Protocol for

Official Title of Study

A Phase 1/2a Dose Escalation and Cohort Expansion Study for Safety, Tolerability, and Efficacy of BMS-986156 Administered Alone and in Combination with Nivolumab (BMS-936558, anti PD-1 Monoclonal Antibody) in Advanced Solid Tumors

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Date: 07-Jul-2015
Revised Date 08-Mar-2019

CLINICAL PROTOCOL CA009002

A Phase 1/2a Dose Escalation and Cohort Expansion Study for Safety, Tolerability, and Efficacy of BMS-986156 Administered Alone and in Combination with Nivolumab (BMS-936558, anti PD-1 Monoclonal Antibody) in Advanced Solid Tumors

Revised Protocol Number 05
Incorporates Administrative Letter 04

Study Director and Medical Monitor

[redacted]

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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 05	08-Mar-2019	This revision reflects to following changes: • Incorporates Administrative Letter 04 • Halts all PK, [redacted] immunogenicity, and [redacted] sampling and analyses • Removes the Response and Survival Follow-up Phases • Removes Retreatment option during Survival follow-up • Includes minor typographical changes throughout
Administrative Letter 04	05-Oct-2018	Change in study personnel and synopsis Retreatment section
Revised Protocol 04	22-Nov-2017	The changes in this amendment include extending treatment for up to total of 2 years, or up to 7 additional cycles.
Revised Protocol 03	31-Jan-2017	Incorporates amendment 07
Amendment 07	31-Jan-2017	The changes in this amendment include addition of dose expansion cohorts using every 4 week dosing in cervical cancer and in a multi-tumor type cohort including tumors allowed in dose escalation in combination of BMS 986156 with nivolumab, Clarifies inclusion criteria for the SCCHN, HCC and ovarian cancer cohorts, Updates clinical safety information, Updates the statistical section Updates the contraceptive language [redacted]
Revised Protocol 02	16-Sep-2016	Incorporates Amendment 05
Amendment 05	16-Sep-2016	The purpose of this amendment is [redacted] to make clarifying changes. Provides clarification for further dose options for BMS-986156 Updates sections of the protocol with the latest safety data for BMS-986156 monotherapy and BMS-986156 in combination with nivolumab Clarifies effective methods of contraception Restrict the population of NSCLC subjects to those with progressive or recurrent disease after prior platinum doublet-based chemotherapy Modify inclusion criteria for subjects with bladder cancer and ovarian cancer [redacted]
Revised Protocol 01	18-Jul-2016	Incorporates Administrative Letter 01 Incorporates Administrative Letter 02
Amendment 03	18-Jul-2016	Identification of additional tumor types to be explored during Part D of the study design Revision of tumor types to be explored Starting dose of BMS-936558 in combination with Nivolumab clarified Dose duration of Nivolumab for Part B & D included

Document	Date of Issue	Summary of Change
		[redacted]
Original Protocol	07-Jul-2015	Not applicable

OVERALL RATIONALE FOR REVISED PROTOCOL 05:

This protocol is being revised to halt all PK, [redacted] and immunogenicity sampling activities. It will also remove the retreatment and response survival follow-up phases of the study.

This revision affects all sites and participants going forward.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	Updated study personnel.	New study personnel.
Synopsis	Updated all corresponding sections to the main report sections (listed below).	Rationale for changes included below.
3.1, Study Design and Duration	Removed references to the Response and Survival follow-up phases.	No longer relevant to study.
3.3.1, Safety Follow-up 3.4, Retreatment During Survival Follow-up	Updated study schematic and text to remove references to the Response and Survival follow-up phases and Re-treatment. Deleted entire section on retreatment during survival follow-up.	No longer relevant to study.
3.8, Post Study Access to Therapy	Updated language to supply study drug after study ends.	No longer relevant to study.
3.9.2, Inclusion Criteria	Removed tumor tissue specimen guidance from criterion 2. h).	No longer relevant to study.
3.12, Post Study Drug Follow-up	Revised language to remove OS as an endpoint.	No longer relevant to study.
4.2, Method of Assigning Subject Identification	Deleted reference to Section 3.4.	No longer relevant to study.
5.1, Flow Chart/Time and Events Schedule	Deleted in-text references to and re-treatment tables: Table 5.1-4, Table 5.1-5, and Table 5.1-6.	No longer relevant to study.
Table 5.1-2: On-Treatment Procedural Outline	Added footnote allowing for ad hoc PK or ADA samples for Grade 3 or 4 AEs/SAEs.	Added for safety.
Table 5.1-3: Follow-up Procedural Outline	Deleted columns referencing Response and Survival Follow-up phases (and all corresponding sample collections). Added footnote allowing for ad hoc PK or ADA samples for Grade 3 or 4 AEs/SAEs.	Response and Survival no longer being tracked.
5.3, Safety Assessments	Deleted references to re-treatment tables: Table 5.1-4, Table 5.1-5, and Table 5.1-6.	No longer relevant to study.
5.5.1, Pharmacokinetic and Immunogenicity Collection and Processing Table 5.5.1-1: Pharmacokinetic and Anti-Drug Antibody Sampling Schedule for every 2 week (Q2W) dosing schedule of	Deleted all assessments from Cycle 7 on, including all follow-up assessments. Added Unscheduled option to Adverse event collection.	Assessments past Cycle 5 are no longer relevant. Unscheduled visit allows for safety collection.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
for BMS-986156 and Nivolumab(Parts A, B, C, and D)		
Table 5.5.1-2: Pharmacokinetic and Anti-Drug Antibody Sampling Schedule for every 4 week (Q4W) dosing schedule of BMS-986156 and Nivolumab [Part E - cohort 9 and cohort 10]	Deleted all assessments from Cycle 5 on, including all follow-up assessments. Added Unscheduled option to Adverse event collection.	Assessments past Cycle 5 are no longer relevant. Unscheduled visit allows for safety collection.
Table 5.5.1-3: PK and ADA Sampling schedule for Retreatment (All Parts)	Deleted table.	No longer relevant to study.
[redacted]		
8.4.3, Efficacy Analyses	Deleted last paragraph regarding OS analysis.	No longer relevant to study.
All	Minor formatting and typographical corrections.	Minor, therefore have not been summarized.

