≥ Grade 2 drug related pneumonitis or neurological AE			X	X	X	X

^a Predose: All predose samples for nivolumab and BMS-986016 should be taken prior to the start of nivolumab infusion.

^b EOI: End of Infusion. EOI samples for both nivolumab and BMS-986016 should be collected after the end of the BMS-986016 infusion. This sample should be taken immediately prior to stopping the infusion (preferably within 2 minutes prior to the end of infusion). If the end of infusion is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.

^c Day 5 sample may be taken during Days 3-5 of a cycle

^d Day 8 sample may be taken during Days 7-9 of a cycle

^e FU: Follow-Up

Table 5.5.1-4: PK and ADA Sampling Schedule for BMS-986016 and Nivolumab for Dose Expansion- Parts C (after first 6 subjects) and for Cohorts with Cross-Over or Re-challenge with every 4 week regimen

Study Day of Sample Collection	Event (Relative to BMS-986016)	Time (Relative To Start of BMS-986016 Infusion) Hour: Min	BMS-986016 PK Sample	Nivolumab PK Sample	BMS-986016 ADA Sample	Nivolumab ADA Sample
Cycle 1						
1	predose ^a	00:00	X	X	X	X
1	EOI ^b	01:00 ^b	X	X		
29	predose ^a	00:00	X	X	X	X
Cycle 2						
1	predose ^a	00:00	X	X	X	X
1	EOI ^b	01:00 ^b	X	X		
Cycle 3						
1	predose ^a	00:00	X	X	X	X
1	EOI ^b	01:00 ^b	X	X		
Alternate Treatment Cycles (Cycles 5, 7, 9 and 11)						
1	predose ^a	00:00	X	X	X	X
End of Treatment and Follow-up Period						
30-Day FU ^c			X	X	X	X
60-Day FU ^c			X	X	X	X
135-Day FU ^c			X	X	X	X
Upon drug-related AE						
Upon occurrence of \geq Grade 2 drug related pneumonitis or neurological AE			X	X	X	X

^a Predose: All predose samples for nivolumab and BMS-986016 should be taken prior to the start of nivolumab infusion.

- ^b EOI: End of Infusion. EOI samples for both nivolumab and BMS-986016 should be collected after the end of the BMS-986016 infusion. This sample should be taken immediately prior to stopping the infusion (preferably within 2 minutes prior to the end of infusion). If the end of infusion is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.
- ^c FU: Follow-Up

5.5.2 Pharmacokinetic Sample Analyses

The serum samples will be analyzed for BMS-986016 and nivolumab by a validated immunoassay. In addition, selected serum samples may be analyzed by an exploratory orthogonal method (e.g., liquid chromatography [LC]-mass spectrometry [MS]/MS) that measures total BMS-986016 and/or nivolumab, but the generated data will not be reported. Only results generated from the validated immunoassay method will be reported. Potential results generated from any orthogonal method are intended as informational for technology exploration purposes and will not be reported.

5.6 Biomarker Assessments

Not applicable.

5.7 Exploratory Biomarker Assessments

The pharmacodynamics of BMS-986016 treatment administered alone or in combination with nivolumab will be assessed in peripheral blood and tumor tissue in all subjects enrolled at each dose level during the dose escalation (Parts A and B) and in select subjects during cohort expansion (Parts A1 and C) phases of the study. Detailed schedules of pharmacodynamic evaluations are provided in [Table 5.7-1](#) and [Table 5.7-2](#). Details regarding the tumor tissues requirements for subjects in all parts of the study are provided in [Table 5.7-3](#). Details regarding the biomarkers to be analyzed are provided in the sections that follow.

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

Table 5.7-1: Part A and B (Dose Escalation): Biomarker Sampling Schedule (For all Subjects in each Dose Level)

Collection Timing	Serum	PBMC ^e		Tumor	Whole Blood	
Study Day	Soluble Biomarkers (Serum Biomarkers)	Immuno-phenotyping / Tetramer (Flow Cytometry/ PBMC)	Ex vivo Functional Assay (Cellular Assay)	Fresh tumor biopsy ^c	Gene Expression (Whole Blood mRNA)	SNP/ WES
Screening				X ^c		
Cycle 1						
Day 1	X	X	X		X	X
Day 5 ^a	X					
Day 8 ^b	X	X				
Day 15 ^f	X	X			X	
Day 29	X	X		X ^c	X	
Day 43 ^f	X	X	X		X	
Cycle 2						
Day 1	X	X	X		X	
Upon Progression						
Upon Progression ^d	X	X	X	X	X	
Upon Drug-related AE						
Upon occurrence of ≥ Grade 2 drug related pneumonitis or neurological AE	X	X	X			

^a Day 5 visit can occur on Day 3 or Day 4.

^b Day 8 visit can occur on Day 7 or Day 9.

^c Archival tissue is optional at baseline, see [Table 5.7-3](#). Fresh tumor biopsy at screening is MANDATORY and on-treatment (pre-dose Days 23-31) biopsy is encouraged to be collected.

^d Optional: to be collected upon confirmation of PD

^e PBMC samples only to be collected for subjects in the US. Collection of PBMCs from Ex-US subjects is optional and encouraged for potential sub studies.

^f For Q4W dosing, Day 15 and Day43 samples are not pre-dose.

Note: All samples are to be drawn pre-dose.

Table 5.7-2: Parts A1 and C (Cohort Expansion) and Cohorts for Crossover or Re-challenge: Biomarker Sampling

Collection Timing	Serum	Plasma	PBMC ^e		Tumor	Whole Blood	
Study Day	Soluble Biomarkers (Serum Biomarkers) ^g	ctDNA ^f	Immuno-phenotyping / Tetramer (Flow Cytometry/ PBMC) ^g	Ex vivo Functional Assay (Cellular Assay) ^g	“Fresh” Tumor Biopsy ^c	Gene Expression (Whole Blood mRNA) ^g	SNP/ WES
Screening					X ^c		
Cycle 1							
Day 1	X	X	X	X		X	X
Day 5 ^a	X						
Day 8 ^b	X		X				
Day 15	X		X			X	
Day 29	X	X	X	X	X ^c	X	
Cycle 2, 3, 5, 7, 9, and 11							
Day 1	X	X	X	X		X	
Upon Progression							
Upon Progression ^d	X	X	X	X	X	X	
Upon Drug-related AE							
Upon occurrence of ≥ Grade 2 drug related pneumonitis or neurological AE	X		X	X			

^a Day 5 visit can occur on Day 3 or Day 4.

^b Day 8 visit can occur on Day 7 or Day 9.

^c Archival tissue is optional at baseline, see [Table 5.7-3](#). Fresh tumor biopsy at screening is MANDATORY for all subjects. On-treatment (pre-dose Days 23-31) biopsy is MANDATORY for 48 subjects treated at US IION sites. For other sites, on-treatment biopsy is encouraged for sub-studies.

^d Optional: to be collected upon confirmation of PD.

^e PBMC samples only to be collected for subjects in the US. Collection of PBMCs from Ex-US subjects is optional and encouraged for potential substudies.

^f At US IION sites for melanoma subjects only. Samples are only required on Cycle 1: Day1, Day29, Cycle 2 Day1 and/or upon progression

^g Peripheral blood collection is mandatory for 48 subjects treated at US IION sites in Part C. At US IION sites, peripheral blood collections are mandatory for subjects in Part A1. Collection of peripheral blood in additional subjects at other sites is encouraged for potential sub-studies.

NOTE: All samples are to be drawn pre-dose

Table 5.7-3: Tumor Tissue Requirements		
Study Part	Part A and B (Dose Escalation)	Part A1, and C (Cohort Expansion)
Subjects	ALL subjects in Part A and B	ALL subjects in Part A1 and C
Type of Specimen Baseline	Archival tissue is optional at baseline for ALL patients. Fresh tumor biopsy at screening is mandatory.	Archival tissue is optional at baseline for ALL patients. Fresh tumor biopsy at screening is mandatory for ALL patients.
On-treatment	Optional “fresh” biopsy pre-dose at Day 23-31 of first cycle	MANDATORY “fresh” biopsies (pre-dose) in 48 subjects from US IION sites between Day 23-31 Optional “fresh” biopsy pre-dose at day 23-31 of first cycle are encouraged for all other subjects and is MANDATORY in all sub study subjects
Upon Progression	Optional “fresh” biopsy upon confirmation of PD	Optional “fresh” biopsy upon confirmation of PD

5.7.1 Soluble Biomarkers (Serum Biomarkers)

Pre-treatment and on-treatment serum levels of chemokines, cytokines, and tumor-associated soluble proteins will be assessed by techniques that may include, but are not limited to, ELISA or multiplex assays. Analyses may include markers of inflammation, immune activation, host tumor growth factors, and tumor-derived proteins, including sLAG3.

5.7.2 Antitumor Antibodies (Serum Biomarkers)

Treatment with BMS-986016 and nivolumab may result in the generation of novel, or an increase in existing, antibodies to tumor-associated antigens. An assessment of antibodies to a panel of > 8000 proteins will be performed using pre-treatment and on-treatment serum in multiplex and ELISAs. These data will be used in a subset of subjects to explore if antitumor antibodies are

associated with clinical response and safety parameters, as well as inform pharmacodynamics of drug administration.

5.7.3 Immunophenotyping (Flow Cytometry/PBMC)

Peripheral blood mononuclear cells (PBMCs) will be used to characterize and quantify the activation and regulatory status of myeloid and lymphoid cells by polychromatic flow cytometry. Subsets of cells to be characterized by immunophenotyping include naive, activated, and exhausted effector and memory T cell populations, regulatory T cells, NK cells, and myeloid-derived suppressor cells.

5.7.4 Ex vivo Functional Assays (Cellular Assay)

To explore whether BMS-986016 and nivolumab will restore T cell activation and function, PBMCs will be isolated and cryopreserved. The functional status of effector T cells, including, but not limited to, IFN- γ and granzyme B, will be assessed by flow cytometric staining.