SYNOPSIS

Clinical Protocol CA009002

Protocol Title: A Phase 1/2a Dose Escalation and Cohort Expansion Study for Safety, Tolerability, and Efficacy of BMS-986156 Administered Alone and in Combination with Nivolumab (BMS-936558, anti PD-1 Monoclonal Antibody) in Advanced Solid Tumors.

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

BMS-986156 (anti-GITR antibody) is supplied as a sterile 10 mg/mL formulation to be administered as an intravenous (IV) infusion. Nivolumab (BMS-936558, an anti-PD-1 antibody) is available as a sterile 10 mg/mL formulation to be administered as an IV infusion.

Each subject will be administered IV doses of BMS-986156 per the cohort assignment as follows:

In Part A (monotherapy dose escalation), the planned dose levels for BMS-986156 are 10, 30, 100, 240, and 800 mg once every 2 weeks (Q2W), in 8-week cycles, for up to 3 cycles of study therapy.

In Part B, combination therapy dose escalation, the planned dose levels for BMS-986156 are 10, 30, 100, 240, and 800 mg Q2W in combination with nivolumab, which will be administered at a dose of 240 mg Q2W, in 8-week cycles, for up to 3 cycles of study therapy. The Sponsor chose 30 mg BMS-986156 in combination with 240 mg nivolumab as the starting dose in Part B, based on the safety profile of Part A (monotherapy dose escalation). No DLT nor any AE (greater than Grade 1), for which no other cause than the investigational drug could be identified, had occurred.

Starting dose level of BMS-986156 was determined based on safety, pharmacokinetics (PK), [redacted] and is one dose level lower than the dose already tolerated Part A (ongoing monotherapy dose escalation).

In Part C, a monotherapy tumor-specific cohort expansion will be carried out at the BMS-986156 monotherapy dose selected from Part A (monotherapy dose escalation), which may represent the maximum tolerated dose (MTD), maximum administered dose (MAD), or an alternate dose(s). Study therapy will be administered Q2W, in 8-week cycles, for up to 3 cycles.

In Part D, a combination therapy cohort expansion will be carried out using the combination dose of BMS-986156 selected from Part B, 240 mg BMS 986156 in combination with 240 mg nivolumab, Q2W dosing, and may represent the MTD, MAD, or an alternate dose(s) for the combination. Study therapy will be administered Q2W, in 8-week cycles, for up to 3 cycles.

In Part E, a combination therapy cohort expansion, exploring Q4W dosing, will be carried our using the combination dose of 480 mg BMS 986156 with 480 mg nivolumab, in cervical cancer (cohort 9) and other tumor types (Cohort 10). Each cohort in Part E will consist of approximately 40 subjects each. Study therapy will be administered Q4W, in 8-week cycles, for up to 3 cycles.

Study Phase: Phase 1/2a

Research Hypothesis: It is anticipated that anti-GITR antibody (BMS-986156), administered as a single agent or in combination with 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/MAD/alternate dose(s) of BMS-986156 administered alone and in combination with nivolumab in subjects with advanced solid tumors.

Secondary Objectives:

- To investigate the preliminary anti-tumor activity of BMS-986156 administered alone and in combination with nivolumab in subjects with advanced solid tumors
- To characterize the PK of BMS-986156 administered alone and in combination with nivolumab
- To characterize the immunogenicity of BMS-986156 administered alone and in combination with nivolumab, and the immunogenicity of nivolumab administered with BMS-986156.

[redacted]

Study Design:

This is a Phase 1/2a, open-label study of BMS-986156 administered as a single agent and in combination with nivolumab in subjects with advanced solid tumors.

The study will be conducted in 5 parts. Parts A and B will consist of dose escalation with BMS-986156 administered as a single agent (Part A) or in combination with nivolumab (Part B) in subjects with advanced solid tumors. Starting dose selection of BMS-986156 for Part B was determined using all available safety (clinical and laboratory), PK[redacted] data and will be one dose level lower than the already tolerated dose in the ongoing monotherapy dose escalation in Part A (See Section 1.1.4 for details). Subsequently, escalation in the Parts A and B will proceed in parallel.

Nivolumab will be administered as a dose of 240 mg administered Q2W for all combination dose cohorts (Parts B and D).

Nivolumab will be administered as a dose of 480 mg every 4 weeks for combination dose cohorts Part E

Cohort expansions were evaluated with BMS-986156 monotherapy (Part C) and combination therapy (Part D).

Part C consists of cohort expansion with BMS-986156 monotherapy in 2 disease-restricted populations, NSCLC with progressive or recurrent disease (per RECIST v1.1) during or after anti-PD-1 or anti-PD-L1 therapy following prior platinum doublet-based chemotherapy, and persistent, recurrent, or metastatic cervical cancer, of approximately 25 subjects each.

Part D consists of cohort expansion with BMS-986156 administered in combination with nivolumab in disease-restricted populations as follows (i) NSCLC, (ii) cervical, (iii) bladder cancer, (iv) squamous cell carcinoma head and neck, (v) ovarian cancer, and (vi) hepatocellular carcinoma of approximately 40 subjects each.

Part E consists of cohort expansion with BMS 986156 administered in combination with nivolumab in cervical cancer (cohort 9) and other solid tumor types (Cohort 10). Each cohort will contain approximately 40 subjects each.

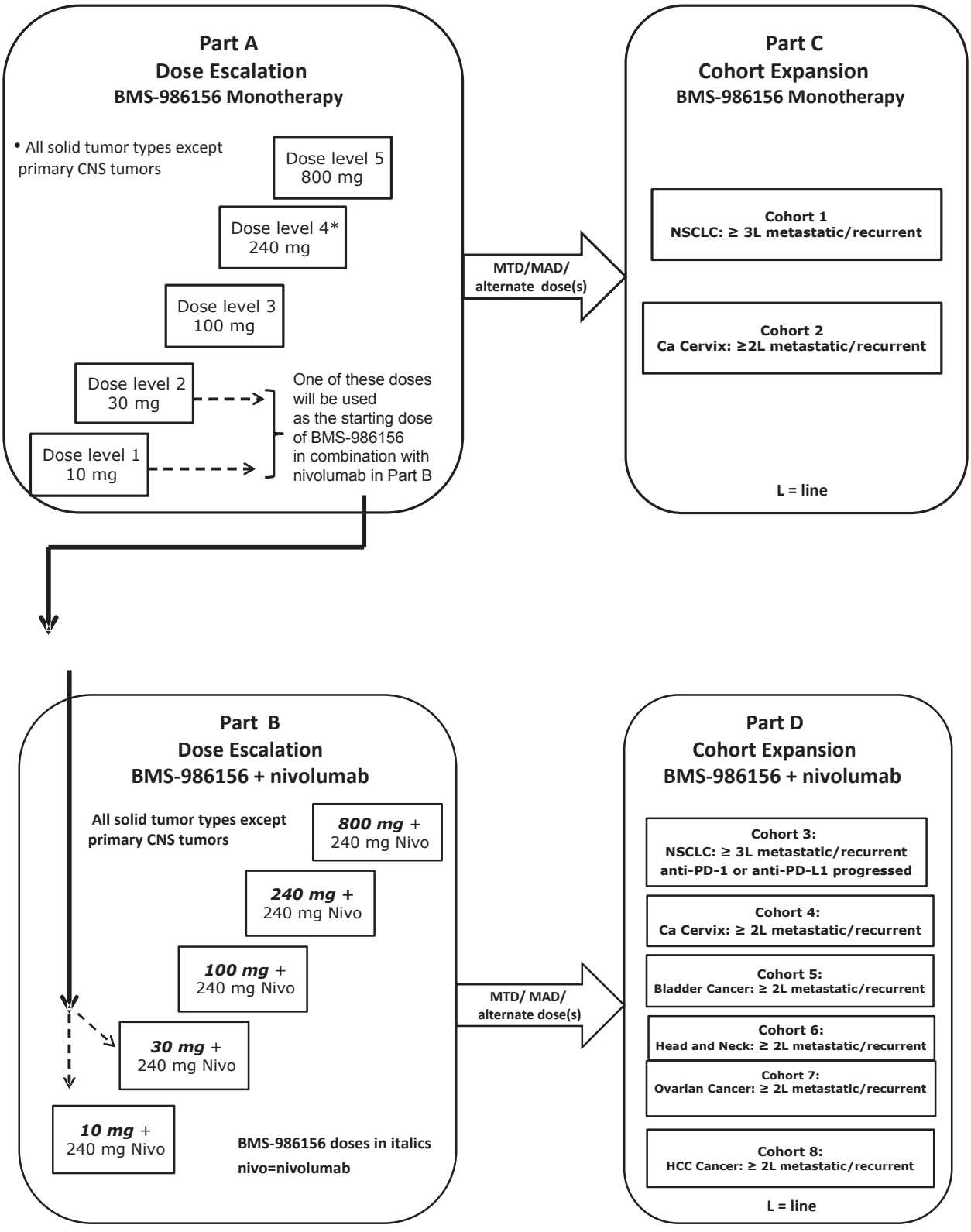
In an effort to limit confounding factors, for all cohorts where applicable, no more than 5 subjects previously found to be “rapid progressors” on anti-PD-1 or anti-PD-L1 therapy will be enrolled per cohort. Rapid progressors are defined as subjects who have progressed as of their first response assessment while on prior PD-1/PD-L1 therapy (if applicable).

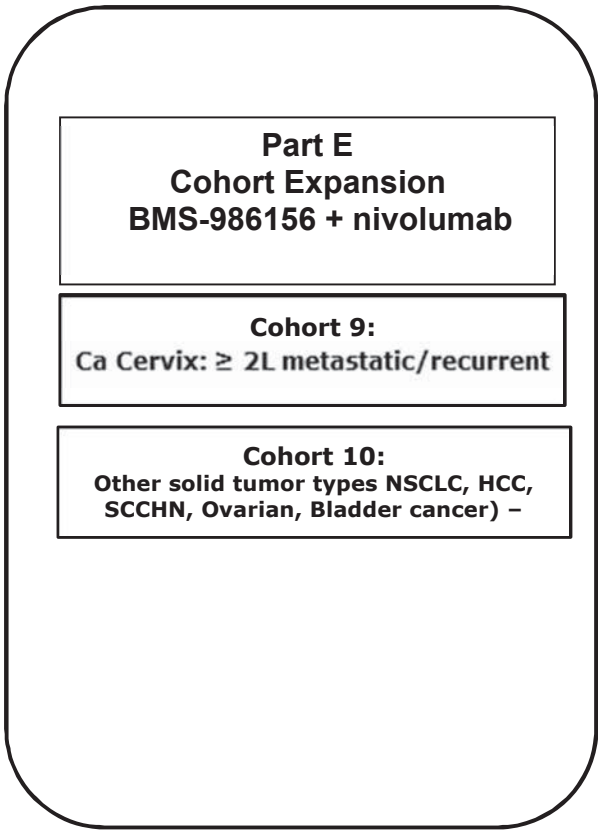
Treatment in Parts C and D will be initiated when the MTD/MAD/alternate dose(s) for monotherapy and combination with nivolumab have each been determined. The doses selected for Parts C and D will not exceed the MTD or MAD

determined in Parts A and B. Treatment in Part E will be 480 mg BMS-986156 with 480 mg nivolumab given every 4 weeks