5.7.5 Peripheral Blood Gene Expression (Whole Blood mRNA) and Tumor Gene Expression

The expression level of genes related to response to BMS-986016 \pm nivolumab will be quantified by RNA seq microarray and/or quantitative reverse transcription polymerase chain reaction (RT-PCR) analysis in whole blood and tumor samples. Analysis may include, but not necessarily be limited to, genes encoding BMS-986016-stimulated effector functions (perforin, granzyme B, and IFN- γ) and genes encoding T cell co-stimulatory receptors (PD-1, PD-L1, and CTLA-4).

5.7.6 Circulating Tumor DNA Analysis (Serum (plasma) Biomarkers) — Melanoma Subjects Part C

The presence of cell-free DNA in circulating blood is a well-documented phenomenon. Fragments of DNA are shed into the blood stream from dividing cells during cell proliferation or cell death. In patients with cancer, a fraction of this DNA is tumor-derived and is termed circulating tumor DNA (ctDNA). Albeit small, fragments of DNA average between 180 to 200 bp and specific genomic regions can be amplified with PCR. Moreover, several studies have detected mutations in ctDNA that exactly correspond to mutations from the parent tumor. Using tissue and plasma from patients with known driver mutations in melanoma or head and neck cancer, BEAMing technology will be utilized to count the frequency of mutations in circulation.

5.7.7 Single Nucleotide Polymorphism Analysis (SNP)

In order to identify potential polymorphisms associated with the safety and efficacy of BMS-986016 selected genes will be evaluated for single nucleotide polymorphisms (SNPs). Genes of interest include, but are not limited to, PD-1, PD-L1, MHC class II, LAG-3, and CTLA-4.

5.7.8 Tumor Biopsy Analysis

Tumor tissue will be collected from all subjects. Immunohistochemistry (IHC) will be used to assess the number and composition of immune infiltrates in order to define the immune cell subsets present within tumor tissue before and potentially after exposure to BMS-986016 and nivolumab. These IHC analyses will include, but not necessarily be limited to, the following markers: CD4,

CD8, LAG-3, MHC II, PD-1, PD-L1, and PD-L2, as well as microsatellite instability (where appropriate). Correlations between gene expression and IHC expression will be made between assays performed if deemed to be informative.

5.7.9 Tumor-Based Biomarker Measures

Paired pre- and on-treatment tumor biopsies are mandatory for the first 16 subjects with melanoma or head and neck cancer who are enrolled in Part C (cohort expansion). Subjects for whom adequate paired pre- and on-treatment biopsies are not collected may be replaced.

Subjects should have at least one lesion large enough to undergo repeated biopsies (pre- and on-treatment biopsies) via core needle (minimum size 18 gauge) or have at least 2 distinct lesions eligible for core needle or excisional biopsies. The expected core needle length should be greater than 5 mm. A punch biopsy is acceptable for cutaneous lesions. Fine needle aspirate biopsies are not accepted. At least two core biopsies will be taken at each timepoint, but collection of additional cores is strongly encouraged if deemed clinically safe by the investigator. **An assessment of biopsy quality by a pathologist is strongly encouraged at the time of the procedure.** All biopsies collected must have a detailed pathology report submitted with the specimen. Detailed instructions regarding the acquisition, processing, labeling, handling, storage, and shipment of biopsy specimens will be provided in a separate procedure manual prior to study initiation.

Tumor biopsy specimens will be obtained from consenting subjects prior to and during treatment with BMS-986016 and nivolumab to characterize immune cell populations and expression of selected tumor markers.

Biopsy samples may be used for the following assessments:

- Characterization of TILs and tumor antigens. Immunohistochemistry will be used to assess the number and composition of immune infiltrates in order to define the immune cell subsets present within tumor tissue before and after exposure to BMS-986016 and nivolumab. These IHC analyses will include, but not necessarily be limited to, the following markers: CD4, CD8, LAG-3, MHC II, PD-1, PD-L1, and PD-L2. Correlations between gene expression and IHC expression will be made between assays performed if deemed to be informative.
- Laser capture microdissection. Isolation of tumor and/or TIL on FFPE sections will be performed by laser capture microdissection (LCM) for profiling of molecular events within the tumor microenvironment.
- Characterization of T cell repertoire. DNA sequencing will be performed on pre- and post-treatment FFPE tumor tissue to assess the composition of the T cell repertoire. Low T cell receptor diversity may be a poor prognostic factor of overall survival in metastatic breast cancer patients.⁴⁸ Currently, there is a poor understanding of T cell receptor diversity as a predictor factor of response to immunotherapy, given that the major mechanism of nivolumab and BMS-986016 is hypothesized to be the functional restoration of T cell antitumor immunity. Therefore, a characterization of the diversity of the T cell compartment in the periphery, and within the tumor, at baseline and on-treatment will be performed by T cell receptor next-generation DNA sequencing. T cell repertoire analysis will also be performed from DNA isolated from peripheral blood to compare the status of tumor and peripheral T cell repertoire pre and post treatment.

- Gene expression profiling. Tumor biopsies that are collected in RNAlater or similar reagent will be examined for mRNA gene expression by Affymetrix gene array technology and/or quantitative real-time polymerase chain reaction (qPCR) and/or RNA seq to detect expression of selected immune-related genes.
- Somatic tumor mutation load determination: Whole exome sequencing of both the tumor and of the germline (peripheral blood or bucal swab) will be compared to identify acquired somatic mutations in the tumor.
- In situ cytokine and negative regulator expression. Tumors biopsies will be quantitatively evaluated for RNA, including but not limited to, CD3, IFN- γ , LAG-3, and PD-1.

Subjects whose screening biopsy yields inadequate tissue quantity or quality will be allowed to continue in the study. If on-treatment biopsy is not successful, subjects may also continue on study. Such subjects may be replaced in order to obtain 48 subjects with adequate paired tumor biopsies. If subjects have a response to treatment, on-treatment biopsies might not be possible. In this case, subjects may also continue on study.

The tumor tissue that is obtained from these biopsies will be divided equally into FFPE and frozen samples, which can be used for histologic confirmation of melanoma as well as for the assays listed above.

The investigator, in consultation with the radiology staff, must determine the degree of risk associated with the procedure and find it acceptable. Biopsies may be done with local anesthesia or conscious sedation. Institutional guidelines for the safe performance of biopsies should be followed. Excisional biopsies may be performed to obtain tumor biopsy samples. Invasive procedures that require general anesthesia should not be performed to obtain a biopsy specimen. However, if a surgical procedure is performed for a clinical indication, excess tumor tissue may be used for research purposes with the consent of the subject.

5.7.10 Additional Research Collection

Residual tissue, blood and their derivatives from biopsies and blood collections will be retained by the BMS Biobank for medical research purposes. No additional sampling is required for residual collections. Retention is mandatory for all subjects, except where prohibited by local laws or regulations. Further details of sample collection and processing will be provided to the site in the procedure manual.

5.8 Outcomes Research Assessments

Not applicable.

5.9 Other Assessments

5.9.1 Immunogenicity Assessments

Serum samples collected at timepoints identified in [Table 5.5.1-1](#) and [Table 5.5.1-2](#) for Q2W dosing and [Table 5.5.1-3](#) and [Table 5.5.1-4](#) for Q4W dosing, will be analyzed by a validated

immunogenicity assay. Selected serum samples may be analyzed by an exploratory orthogonal method that measures anti-BMS-986016 or anti-nivolumab. Potential results generated from any orthogonal method are intended as informational for technology exploration purposes and will not be reported.

In addition, ad hoc serum samples designated for PK or biomarker assessments may also be used for immunogenicity analysis if required (e.g., insufficient volume for complete immunogenicity assessment or to follow up on suspected immunogenicity related AE).

5.10 Results of Central Assessments

The effect of BMS-986016 on QTc interval when administered alone or in combination with nivolumab will be evaluated by a central reader using ECG data collected via Holter monitors supplied by a core laboratory; these results will be summarized at the end of the study. For the purposes of monitoring subject safety, Investigators will review 12-lead ECGs per the protocol-specified schedule (see [Table 5.1-2](#)) using their site's standard electrocardiogram machines.

6 ADVERSE EVENTS

An *Adverse Event (AE)* is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered an investigational (medicinal) product 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 investigational product, whether or not considered related to the investigational product.

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.)

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.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See [Section 6.6](#) for the definition of potential DILI.)

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

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) 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 therapy (e.g., death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported) should be reported as 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).

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

6.1.1 Serious Adverse Event Collection and 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 135 days of discontinuation of dosing. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (e.g., a follow-up skin biopsy).

The investigator should 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 should 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 should 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. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). The preferred method of SAE data reporting collection is through the 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. The paper forms should be used and submitted immediately, only in the event the electronic system is unavailable for transmission. 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 should 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, a follow-up SAE report should be sent within 24 hours to the BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

6.2 Nonserious Adverse Events

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

6.2.1 Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug and continue for 135 days after discontinuation of dosing.

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.

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 (paper or electronic) as appropriate:

- 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 (e.g., 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 investigational product exposure, including during at least 5 half-lives plus 30 days after product administration, the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours 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 (e.g., dose tapering if necessary for subject safety).

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

The investigator must immediately notify the BMS (or designee) Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours and in accordance with SAE reporting procedures described in Section 6.1.1.

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 potential drug-induced liver injury (DILI) event. All occurrences of potential DILIs, 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. AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)
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 AT elevation and hyperbilirubinemia, including, but not limited to, tumor progression, acute viral hepatitis, cholestasis, pre-existing hepatic disease or the administration of other drug(s), herbal medications and substances known to be hepatotoxic.

Given the organ specific nature of hepatocellular carcinoma (HCC) the definition of potential drug induced liver injury is defined differently specifically for HCC subjects. The rationale for HCC specific DILI language as follows: 1) Standardization of the DILI definition so that a unified approach is taken across the BMS HCC program, 2) Concern that the previous language may not be sensitive to capture all potential cases given the lack of a requirement for a concomitant elevation in transaminases and bilirubin, and the significant increase in total bilirubin regardless of baseline value, and 3) alignment with the Daclatasvir DAA program which has criteria that have been developed after consultation with health authorities for subjects with chronic HCV infection with underlying liver disease and therefore consistent with the patient population in this study.