A schematic of the study is provided in Figure -1.

Figure -1: Study Schematic





Subjects will complete up to 3 periods of the study: Screening, Treatment, and Safety follow-up, as described below:

Screening (up to 28 days): Subjects will sign consent and be evaluated for study eligibility

Treatment Period consists of up to three, 8-week treatment cycles. In Parts A and C, each treatment cycle will comprise 4 doses of BMS-986156 administered Q2W on Days 1, 15, 29, and 43 of the treatment cycle. In Parts B and D, each treatment cycle will comprise 4 doses of BMS-986156 (administered on Days 1, 15, 29 and 43) in combination with 4 doses of nivolumab administered on Days 1, 15, 29, and 43 of the treatment cycle. In Part E, each treatment cycle will comprise 2 doses of BMS-986156 (administered on Days 1 and 29) in combination with 2 doses of nivolumab administered on Days 1 and 29, of the treatment cycle. In Parts B, D, and E when both study drugs are given, nivolumab will be given first followed by BMS-986156 at least 30 minutes after completion of the infusion of nivolumab.

Treatment beyond progression may be allowed in select subjects with initial RECIST v1.1-defined progressive disease (PD) after discussion and agreement with the BMS Medical Monitor that the benefit/risk assessment favors continued administration of study therapy (e.g., subjects are continuing to experience clinical benefit as assessed by the Investigator, tolerating treatment, absence of signs or symptoms indicating disease progression, and do not meet treatment discontinuation criteria as specified in Section 3.12.1).

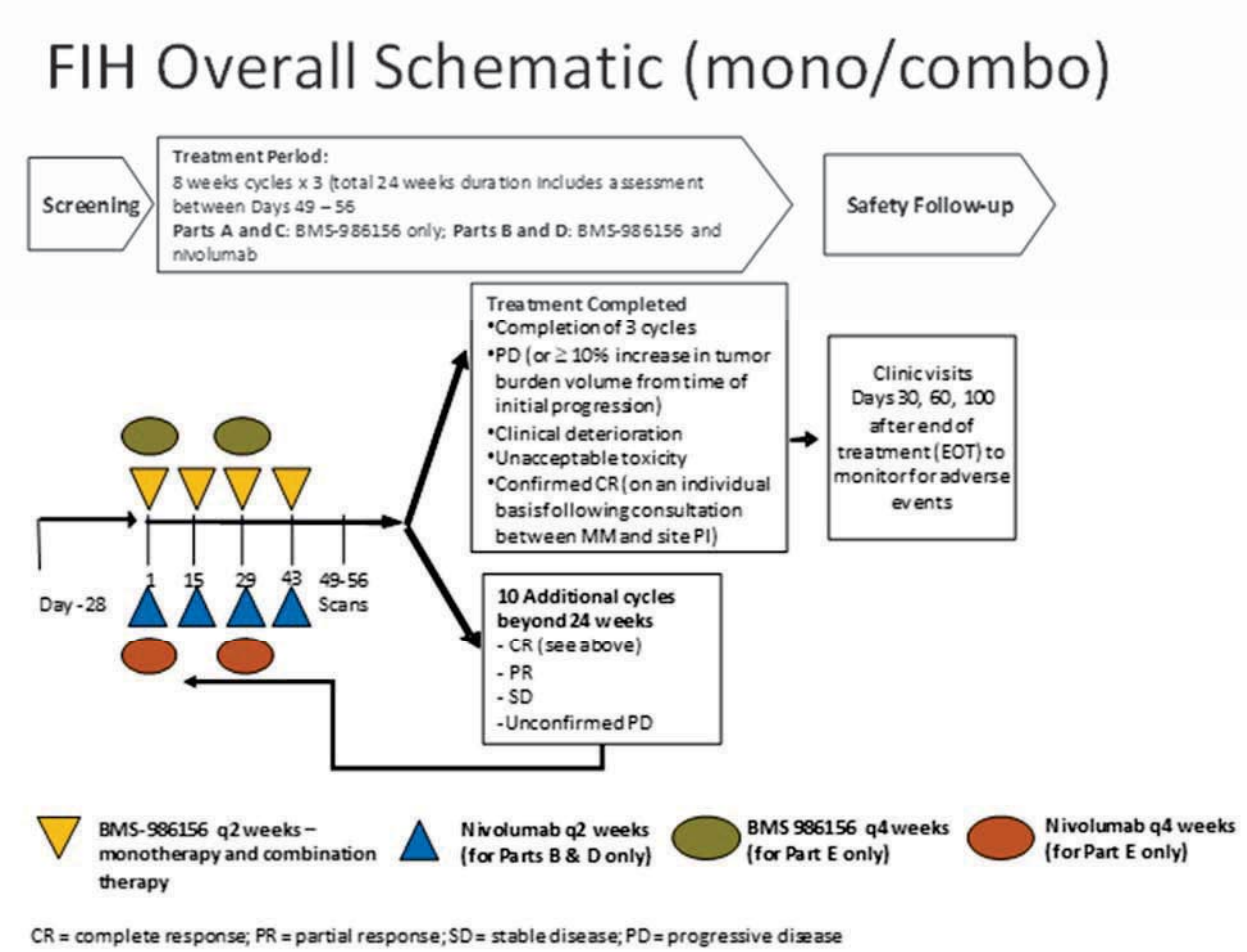
Treatment with Additional Cycles beyond 24 weeks: Subjects completing approximately 24 weeks of treatment with ongoing disease control (complete remission (CR), partial remission (PR) or stable disease (SD) or unconfirmed progressive disease (PD) may be eligible for an additional 3 cycles of study therapy in both monotherapy (Parts A and C) and combination therapy (Parts B and D) beyond the initial 24 weeks, on a case-by-case basis, after careful evaluation and discussion with the BMS Medical Monitor to determine whether the risk/benefit ratio supports administration of further study therapy. All subjects completing approximately 48 weeks of treatment with ongoing disease control (CR, PR or SD) or unconfirmed PD, may be eligible for an additional 7 cycles of study therapy in

combination therapy (Parts D and E) beyond the initial 48 weeks, on a case-by-case basis, after careful evaluation and discussion with the BMS Medical Monitor to determine whether the risk/benefit ratio supports administration of further study therapy.

Safety Follow-up period (100 days following study drug discontinuation): Subjects who discontinue the treatment period will enter a Safety Follow-up period with visits scheduled on days 30, 60 and 100 to monitor for adverse events.

The study design schematic is presented in Figure -2.

Figure -2: Study Schematic for Parts A, B, C, and D



CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease

Dose Escalation

Parts A and B:

The dose-escalation period of the study will evaluate the MTD/MAD/alternate dose(s) of BMS-986156 alone or in combination with nivolumab based on DLTs using a Bayesian Logistic Regression Method (BLRM) (-Copula) model, where the BLRM is designed to guide BMS-986156 monotherapy dose escalation and BLRM (-Copula) is for the dose escalation of BMS-986156 in combination with Nivolumab The Bayesian model will be used for

recommendation of next dose level to be investigated. The BLRM (-Copula) with an overdose control principle (escalation with overdose control)1 will be employed to ensure that safety is not compromised during dose escalation.

The initial dose level of BMS-986156 in Part A will be 10 mg flat dose administered as an IV infusion over 60 minutes every 2 weeks (See Section 1.1.2). Expected dose levels for dose escalation (determined by half log increments from starting dose)[1] are provided in Table -1.

Starting dose selection of BMS-986156 for Part B (combination with nivolumab) will be determined using data available from all doses evaluated in Part A, including clinical and safety laboratory, PK, [redacted] and modeling recommendation within Bayesian hierarchical modeling framework by incorporating single agent toxicity profiles of both BMS-986156 (Part A) and nivolumab (CA209-003, a Phase 1 nivolumab monotherapy data in advanced solid tumors) and will be one dose level lower than a dose already tested and shown to be tolerated in ongoing monotherapy dose escalation in Part A (see Section 1.1.4 for details).

Dose levels considered for the next cohort were be based on evaluating three potential recommendations by BLRM (-Copula): escalate, de-escalate, or stay at same dose level. Final dose selection for next cohort/dose level will be made in conjunction with all data available from all dosed subjects, including clinical and laboratory safety assessments, PK[redacted] data, will not allow escalation by more than one dose level and will be made after discussion and agreement between investigators and BMS medical monitor. Accordingly, intermediate or lower doses, or less frequent dosing of BMS-986156 may be tested if none of the planned doses/schedules are found to be tolerated as monotherapy or in combination with nivolumab.

Cohort tolerability assessment and subsequent dose recommendation will occur according to BLRM (-Copula) recommendation and after completion the 4 week DLT observation period. Continuous re-assessment of dose recommendation by BLRM (-Copula) will be carried out at each dose level.

Approximately 30 subjects each will be treated in dose escalation phases in monotherapy (Part A) and combination therapy (Part B).

No intra-subject dose escalation or reduction is allowed.

Sentinel Subject (Parts A and B only): During dose escalation, a staggered dosing (sentinel subject) approach will be used for the first subject in the first dose level of both monotherapy and combination cohorts. The first subject in both Part A and Part B will receive Cycle 1 Day 1 dose of study drug/s, and be observed for 5 days before additional subjects, i.e. subject two onward in that cohort receive study drug. The first subjects to be dosed in subsequent cohorts will not be required to observe the 5-day interval between treatment start dates.

Table -1: Dose Escalation Schedule for Parts A and B[a b c]

Dose Level	BMS-986156 Part A and Part B	Nivolumab Only Part B
-1	3 mg	240 mg IV Q2W
1	10 mg	240 mg IV Q2W
2	30 mg	240 mg IV Q2W
3	100 mg	240 mg IV Q2W
4	240 mg	240 mg IV Q2W
5	800 mg	240 mg IV Q2W

Abbreviations: IV, intravenous; MAD, maximum administered dose; MTD, maximum tolerated dose; PK, pharmacokinetics; Q2W, every 2 weeks.