Therefore, Potential drug induced liver injury for HCC subjects is defined as:

1. AT (ALT or AST) elevation > 10 times upper limit of normal (ULN)
AND
2. Total bilirubin > 2 times ULN or baseline value (if elevated bilirubin at study entry)
AND
3. No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, tumor progression, acute viral hepatitis, cholestasis, pre-existing

hepatic disease or the administration of other drug(s), herbal medications and substances known to be hepatotoxic.

This change in pDILI definition is not anticipated to pose any risk for subjects since management of hepatic events will follow pre-established algorithms that are not impacted by the DILI definition, and include dose delay and/or discontinuation as well as intervention with immunosuppressants.

6.7 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiogram, radiologic exams, 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

7.1 Data Monitoring Committee

A Data monitoring committee (DMC) will be utilized in Part C only if further expansion of a total of 90 to 120 subjects is triggered. The DMC will provide oversight of safety evaluation and to provide advice to the sponsor regarding actions the committee deems necessary for the continuing protection of subjects enrolled in this stage.

7.2 Blinded Independent Central Review committee

A Blinded Independent Central Review Committee (BICR) may be used in selected disease cohorts in Part C.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

8.1.1 Dose Escalation (Parts A and B)

Sample size at each dose depends on observed toxicity and cannot be precisely determined. Part A and B will have 3 to 9 subjects in each cohort.

8.1.2 Cohort Expansion (Part C)

The objective of this expansion in combination with nivolumab is to support further clinical testing by demonstrating adequate safety and tolerability as well as favorable risk/benefit by assessing preliminary efficacy measured by objective response rate (ORR) and other clinically relevant efficacy measures such as duration of response and disease control rate. However, the sample size is strictly based on efficacy, specifically based on the target ORR relative to historic ORR.

Disease-, as well as prior IO therapy-, restricted cohorts will be investigated in the Part C cohort expansion: NSCLC progressed on IO therapy; Melanoma progressed on anti-PD-1/anti-PD-L1; RCC naive to IO therapy; NSCLC 1st or 2nd line naive to IO therapy; Melanoma 1st line; SCCHN naive to IO therapy; Gastric cancer naive to IO therapy; and HCC naive to IO therapy. The NSCLC progressing on IO therapy cohort will be analyzed as a whole and as two separate sub-groups,

refractory and relapsed, as defined in [Section 3.3.1](#). All disease-cohorts will be handled independently and there will be no multiplicity adjustment.

A multi-stage design will be used as a guide for each expansion cohort in order to decide whether the treatment of BMS-986016 in combination with nivolumab warrants more extensive development. At first, a 2-stage design with a reasonable false positive rate (eg, FPR < 10%) and false negative rate (eg, FNR < 10%) will be used for the decision making based on assumptions of true (target) and historic/standard-of-care response rate for each cohort. The assumed historic and target response rates may change over time and may need to be adjusted by the time of response data from this study are available. Using a 2-stage design provides an option to stop early for futility as well as a signal of preliminary antitumor activity for strong-go early on. Enrollment may continue into stage 2 while the planned number of subjects for stage 1 are followed for efficacy evaluable tumor assessments. There will be no stopping of a disease cohort for efficacy, although early plan for the next stage of clinical development may be initiated.

The ORRs considered to be of clinical value for further expansion of selected populations, sample size, and operational characteristics of using a 2-stage design, as an example, are provided in Table 8.1.2-1, although this is not used for statistical hypothesis testing.

Table 8.1.2-1: Example of a Two-stage Design Characteristics

Cohort	Historic/T arget rate (%)	Stage	Cum sample size	Conclude inefficacy if R ^a	Conclude efficacy if R	PET ^b for futility (%)	PEE ^c for efficacy (%)
Gastric IO naïve							
HCC IO naïve	10/30	1	15	≤ 1	≥ 4	55	70
		2	26	≤ 5	≥ 6		
Melanoma progressed on anti- PD-1/PD-L1							
RCC IO naïve	25/50	1	11	≤ 2	≥ 6	46	50
		2	26	≤ 9	≥ 10		
NSCLC IO refractory	5/20	1	12	0	≥ 3	54	44
NSCLC IO relapsed		2	37	≤ 3	≥ 4		
NSCLC 1/2L, IO naïve	20/45	1	14	≤ 3	≥ 7	70	45
		2	25	≤ 7	≥ 8		
Melanoma 1L	40/65	1	13	≤ 5	≥ 10	57	28
		2	28	≤ 14	≥ 15		
SCCHN IO naïve	20/40	1	20	≤ 4	≥ 8	63	58
		2	36	≤ 10	≥ 11		

- ^a R is the cumulative number of responses at the end of stage
^b probability of early termination
^c probability of early expansion

Once there is preliminary evidence of the treatment effect that may represent substantial improvement over available therapies, sufficient additional subjects will be treated to demonstrate a substantial and clinically meaningful effect in ORR that is supported by duration of the effect. The total sample size at this stage will be determined based on the ability to produce a CI which would exclude an ORR of the historic response and to provide sufficient information for a reliable understanding of the safety profile. With 90 to 120 subjects in total, this design yields a less than 5% 2-sided Type I error rate and at least 80% power depending on tumor type with specified historic/SOC and target rates. Table 8.1.2-2 summarizes the 95% exact CI for various observed ORRs with sample sizes of 90, 100, and 120.

Guided by [Table 8.1.2-1](#) initially, approximately 11 RCC subjects, for example, will be treated in Stage 1. Assuming the true response rate is 50% when treated with BMS-986016 in combination with nivolumab, if there are 6 or more responses in 11 subjects, it may be decided to expand further up to approximately 90 subjects in total after careful evaluation of all available data including duration of response and safety profile. The probability of early decision to expand further for efficacy is approximately 50% if in fact the treatment is efficacious. If there are 2 or fewer responses in 11 treated subjects, the cohort may be stopped for futility. The probability of early stopping for futility is approximately 46% if in fact the treatment is inefficacious, eg, 25%. If there are 3-5 responses, additional 15 subjects may be treated to collect more data. At the end of Stage 2, if there are 10 or more responses, additional 64 subjects may be treated up to a total of 90 subjects. Table 8.1.2-2 shows that at observed ORR $\geq 36\%$, the lower bound of the 95% CI excludes 25% with a sample size of 90.

Table 8.1.2-2: Observed ORR with Exact 95% CI

Sample Size	Number of Responses	ORR	95% Exact CI
90	18	20%	[12.3%, 29.8%]
	27	30%	[20.8%, 40.6%]
	32	36%	[25.7%, 46.4%]
	37	41%	[30.8%, 52.0%]
	46	51%	[40.4%, 61.8%]
100	20	20%	[12.7%, 29.2%]
	30	30%	[21.2%, 40.0%]
	35	35%	[25.7%, 45.2%]
	40	40%	[30.3%, 50.3%]
	50	50%	[39.8%, 60.2%]
120	24	20%	[13.3%, 28.3%]
	36	30%	[22.0%, 39.0%]
	42	35%	[26.5%, 44.2%]

Table 8.1.2-2: Observed ORR with Exact 95% CI

Sample Size	Number of Responses	ORR	95% Exact CI
	48	40%	[31.2%, 49.3%]
	60	50%	[40.7%, 59.3%]

8.1.3 Cohort Expansion- Monotherapy (Part A1)

A sample size of 6 subjects per cohort allows for estimation of the proportion of subjects with objective response (i.e., a BOR of CR + PR) within a cohort such that the maximum distance between the estimated rate and either limit of the exact 2-sided 95% Clopper-Pearson confidence interval is 47.5%.

A sample size of 12 subjects per cohort allows for estimation of the proportion of subjects with objective response (i.e., a BOR of CR + PR) within a cohort such that the maximum distance between the estimated rate and either limit of the exact 2-sided 95% Clopper-Pearson confidence interval is 32.2%.

8.2 Populations for Analyses

- **All Enrolled Subjects Analysis Set:** This analysis set contains all subjects (including screen failures) who signed an informed consent for the study.
- **All Treated Subjects-Analysis set:** This analysis set includes all subjects who receive either drug.
- **Response-Evaluable Subjects:** This analysis set includes all subjects who receive either study drug, have a baseline tumor assessment with measurable disease, and one of the following: (1) at least one evaluable on-treatment tumor assessment, (2) clinical progression, or (3) death prior to the first on-treatment tumor evaluation.
- **BMS-986016 Pharmacokinetic Analysis Set:** This analysis set includes all subjects who receive BMS-986016 and have at least one valid PK parameter to be included in statistical analyses of BMS-986016 PK data.
- **BMS-986016 Immunogenicity Analysis Set:** This analysis set includes all subjects who receive BMS-986016, and have baseline and at least one post baseline pre-infusion BMS-986016 immunogenicity assessment.
- **Nivolumab Immunogenicity Analysis Set:** This analysis set includes all subjects who receive BMS-986016, and have baseline and at least one post baseline pre-infusion BMS-986016 immunogenicity assessment.
- **Pharmacodynamic Analysis Set:** This analysis set includes all treated subjects for whom pharmacodynamic measurements are available at baseline and at least one other timepoint.

8.3 Endpoints

8.3.1 Primary Endpoints

The primary endpoint of this Phase 1/2a study is safety as measured by the rate of AEs, serious adverse events (SAEs), AEs leading to discontinuation of treatment, deaths, and laboratory abnormalities, assessed during treatment and for up to 135 days of follow-up. All subjects who receive at least one dose of BMS-986016 or nivolumab will be analyzed for safety.

Objective response rate (ORR), disease control rate (DCR), and duration of response (DOR) by BICR using RECIST v1.1, where applicable, in selected disease cohorts in Part C will be the co-primary efficacy endpoints.

- ORR is defined as the total number of subjects whose BOR is either CR or PR divided by the total number of treated subjects in the population of interest.

Best overall response (BOR) per RECIST v1.1 is defined as the best response designation recorded between the date of first dose and the date of first objectively documented progression per RECIST 1.1 or the date of subsequent therapy, whichever occurs first. CR or PR determinations included in the BOR assessment must be confirmed by a second scan no less than 4 weeks after the criteria for response are first met. For subjects who continue treatment beyond progression per RECIST 1.1 or begin subsequent therapy, the BOR should be determined based on response designations recorded up to the time of the initial progression or subsequent therapy, whichever occurs first. For subjects without documented progression or subsequent therapy, all available response designations should contribute to the BOR assessment.

- DCR is defined as the total number of subjects whose BOR is either CR, PR or SD for at least 12 weeks divided by the total number of treated subjects in the population of interest.
- DOR computed only for subjects with a BOR of CR or PR is defined as the number of days between the date of first response and the date of first objectively documented disease progression based on the criteria (RECIST v1.1) or death, whichever occurs first. For those subjects who remain alive and have not progressed, duration of response will be censored on the date of last tumor assessment. Subjects who receive subsequent therapy without a prior reported progression will be censored at the date of last tumor assessment prior to the start of subsequent anticancer therapy.

8.3.2 Secondary Endpoints

8.3.2.1 Pharmacokinetics

The PK of BMS-986016 administered both alone and in combination with nivolumab will be assessed as a secondary objective using the following endpoints derived from serum concentration versus time data in Cycle 1 and Cycle 3:

C _{max}	Maximum observed serum concentration
T _{max}	Time of maximum observed serum concentration
C _{trough}	Trough observed serum concentration
C _{tau}	Concentration at the end of a dosing interval (eg concentration at 336 hours)
C _{ss,avg}	Average concentration over a dosing interval ($[AUC(TAU)]/\tau$)

AUC(TAU)	Area under the concentration-time curve in one dosing interval
CLT	Total body clearance
Vss	Volume of distribution at steady state
T-HALFeff AUC	Effective elimination half-life that explains the degree of AUC accumulation observed
T-HALFeff Cmax	Effective elimination half-life that explains the degree of Cmax accumulation observed
AI_AUC	Accumulation index; ratio of AUC(TAU) at steady state to AUC(TAU) after the first dose
AI_Cmax	Cmax accumulation index; ratio of Cmax at steady state to Cmax after the first dose
AI_Ctau	Ctau accumulation index; ratio of Ctau at steady state to Ctau after the first dose
DF	Degree of fluctuation or fluctuation index ($[C_{max} - C_{tau}]/C_{ss,avg}$)

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

8.3.2.2 Efficacy

The BOR, ORR, DCR, DOR, and PFS rates at pre-specified timepoints (eg, 24 weeks) based on investigator assessment using RECIST v1.1 will be the secondary efficacy endpoints. PFS rates at pre-specified timepoints based on BICR assessment, where applicable, will also be the secondary efficacy endpoints.

BOR, ORR, DCR, and DOR were defined under the primary endpoints. Progression Free Survival (PFS) is defined as the time from first dose to the date of first objectively documented progression, per RECIST 1.1, or death due to any cause, whichever occurs first. Clinical deterioration in the absence of objectively documented progression per RECIST 1.1 is not considered progression for the purpose of determining PFS. Subjects who die without a reported progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment. Subjects who did not have any on study tumor assessments and did not die will be censored on the date of first dose. Subjects who started any subsequent anti-cancer therapy, including tumor-directed radiotherapy and tumor-directed surgery, without a prior reported progression will be censored at the last evaluable tumor assessment prior to initiation of the subsequent anti-cancer therapy. The progression free survival rate at time T is defined as the probability that a subject has not progressed and is alive at time T following first dose.

8.3.2.3 Immunogenicity

The endpoints to characterize the immunogenicity of BMS-986016 and nivolumab will be detailed in the statistical analysis plan (SAP). Baseline ADA-positive subject is defined as a subject who has an ADA-detected sample at the last sample prior to the initiation of the treatment. ADA-positive subject is defined as a subject with at least 1 ADA-positive sample relative to baseline after initiation of the treatment. To examine the potential relationship between immunogenicity

and safety, a table summarizing the frequency and type of AEs of special interest may be explored by immunogenicity status.

8.3.2.4 Centrally Read ECGs (Parts A and B)

In Part A and Part B, QTc will be assessed by a central reader at follow-up visit 1, and on day 1 of Cycle 1 and Cycle 3 (pre-dose and 4 hour post-dose time points). These assessments will be used to address the secondary objective of assessing the effect of BMS-986016 administered alone and in combination with nivolumab on QTc.

ECGs assessed locally by the investigator are also collected at the start of each cycle. QTc will be calculated by the sponsor for these ECGs. However, results will be summarized separately, and are not considered part of the secondary objective.

8.3.3 Exploratory Endpoints

8.3.3.1 Biomarkers

Biomarker endpoints from peripheral blood will generally be measured at multiple timepoints, and evaluated as both predictive and pharmacodynamic markers in the context of the exploratory biomarker objectives. These may include measures such as levels and change from baseline in levels of the following at each scheduled timepoint:

- Serum soluble factors
- The proportion of specific lymphocyte subsets/expression levels of T cell co-stimulatory markers assessed using flow cytometry
- Expression of genes encoding BMS-986016-stimulated effector functions (perforin, granzyme B, and IFN- γ) and genes encoding T cell co-stimulatory receptors (PD-1, PD-L1, and CTLA-4). Note: only results for selected genes will be presented.

Biomarker endpoints from tumor biopsies will be explored predominantly in an effort to identify baseline markers predictive of efficacy, since they are only measured at baseline for most subjects. For the subset of subjects who have both pre-treatment and on-treatment biopsies, pharmacodynamic associations may be explored. Endpoints may include measures such as pre-treatment levels and change in levels observed on-treatment of:

- Functional status of lymphocytes measured as the percent of CD8+ T-cells positive for IFN- γ and granzyme B expression, and the geometric mean intensity (log-scale) of CD8+ cells that are positive for IFN- γ and granzyme B expression (via ex vivo functional assay)
- Expression of genes encoding BMS-986016-stimulated effector functions (perforin, granzyme B, and IFN- γ) and genes encoding T cell co-stimulatory receptors (PD-1, PD-L1, and CTLA-4)
- IHC assessment of the presence/absence and intensity (measured using a discrete scale: such as 0, 1, 2, 3, 4) of T-cell infiltration and expression of LAG-3, MHC class II, PD-1, PD-L1, and PD-L2.
- Assessment of somatic mutation/neoantigen load.

Appropriate functional transformation of these exploratory measures will be applied as necessary. Measures not available at the time of the clinical study report may be summarized in a separate report.

8.3.3.2 Pharmacokinetics

Nivolumab concentration-time data at scheduled trough (C_{trough}) and end-of-infusion timepoints will be evaluated as an exploratory endpoint. Measurements will be collected on treatment (up to 12 cycles) and for up to 135 days during the post-treatment follow-up.

8.3.3.3 Efficacy

Landmark 1 year and 2 year OS rates will be assessed as exploratory efficacy endpoints.

8.4 Analyses

Unless otherwise specified, data from Part A (monotherapy-dose escalation) and Part A1 (monotherapy-dose expansion) will be presented separately from data collected in Parts B and C (sequential combination therapy). Safety data from dose-escalation phase will be summarized by dose and across all doses. Safety data from dose-expansion phase will be summarized for each disease cohort and overall by dose and across doses. Efficacy data from dose-expansion phase will be summarized for each disease cohort by dose and across doses. Efficacy data from Parts dose-escalation phase will be summarized by dose and listed by tumor type.

Descriptive statistics will include the number of observations and percentage in each category for categorical variables. For continuous variables, the number of observations, mean, median, standard deviation, minimum, and maximum will be presented unless otherwise specified. All available data will be included in-subject listings.

8.4.1 Demographics and Baseline Characteristics

Frequency distributions of gender, race, ethnicity, and other categorical baseline characteristics will be tabulated. Baseline body mass index (BMI) will be derived from measurements of baseline body weight and height. Summary statistics for age, body weight, height, and BMI will be tabulated.

8.4.2 Efficacy Analyses

Individual BOR, DOR, and PFS will be determined based on RECIST v1.1 criteria. BOR outcomes will be summarized using frequency tables. Time to event distribution (eg. PFS and DOR) will be estimated using Kaplan-Meier (K-M) method. When appropriate, the median along with 95% CI will be provided using Brookmeyer and Crowley methodology (using log-log transformation for constructing the confidence intervals). Rates at fixed timepoints (e.g. PFSR 24 weeks) will be derived from the K-M estimate and corresponding confidence interval will be derived based on Greenwood formula. Confidence intervals for binomial proportions will be derived using the Clopper-Pearson method. OS data will be analysed similarly to PFS data analysis.

8.4.3 Safety Analyses

All subjects who receive study drug therapy will be evaluated for safety endpoints. All recorded AEs and SAEs will be listed and tabulated by system organ class, preferred term, and dose and

coded according to the most current version of MedDRA. Vital signs and clinical laboratory test results will be listed and summarized by treatment. In addition, the worst grade of a laboratory measure observed on-study by the baseline grade (per CTCAE v 4) will also be generated for selected laboratory tests. Any significant physical examination findings and results of clinical laboratory tests will be listed. ECG results will be evaluated by the investigator and abnormalities, if present, will be listed. In Parts A and B, ECG will be assessed by a central reader at specific timepoints. All ECG data analyses including summaries of each ECG parameters, frequency distributions of subjects' maximum values/changes, and scatter plots will be performed following the current practice of ECG data analysis. Concentration-response analysis may be performed using mixed effect model, if appropriate. The details of ECG data analysis will be provided in statistical analysis plan.

8.4.4 Pharmacokinetic Analyses

PK parameters for BMS-986016 will be calculated using noncompartmental analyses. Summary statistics will be tabulated for the PK parameters of BMS-986016 by dose and study day/cycle. To describe the association of these parameters with dose of BMS-986016, scatter plots of C_{max} and AUC(TAU) versus dose may be provided for each day/cycle measured. Dose proportionality of BMS-986016 when administered alone or co-administered with nivolumab may also be assessed based on a power model. Trough concentrations of BMS-986016 will be plotted versus study day and cycle. Nivolumab end-of-infusion and trough (C_{trough}) concentrations will be tabulated using summary statistics. These data may also be pooled with other datasets for population PK analysis which will be presented in a separate report.