[1] Babb 1998; Neuenschwander 2008.

a Additional subjects may be added for a total of up to 12 subjects per selected dose levels to provide additional safety, tolerability and PK data. This information will be incorporated into final recommendation for MAD/MTD/alternate dose(s) of BMS-986156

b Dose -1 (3 mg) will be evaluated if 10 mg (dose level 1) exceeds MTD

c Starting dose for Part B will be one dose level lower than a dose already tested and shown to be tolerated in ongoing monotherapy dose escalation in Part A (Section 1.1.4 for details)

Cohort Expansion (Parts C, D, and E): The purpose of cohort expansion is to gather additional safety, tolerability, preliminary efficacy, PK[redacted] information regarding BMS-986156 as monotherapy or in combination with nivolumab.

Continuous evaluation of toxicity events in the cohort expansions will be performed throughout enrollment in the expansion cohorts. If, at any time, the aggregate rate of treatment-related toxicities meeting DLT criteria exceeds 33% across all subjects treated in the Part C cohort expansions, the findings will be discussed and further enrollment may be interrupted. Depending on the nature and grade of the toxicity and after assessing the risk: benefit ratio, a new dose(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.

Part C consists of cohort expansions with BMS-986156 monotherapy in 2 disease-restricted populations: (i) NSCLC subjects with progressive or recurrent disease (per RECIST v1.1) during or after anti-PD-1 or anti-PD-L1 therapy following prior platinum doublet-based chemotherapy and (ii) persistent, recurrent or metastatic cervical cancer.

Part D consists of cohort expansion with BMS-986156 administered in combination with nivolumab in disease-restricted populations as follows: (i) NSCLC, (ii) cervical, (iii) bladder cancer, (iv) squamous cell carcinoma head and neck, (v) ovarian cancer, and (vi) hepatocellular carcinoma.

In an effort to limit confounding factors, for all cohorts where applicable, no more than 5 subjects previously found to be "rapid progressors" on anti-PD-1 or anti-PD-L1 therapy will be enrolled per cohort.

Rapid progressors are defined as subjects who have progressed as of their first response assessment while on prior PD-1/PD-L1 therapy (if applicable).

Parts E includes two cohorts with one as cervical and another for other solid tumors for signal seeking and exploration of Q4W dosing respectively. Due to the purpose of signal confirming in cervical cancer and heterogeneity of response rates of the other solid tumors cohort (I-O experienced NSCLC, ovarian cancer, bladder cancer, SCCHN, and HCC), approximately 40 subjects are planned for each cohort in part E. For initial safety evaluation of 480 mg BMS-986156/480 mg nivolumab Q4W 6 subjects for a safety lead-in will be enrolled and followed for a minimum of two weeks (refer to Section 3.7 for the rationale for two week period) prior to opening full enrollment of Part E.

Table -2: Expansion Cohorts

Cohorts		Total Subjects (Approximate Number)
Part C: BMS-986156		
1	NSCLC	25
2	Cervical Cancer	25
Part D: BMS-986156 + Nivolumab		
3	NSCLC	40
4	Cervical cancer	40
5	Bladder	40
6	Squamous cell carcinoma head and neck	40
7	Ovarian Cancer	40

Table -2: Expansion Cohorts

Cohorts		Total Subjects (Approximate Number)
8	Hepatocellular	40
Part E: BMS-986156 + Nivolumab		
9	Cervical	40
10	Mixed solid tumor types	40

Abbreviation: NSCLC, non-small cell lung cancer.

Dose-Limiting Toxicity (DLTs): For the purpose of guiding dose escalation, DLTs will be defined based on the incidence and grade of adverse events (AEs) for which no alternate cause can be identified (Section 4.3.1). The incidence of DLTs which occur within 4 weeks following the start of study therapy will guide dose escalation decisions. AEs will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for AEs version 4.03 (CTCAE v4.03). For the purposes of subject management, drug-related AEs occurring at any time which meet the DLT definition will lead to dose interruption and or permanent discontinuation of study drug as defined in Sections 3.7 and 4.3.1.

Part E will consist of an initial safety lead in period of up to 12 subjects. Six subjects need to complete the 14-day observation period before the full expansion cohorts, of up to 40 subjects, are opened. Patients who discontinue for reasons other than disease progression, death, or treatment-related toxicity may be replaced. An observation period of 14 days has been chosen based on pharmacokinetic (PK) modeling and simulation for BMS-986156, based on PK parameters derived from preclinical studies (Section 1.1.5).

Duration of Study: The total duration of time for any individual subject in both monotherapy and combination arms of the study is expected to be approximately 3.1 years.

Number of Subjects: Approximately 310 subjects will be dosed.

Study Population:

Male and/or female subjects who are at least 18 years old, and satisfy eligibility criteria by medical history, physical examination (PE), 12-lead electrocardiogram (ECG), and clinical laboratory evaluations will be included to participate in the study as follows:

For Dose Escalation in Parts A and B: Subjects with any solid tumor type (with the exception of primary central nervous system tumors) are eligible to enroll. All subjects will be required to document availability of archival tumor tissue before study drug is administered. If archival tumor tissue is not available, subjects must consent to a tumor biopsy.

For Cohort Expansion (Parts C, D, and E): Subjects must have one of the tumor types defined above.

[redacted]

Women of childbearing potential (WOCBP) must not be nursing or pregnant and must be using an acceptable method of contraception for at least 4 weeks before dosing. WOCBP must have a negative pregnancy test within 24 hours prior to dosing with study medication.

Study Drug: Includes Investigational Product (IP) as listed:

Study Drug for BMS-986156 and Nivolumab

Medication	Potency	IP/Non-IP
BMS-986156 Injection	100 mg/vial (10 mg/mL)	IP
nivolumab Injection	100 mg/vial (10 mg/mL)	IP

Study Assessments:

- **Safety Outcome Measures**: Safety assessments will be based on comprehensive medical review of adverse event reports, vital sign measurements, ECGs, physical examinations, and results of laboratory tests. AEs will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA) and the incidence of observed adverse events will be tabulated and reviewed for potential significance and clinical importance. Adverse events will be assessed continuously during the study and for 100 days after the last treatment. Both AEs and laboratory tests will be graded using the NCI CTCAE v4.03.