8.4.5 Biomarker Analyses

Not applicable.

8.4.6 Exploratory Biomarker Analyses

Pharmacodynamic effect in subjects who undergo biopsy will be assessed using summary statistics and plots. As an example, the correlation of TIL changes and tumor marker expression with measures of peripheral blood markers may be explored graphically and using appropriate modeling approaches based on data availability. The pharmacodynamic effect of BMS-986016 on LAG-3 receptor occupancy and on markers in peripheral blood and serum proteins may be explored using summary statistics, and investigated graphically to explore patterns of change over time, and whether the time profiles differ among dose levels or exposure. If there is a meaningful indication in the pattern over time, further analysis (e.g., by linear mixed model) may be performed to characterize the relationship. Associations between biomarker measures from peripheral blood or tumor biopsy and clinical outcomes may also be explored graphically and further assessed as needed by methods such as, but not limited to, logistic regression, and characterized by appropriate statistics.

8.4.7 Outcomes Research Analyses

Not applicable.

8.4.8 Other Analyses

8.4.8.1 Immunogenicity Analyses

A listing will be provided for all available immunogenicity data. For each drug, the number and percent of subjects who meet the endpoint definitions in [Section 8.3.2.3](#) will be summarized; specifically, those with: an ADA positive sample at baseline, those who meet the definition of being ADA positive and, those who are persistently ADA positive. To examine the potential relationship between immunogenicity and safety, a table summarizing the frequency and type of AEs of special interest may be explored by immunogenicity status. In addition, potential relationships between immunogenicity and efficacy and/or PK may also be explored.

8.5 Interim Analyses

Data emerging from this study may be needed for timely decisions about adjustments to procedures in subsequent parts of the study. Therefore data may be reviewed prior to the final lock of the study database. Additional interim analyses may also be performed for administrative purposes or publications. No formal inferences requiring adjustment to the 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

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.

9.1.3 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.

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 investigational product (those supplied by BMS) is maintained at each study site where study drug are inventoried and dispensed. 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
- retain samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

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 paper or electronic SAE form and Pregnancy Surveillance form, respectively. 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, including any paper or electronic 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 considering the following criteria:

- Subject recruitment (e.g., 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
Adverse Reaction	An adverse event that is considered by either the investigator or BMS as related to the investigational product
Unexpected Adverse Reaction	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, Investigator Brochure for an unapproved investigational product)
Serious Adverse Event	Serious adverse event defined as 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; 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.). For reporting purposes only, BMS also considers the occurrence of pregnancy, overdose (regardless of association with an AE), and cancer as important medical events.

11 LIST OF ABBREVIATIONS

Term	Definition
ADA	anti-drug antibody
AE	adverse event
AFP	alpha-fetoprotein
AI	accumulation index
AI_AUC	AUC Accumulation Index; ratio of AUC(TAU) at steady state to AUC(TAU) after the first dose
AI_Cmax	Cmax Accumulation Index; ratio of Cmax at steady state to Cmax after the first dose
AI_Ctau	Ctau Accumulation Index; ratio of Ctau at steady state to Ctau after the first dose
AJCC	American Joint Committee on Cancer
ALK	anaplastic lymphoma kinase
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AT	Aminotransaminase
AUC	area under the concentration-time curve
AUC(INF)	area under the concentration-time curve from time zero extrapolated to infinite time
AUC(0-T)	area under the concentration-time curve from time zero to the time of the last quantifiable concentration
AUC(TAU)	area under the concentration-time curve in one dosing interval
βhCG	beta-human chorionic gonadotrophin
BMI	body mass index
BMS	Bristol-Myers Squibb
BOR	best overall response
BUN	blood urea nitrogen
CEA	carcinoembryonic antigen
CHO	Chinese hamster ovary
CL	Clearance
CLT	total body clearance

Term	Definition
CLTp	systemic clearance
CLT	apparent total body clearance
C _{max}	maximum observed concentration
C _{min}	trough observed concentration
CNS	central nervous system
CR	complete response
CRF	case report form, paper or electronic
CRP	C-reactive protein
C _{ss,avg}	Average concentration over a dosing interval ($[AUC(TAU)/tau]$)
CT	computed tomography
ctDNA	circulating tumor DNA
C _{tau}	Concentration in a dosing interval (eg, concentration at 24 hours, concentration at 12 hours, etc.)
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T lymphocyte-associated antigen 4
C _{trough}	Trough observed plasma concentration
CV	coefficient of variation
DCR	disease control rate
DF	degree of fluctuation or fluctuation index ($[C_{max} - C_{tau}]/C_{ss,avg}$)
DICOM	Digital Imaging and Communications in Medicine
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DOR	duration of response
EBV	Epstein-Barr virus
ECG	Electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
ELISA	enzyme-linked immunosorbent assay
EOI	end-of-infusion
FFPE	formalin-fixed paraffin-embedded

Term	Definition
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
GLP	Good Laboratory Practice
GM-CSF	granulocyte macrophage-colony stimulating factor
HBsAg	hepatitis B surface antigen
HCC	Hepatocellular cancer
HCV Ab	anti-hepatitis C antibody
hCG	human chorionic gonadotropin
HED	human equivalent dose
HepA IgM	hepatitis A antibody
HER-2	human epidermal growth factor receptor 2
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HNC	head and neck cancer
HNSTD	highest non-severely toxic dose
HPV	human papilloma virus
HR	heart rate
HRT	hormone replacement therapy
ICF	informed consent form
ICH	International Conference on Harmonisation
ICMAR	immune cell-modulating antibody regimen
IEC	Independent Ethics Committee
IFN- γ	interferon gamma
IHC	Immunohistochemistry
IION	International Immuno-Oncology Network
IND	Investigational New Drug application
irAE	immune-related adverse event
IRB	Institutional Review Board
irRECIST	immune-related Response Evaluation Criteria in Solid Tumors

Term	Definition
ISH	in situ hybridization
ITIM	immunoreceptor tyrosine-based inhibitory motif
IU	International Unit
IV	Intravenous
IVRS	interactive voice response system
LAG-3	lymphocyte activation gene 3
LC	liquid chromatography
LCMV	lymphocytic choriomeningitis virus
LDH	lactate dehydrogenase
mAb	monoclonal antibody
MAD	maximum administered dose
MedDRA	Medical Dictionary for Regulatory Activities
MHC	major histocompatibility complex
MRI	magnetic resonance imaging
MRSD	maximum recommended starting dose
MS	mass spectrometry
MTD	maximum tolerated dose
mWHO	modified World Health Organization
N	number of subjects or observations
NCI	National Cancer Institute
N/A	not applicable
NK	natural killer
NOAEL	no-observed-adverse-effect level
NOD	non-obese diabetic
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
ORR	objective response rate
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed cell death protein 1

Term	Definition
PD-L1	programmed cell death protein ligand 1
PFS	progression-free survival
PFSR	progression-free survival rate
PID	patient identification number
PK	pharmacokinetic(s)
PPK	population pharmacokinetics
PR	partial response
PSA	prostate-specific antigen
Q2W	every 2 weeks
RANK-L	receptor activator of nuclear factor kappa-B ligand
RCC	Renal Cell Carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SC	Subcutaneous
SCCHN	Squamous Cell Carcinoma of the Head and Neck
SmPC	summary of product characteristics
SOP	standard operating procedure
STD10	severely toxic dose in 10% of the animals
T3	Triiodothyronine
TF	tumor-free
TGI	tumor growth inhibition
T-HALF	Terminal half-life
T-HALFeff_AUC	Effective elimination half life that explains the degree of AUC accumulation observed
T-HALFeff_Cmax	Effective elimination half life that explains the degree of Cmax accumulation observed)
TIA	transient ischemic attack
TIGIT	T cell immunoreceptor with Ig and ITIM domains
TIL	tumor infiltrating lymphocyte
TIM-3	T cell immunoglobulin domain and mucin domain 3

Term	Definition
Tmax	time of maximum observed concentration
TMDD	target-mediated drug disposition
Treg	regulatory T cell
TSH	thyroid-stimulating hormone
US ION sites	Dana Farber Cancer Institute, Boston, MA Memorial Sloan Kettering Cancer Center, NY, NY John Hopkins University, Baltimore, MD University of Chicago, Chicago, IL Portland Providence Cancer Center, Portland, OR
Vss	apparent volume of distribution at steady state
Vz	Volume of distribution of terminal phase (if IV and if multi-exponential decline)
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential

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APPENDIX 1 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

Anti-LAG-3 has not undergone the requisite preclinical testing for teratogenicity and therefore **requires two forms of contraception**. One method must be highly effective and the second method may also be highly effective or selected from the list of other contraceptive methods. Women and men who are not capable of reproduction or choose to be abstinent shall be exempt from following the pregnancy prevention requirements specified below.

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

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

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

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

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

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

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

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 135 days after the end of study treatment, plus 30 days, a total of 24 weeks.

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

<p>Highly Effective Contraceptive Methods That Are User Dependent</p> <p><i>Failure rate of <1% per year when used consistently and correctly.^a</i></p> <ul style="list-style-type: none"> • Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation^b <ul style="list-style-type: none"> – oral – intravaginal – transdermal • Progestogen-only hormonal contraception associated with inhibition of ovulation^b <ul style="list-style-type: none"> – oral – injectable
<p>Highly Effective Methods That Are User Independent</p> <ul style="list-style-type: none"> • Implantable progestogen-only hormonal contraception associated with inhibition of ovulation^b • Intrauterine device (IUD)^c • Intrauterine hormone-releasing system (IUS)^c • Bilateral tubal occlusion • Vasectomized partner <p><i>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.</i></p> <ul style="list-style-type: none"> • Sexual abstinence <p><i>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.</i></p> <ul style="list-style-type: none"> • 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 3.3.3. • 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

Less Than Highly Effective Contraceptive Methods That Are User Dependent

Failure rate of >1% per year when used consistently and correctly.

- Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously
- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal Sponge with spermicide
- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action

Unacceptable Methods of Contraception

- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal(coitus interruptus).
- Spermicide only
- Lactation amenorrhea method (LAM)

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 the end of relevant systemic exposure defined as 33 weeks after the end of treatment in the male participant.
- 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 33 weeks 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 33 weeks after the end of treatment.
- Refrain from donating sperm for the duration of the study treatment and for 33 weeks after the end of treatment.

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in [Section 6.4](#) and the Appendix for Adverse Events and Serious Adverse Events Definitions and procedures for Evaluating, Follow-up and Reporting.

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 is 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 30 days before the beginning of the treatment.

1.4.2 Method of assessment

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

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).

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 qualify for unequivocal progression status.

3.2.1.2 When the subject has only non-measurable disease

- To achieve ‘unequivocal progression’ on the basis of the non-target disease, there must be an overall level of substantial worsening such that the overall tumor burden has increased sufficiently to merit discontinuation of therapy.

- A modest ‘increase’ in the size of 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.

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.*

4 RESPONSE CRITERIA

4.1 Timepoint 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. Timepoint Response: Subjects with Target (± Non-Target) Disease

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

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 within 4 weeks 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:** Progression of disease should be verified in cases where progression is equivocal. If repeat scans confirm PD, then progression should be declared using the date of the initial scan. If repeat scans do not confirm PD, then the subject is considered to not have progressive disease. Additionally, see protocol [section 4.3.4](#) “Treatment beyond Disease Progression” for information regarding verification of progression in select subjects treated beyond initial PD. Evaluation of further PD is required for subjects with treatment beyond progression.

4.2 Best overall response: All timepoints

The best overall response is determined once all the data for the subject are known. It is the best response recorded from the start of the study treatment until the 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. Tumor assessments performed after subsequent antitumor therapy is initiated will not be considered in the best overall response assessment.

Best response is defined as the best response across all timepoints with subsequent confirmation. Complete or partial responses may be claimed only if the criteria for each are met at a subsequent timepoint as specified in the protocol (≥ 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, measurements must have met the SD criteria at least once no less than 6 weeks after study entry.

Table 2. Best overall response (confirmation of CR and PR required)

Overall Response First Timepoint	Overall Response Subsequent Timepoint	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR ^a
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

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 (i.e., 6 weeks from baseline assessment). 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 AND KARNOFSKY PERFORMANCE STATUS

PERFORMANCE STATUS CRITERIA: ECOG Score	
ECOG (Zubrod)	
Score	Description
0	Fully active; able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all self care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of only limited self care; confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self care; totally confined to bed or chair.

PERFORMANCE STATUS CRITERIA: Karnofsky Score	
Score	Description
100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease.
80	Normal activity with effort; some signs or symptoms of disease.
70	Cares for self; unable to carry on normal activity or to do active work.
60	Requires occasional assistance, but is able to care for most of their personal needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled; requires special care and assistance.
30	Severely disabled; hospital admission is indicated although death not imminent.
20	Very sick; hospital admission necessary; active supportive treatment necessary.
10	Moribund; fatal processes progressing rapidly.
0	Dead

APPENDIX 4 NIVOLUMAB MANAGEMENT ALGORITHMS

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology agents and regimens.

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

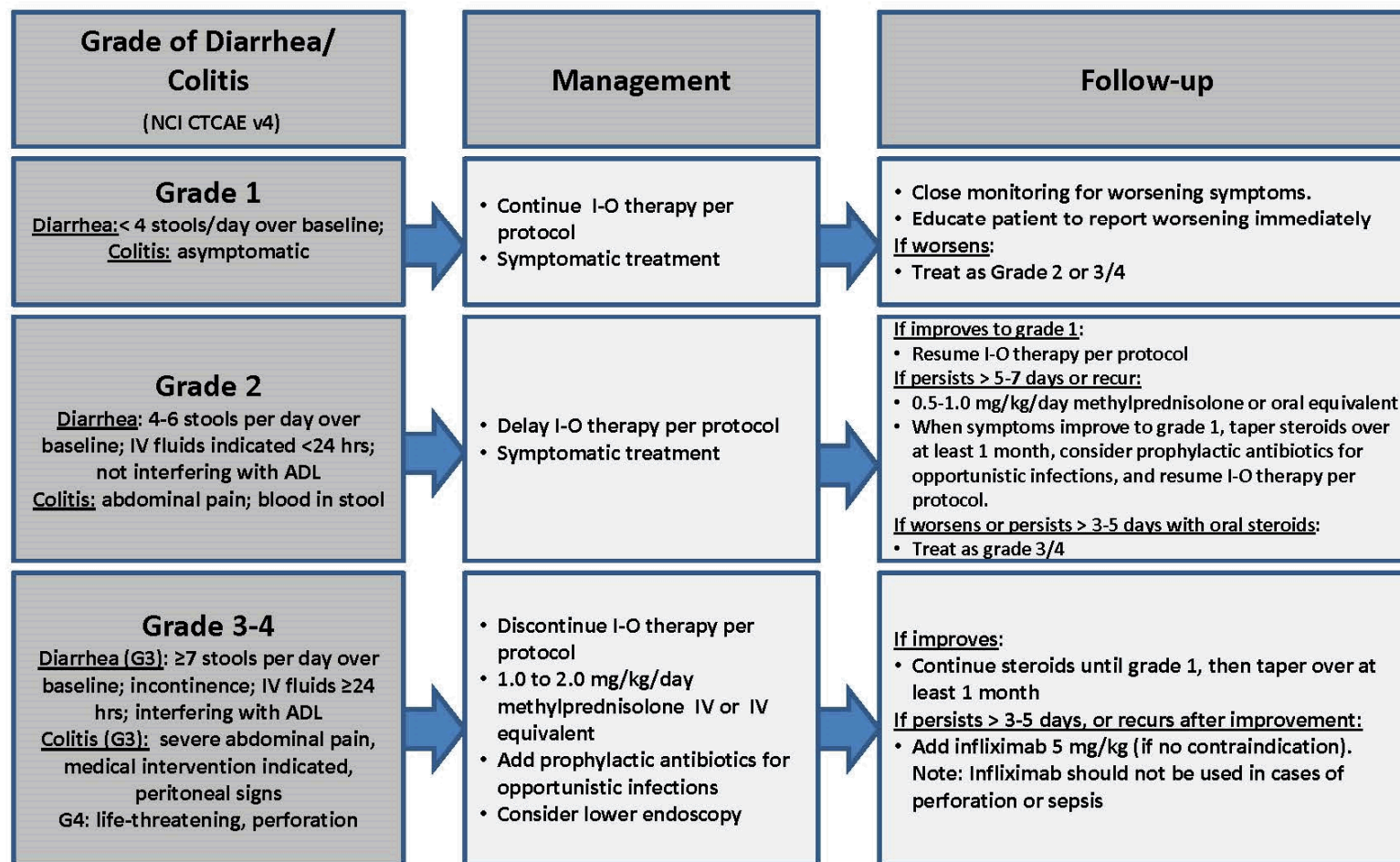
Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

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

These Algorithms are from Nivolumab IB v 15, 2016.

GI Adverse Event Management Algorithm

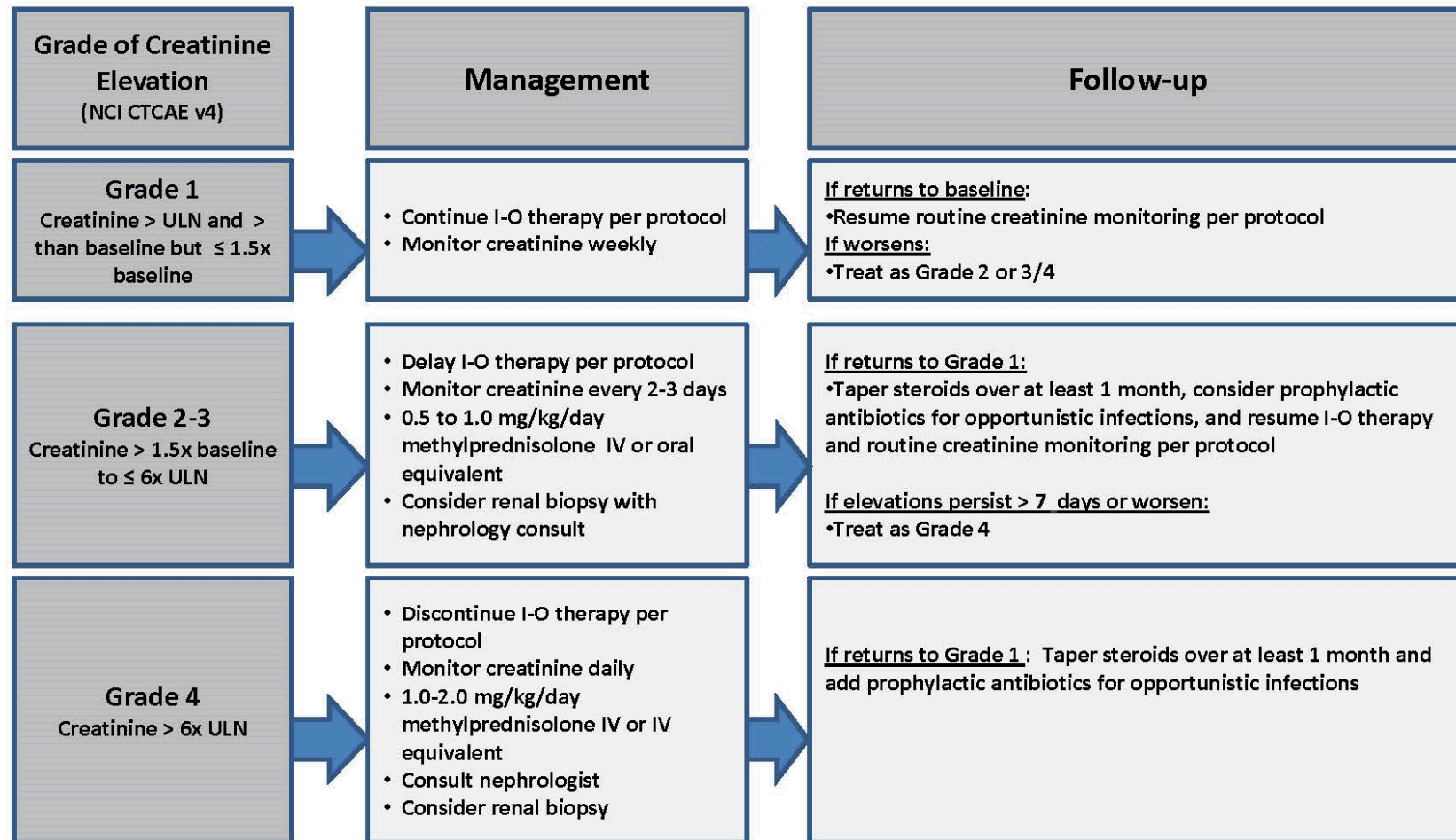
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



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.