- **Efficacy Measures**: Disease assessment with computed tomography (CT) and/or magnetic resonance imaging (MRI), as appropriate, will be performed at baseline and every 8 weeks until disease progression. Once disease progression is noted, no more protocol required tumor assessments are needed unless treatment is continued beyond progression. For those subjects who continue study therapy beyond initial disease progression, tumor assessments will continue every 8 weeks until confirmed disease progression or study treatment is discontinued. Tumor responses will be derived as defined by RECIST v1.1 based on recorded tumor measurements (see Appendix 3).

- **Pharmacokinetic Measures**: Serial serum samples will be collected from all subjects at specified time points to evaluate concentrations of BMS-986156. PK parameters such as Cmax, Ctrough, Tmax, T-HALF, AUC (TAU), CLT, and accumulation index (AI) will be derived, if feasible, from serum concentration versus time data. [redacted]

- **Immunogenicity Measures**: Serum samples to evaluate development of anti-drug antibody (ADA) response to BMS-986156 alone, and in combination with nivolumab will be collected at specified time points.

[redacted]

Statistical Considerations:

Sample Size:

Dose Escalation:

As a Phase 1 dose-escalation trial, the sample size at each dose in these arms depends on observed toxicity and posterior inference. Approximately 60 subjects are expected to be treated during the dose-escalation phase (around 30 subjects for BMS-986156 monotherapy and around 30 subjects for BMS-986156 in combination with nivolumab). Initially up to 3 subjects will be treated at the starting dose levels of BMS-986156 or BMS-986156 in combination with nivolumab. Additional cohorts of approximately 3 evaluable subjects will be treated in recommended dose levels per BLRM (-Copula) during the dose-escalation phase. At most 12 DLT-evaluable subjects will be treated at each dose level.

Cohort Expansion:

Part E includes two cohorts with one as Cervical and another one as the mixed tumors for signal seeking and exploration of Q4W dosing. Due to the purpose of signal confirming in cervical cancer and heterogeneity of response rates of the mixed tumors cohort, approximately 40 subjects are planned for each cohort in part E. For initial safety evaluation of 480 mg BMS-986156/480 mg nivolumab Q4W in Part E, 6 subjects will be enrolled and followed for a minimum of 2 weeks (please refer to Section 3.7 for the rationale for 2 week period) prior to opening Part E to full enrollment.

The planned sample size for each of the expansion cohorts serve as a guidance. Final decision will be made by the sponsor based on totality of data available by then.

If in a cohort of 40 subjects 10, or 15 responses are observed, then the lower limit of the one-sided 90% exact binomial CI for the ORR is 16%, and 27% respectively. These calculations are made using the Clopper-Pearson method for exact confidence intervals. If the true ORR in a tumor type is 40%, then with 40 subjects in a tumor type, there is 93% chance of observing at least 12 responses, and 87% chance of observing at least 13 responses, and there is 7% chance of observing 11 or fewer responses (false negative rate).

Primary Endpoints:

- The primary objective of the study is to establish MTD/MAD/alternate dose(s). The assessment of safety will be based on the incidence of AEs, serious adverse events (SAEs), adverse events leading to discontinuation, and deaths. In addition clinical laboratory test abnormalities will be examined.

Secondary endpoints:

- The ORR, duration of response, and progression free survival rate (PFSR) at 24 weeks will be assessed based on RECIST v1.1 criteria. The above will be determined based on tumor measurements occurring every 8 weeks during the Treatment Period.
- Pharmacokinetics: Selected BMS-986156 parameters, such as Cmax, Ctrough, Tmax, T-HALF, AUC-(TAU), CLT and AI, will be assessed, if feasible, from concentration-time data during Cycle 1 and Cycle 3.
- Immunogenicity: Incidence of specific ADA to BMS-986156 and or nivolumab. Samples will be collected at multiple time points.

[redacted]

Analyses:

Safety analysis: All recorded adverse events will be coded according to the most current version of MedDRA, listed and tabulated by system organ class, preferred term, treatment arm, and dose level. Vital signs and clinical laboratory test results will be listed and summarized by treatment arm and dose. Any significant physical examination findings and results of clinical laboratory test will be listed. ECG listings will be evaluated by the investigator and abnormalities, if present, will be listed.

Efficacy analysis: Listing of tumor measurements will be provided by subject and study day in each arm and dose level. Individual subject's BOR will be listed based on RECIST v1.1.

To describe the anti-tumor activity of BMS-986156 in single agent and in combination with nivolumab, ORR will be calculated. ORR and corresponding 2-sided exact 95% exact confidence interval by the Clopper and Pearson method will be provided by treatment arm and dose level. Median duration of response and corresponding two-sided 95% confidence interval will be reported by treatment arm and dose level. Duration of response will be analyzed using the Kaplan-Meier method. PFSR at 24 weeks will be estimated by the Kaplan-Meier methodology and the corresponding 90% confidence interval will be presented.

Pharmacokinetic analysis: PK parameters for BMS-986156 will be calculated using non-compartmental analyses. All individual PK parameters will be listed including any exclusions and reasons for exclusion from summaries. Summary statistics will be tabulated for each PK parameters by treatment and study day/week. BMS-986156 PK dose dependency will be accessed in Part A and B. PK scatter plots of Cmax and AUC(TAU) versus dose may be provided for each day measured. Dose proportionality of BMS-986156 when administered alone or co-administered with nivolumab may also be assessed based on a power model. [redacted]

Immunogenicity analysis: Immunogenicity analysis: A listing of all available immunogenicity data will be provided by treatment, dose and immunogenicity status. The frequency of subjects with a baseline and at least one positive anti-drug antibody (ADA) assessment of BMS-986156 or nivolumab will be summarized.