Renal Adverse Event Management Algorithm

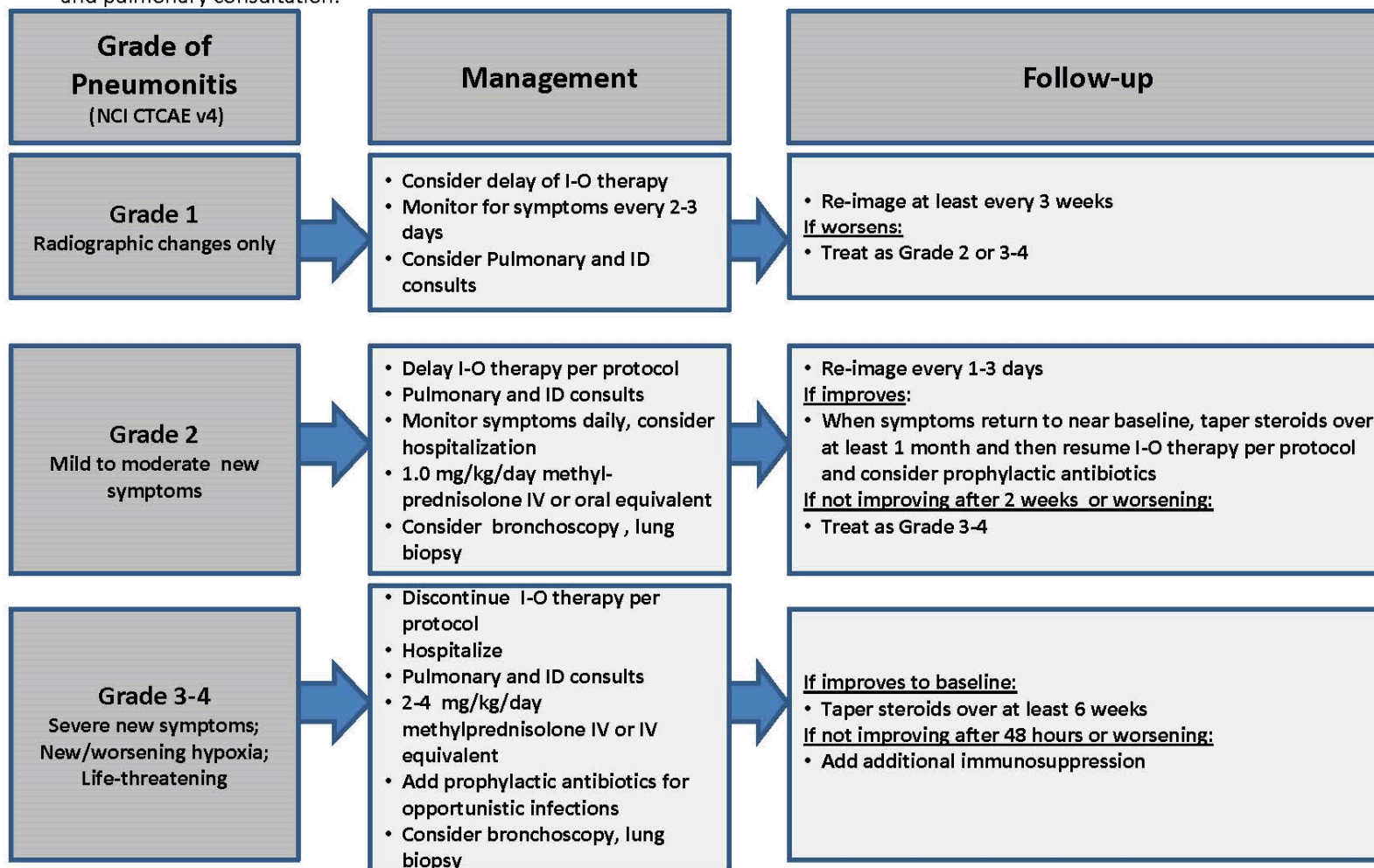
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy



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.

Pulmonary Adverse Event Management Algorithm

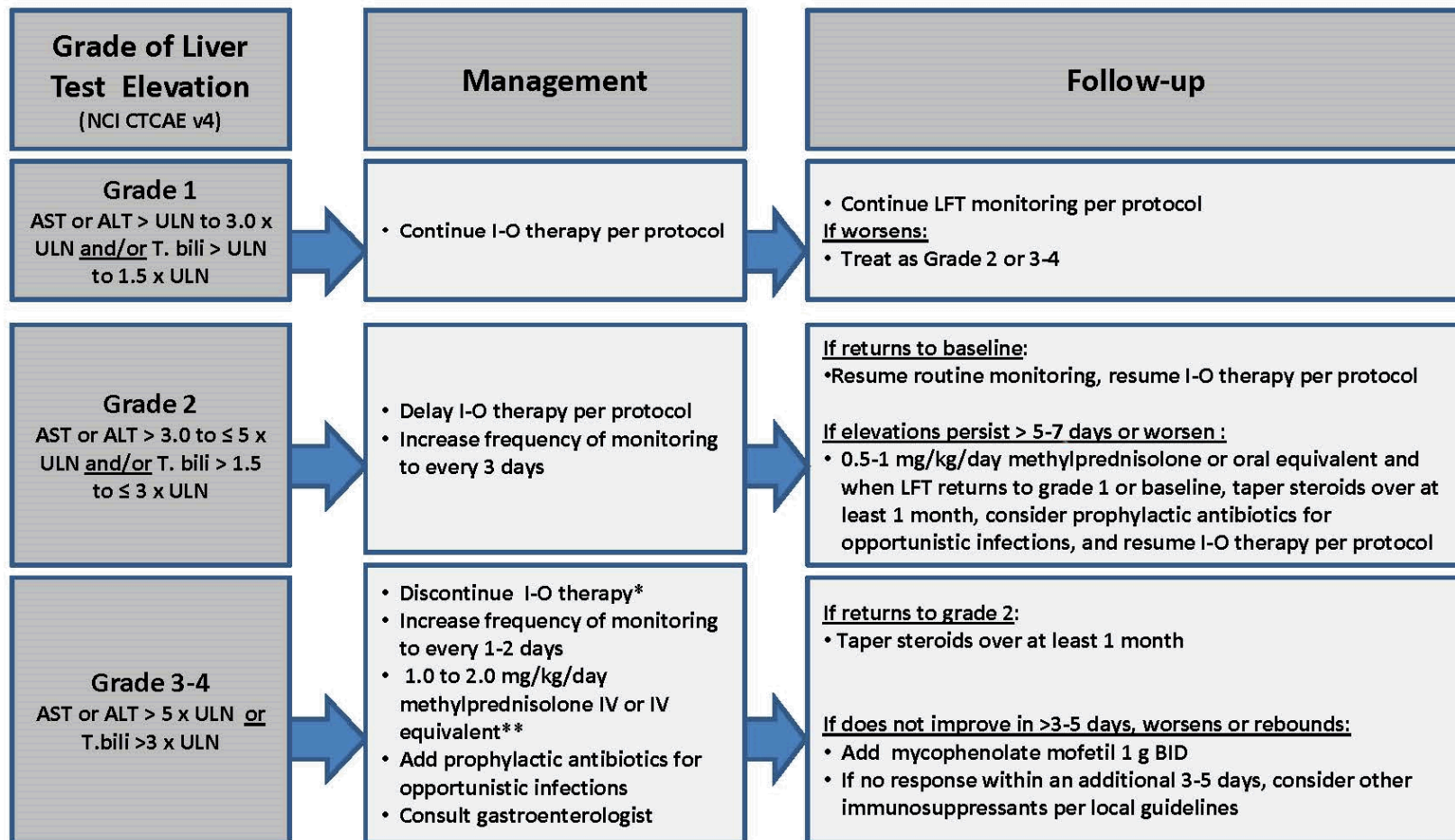
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



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.

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.



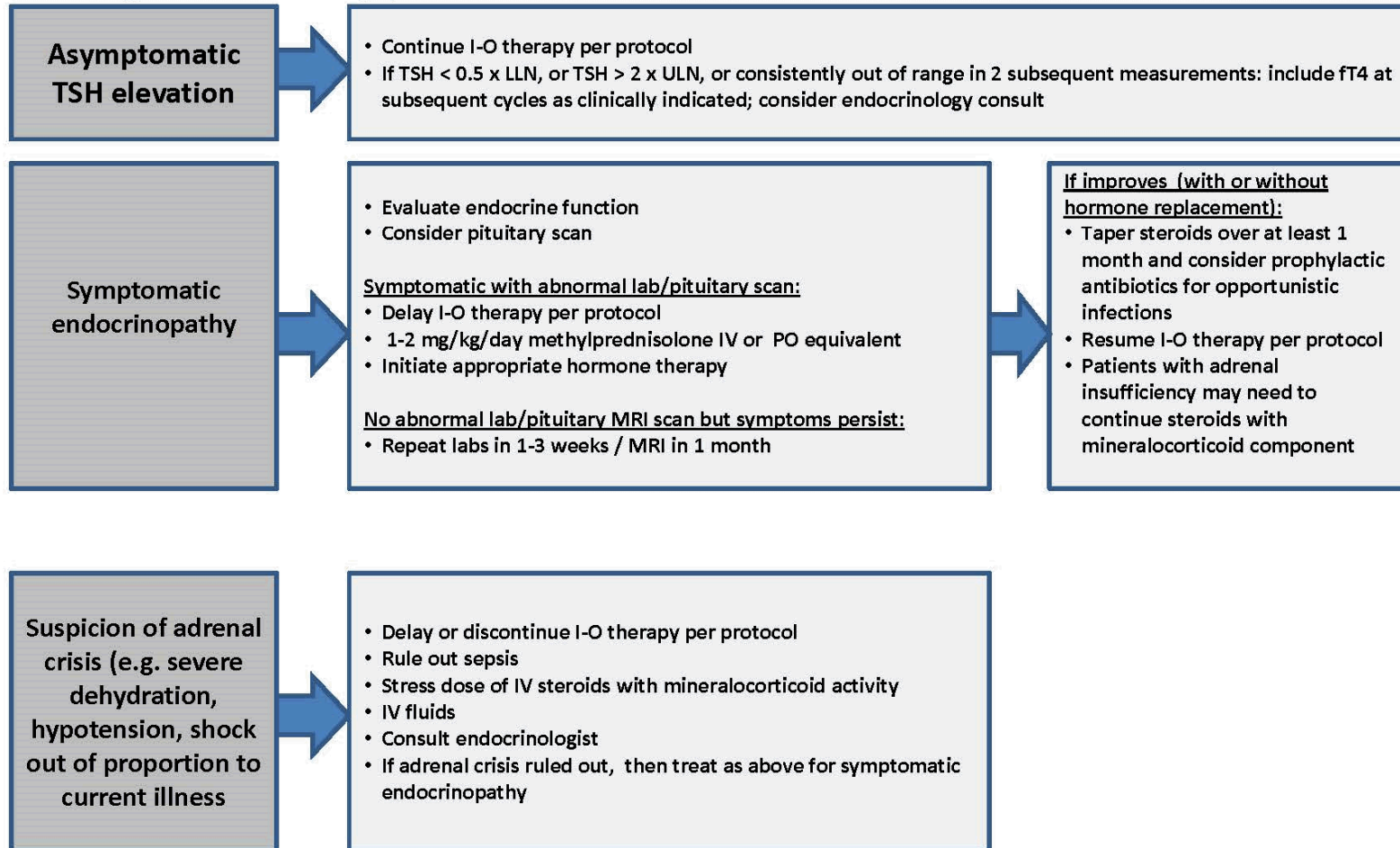
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

*I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN.

**The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

Endocrinopathy Management Algorithm

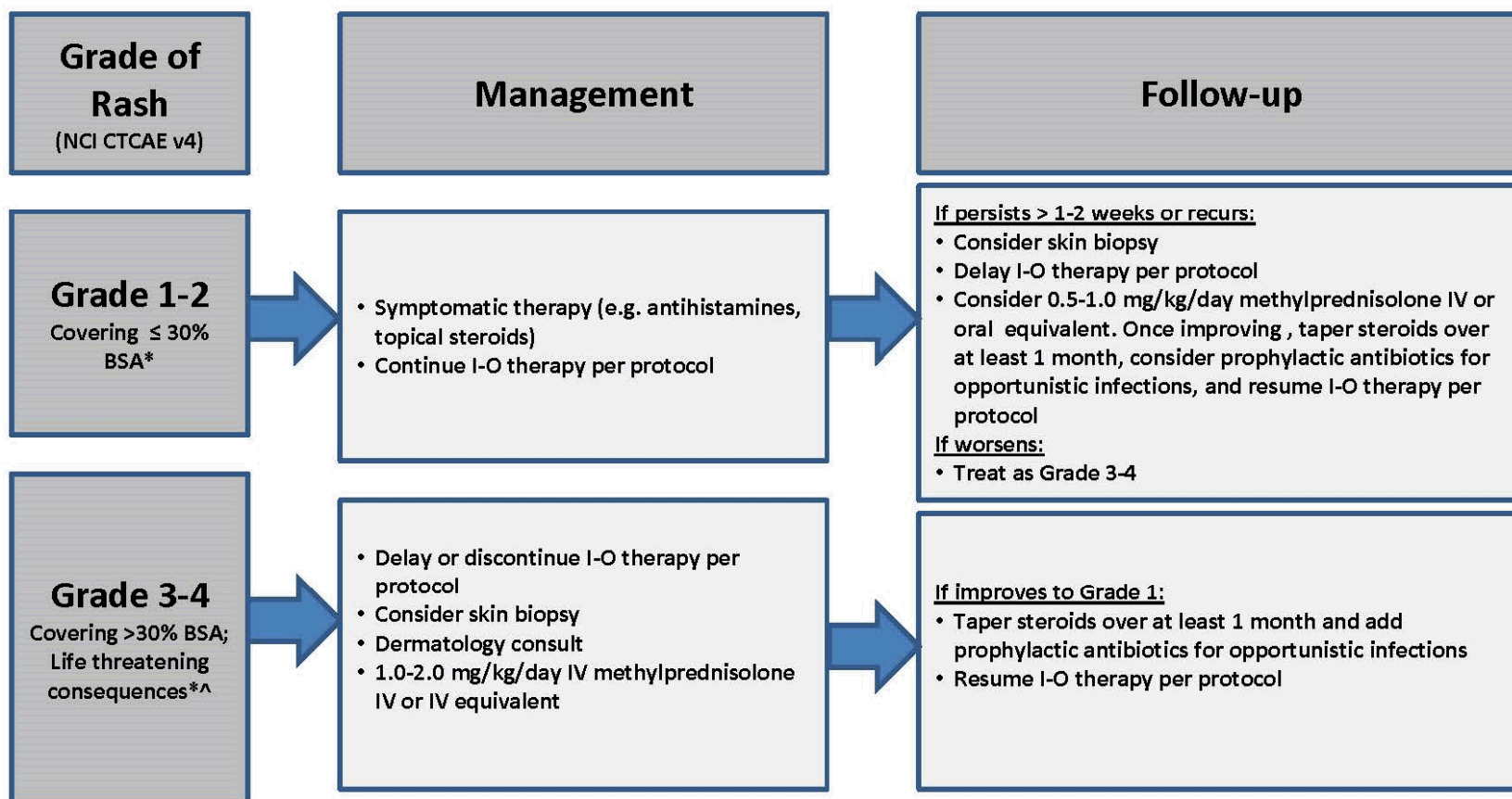
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



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.

Skin Adverse Event Management Algorithm

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



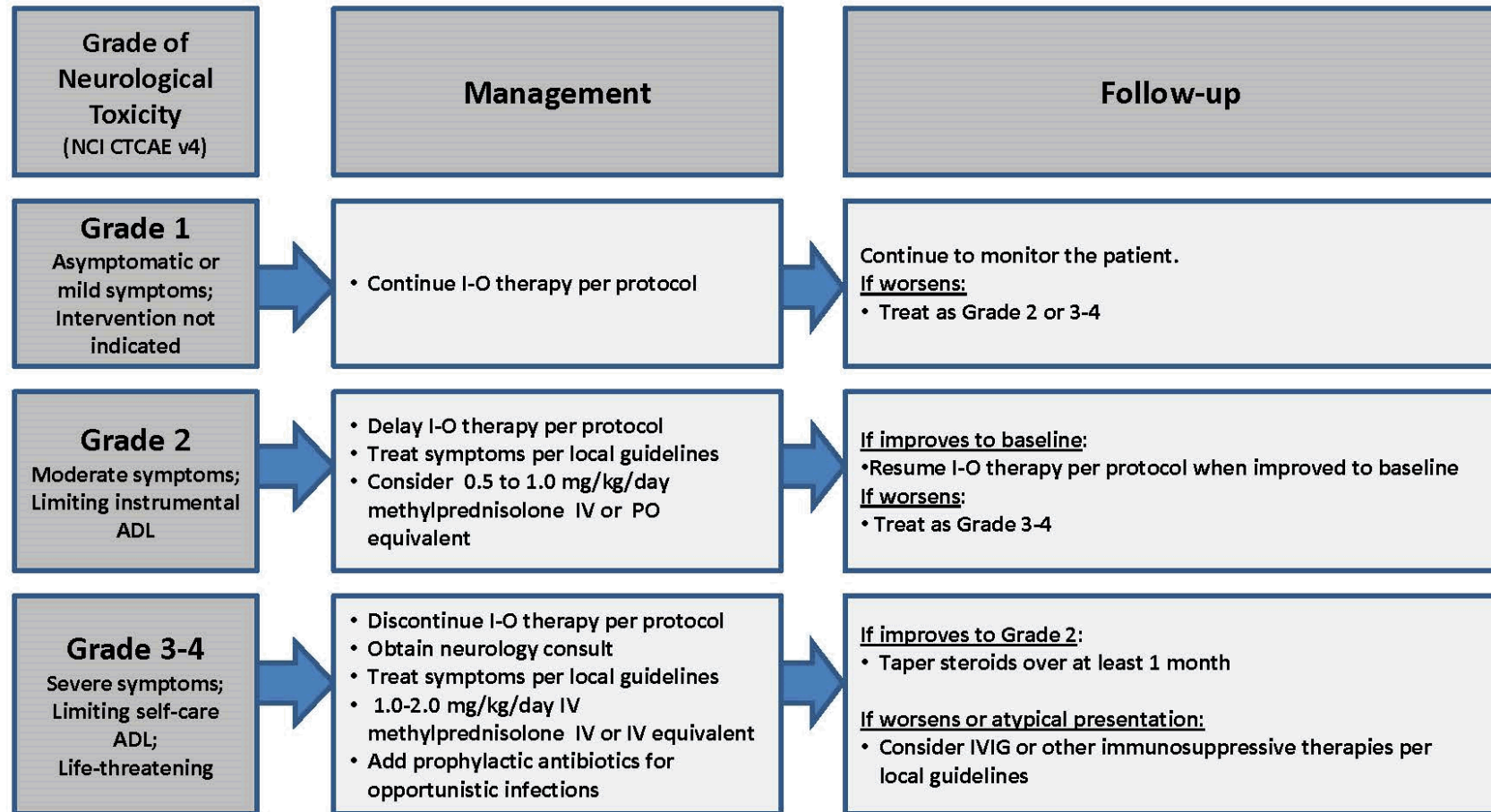
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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.