[redacted]

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1 INTRODUCTION AND STUDY RATIONALE

Antibody-based therapy for cancer has become established in recent years and is now one of the most successful and important strategies for treating patients with hematological malignancies and solid tumors.[1] Aside from targeting antigens that are involved in cancer cell proliferation and survival, antibodies can also function to either activate or antagonize immunological pathways that are important in cancer immune surveillance. It is now clear that an antigen-specific anti-cancer immune response is the result of a complex dynamic interplay between antigen-presenting cells (APC), T lymphocyte (T) cells, and the target cancer cells.[2] The critical balance of T-cell activity that dictates whether endogenous anti-tumor immune responses will be effective, are largely understood to be controlled by antigen-specific stimuli sensed by the T-cell receptor and by the combined activity of both positive (co-stimulatory) and negative (co-inhibitory) T-cell surface molecules.[3] Within the past decade, antibodies against these key receptors have been designed and evaluated in the clinic with impressive results, heralding the onset of immunotherapy as a key pillar of anticancer therapy.[4]

The most extensively studied immunotherapies in cancer are the negative regulatory receptors, cytotoxic T lymphocyte associated antigen 4 (CTLA-4), and programmed death-1 (PD-1).[5] Inhibition of these negative regulatory receptors, referred to as immune checkpoint blockade, results in the enhanced activation of T-cell responses and potent antitumor activity in preclinical models. Trials with CTLA-4 blockade provided the first clinical evidence of improvement in overall survival with immune modulatory anticancer therapy in patients with metastatic melanoma.[6,7] Following that, Topalian et al. showed that anti-PD-1 antibody produced objective responses in patients with non-small cell lung cancer (NSCLC), melanoma, and renal-cell cancer (RCC).[8]

Following on the success of CTLA-4 and anti-PD-1 pathway-targeted agents, the field of tumor immunotherapy is beginning to expand rapidly. In addition to blocking co-inhibitory pathways, activating co-stimulatory pathways to potentiate antitumor immune responses is being considered as a promising approach.[9] Members of the tumor necrosis factor receptor superfamily (TNFRsf) include several co-stimulatory proteins with key roles in B and T cell development, survival, immune activation, and antitumor immune responses.[10] Preclinical data have provided the basis for the trial of agonist antibodies to TNFRsf co-stimulatory receptors 4-1BB,[11,12] OX40,[13,14] glucocorticoid-induced TNFR-(GITR)-related gene,[15,16] and CD27[17,18] as potential therapies for patients with cancer. Overall, enhancement of the magnitude and potency of tumor antigen-specific adaptive cellular responses by CD8 and CD4 T cells is now considered a major goal in cancer immunotherapy.

With these recent emerging clinical lines of evidence of significant activity of single agent immunotherapies, it is possible that combination therapies could potentially lead to greater depth of response and overall survival as has been noted with the combination of anti-PD-1 and anti-CTLA4 in advanced melanoma patients.[19 20] This raises the possibility that combining strategies

involving a broader range of immunotherapies, e.g. checkpoint blocking antibodies with antitumor immune pathways such as agonist antibodies to T-cell co-stimulatory molecules, could potentially lead to durable, long term responses and possibly even cures in this high unmet medical need population of patients with metastatic or refractory tumors. Pre-clinical data from evaluation of combinations in mouse tumor models indicate that treatment with the combination of both agents can lead to enhanced antitumor activity above that from each agent alone[21] Patients with metastatic or refractory tumors have a very poor prognosis.[22] Traditional or conventional treatment options for patients with advanced cancer include surgery, radiation, chemotherapy, hormone therapy, and immunotherapy, all of which have differing mechanisms of action. Despite advances in multimodal therapy, increases in overall survival in this patient population have been limited.

CA009002 is a Phase 1/2a, first-in-human (FIH), ascending multiple-dose study of BMS-986156, an anti-GITR agonistic antibody, in humans with advanced/metastatic solid tumors as monotherapy and in combination with nivolumab. This study will evaluate the safety profile, tolerability, preliminary efficacy, PK, [redacted] of intravenous (IV) doses of BMS-986156 administered every 2 weeks as monotherapy and in combination with nivolumab in advanced solid tumors and is expected to determine the maximum tolerated dose (MTD)/maximum administered dose (MAD) or an alternate dose(s) of BMS-986156 to be used in future monotherapy and combination with nivolumab therapy trials. In addition, the study will evaluate BMS-986156 as monotherapy and in combination with nivolumab in the following disease-restricted populations, as follows: NSCLC with progressive disease during, or recurrent disease, during or after anti-PD-1 or anti-programmed death-ligand (PD-L1), and persistent, recurrent, or metastatic cervical cancer. Additional tumor types are bladder cancer, head and neck squamous cell cancer, ovarian cancer, and hepatocellular carcinoma (HCC) (see Section 3.9.1).

Non-Small Cell Lung Cancer

Non-small cell lung cancer remains the leading cause of cancer-related mortality worldwide, accounting for approximately 18% of all cancer deaths.[23] Lung cancer is also the leading cause of cancer death in the US. In 2014, an estimated 224,210 new cases were expected to be diagnosed, and 159,260 deaths are estimated to occur because of the disease, accounting for 27% of all deaths due to cancer.[24]

Most lung cancers (~ 80%) are NSCLC.[25] Of these patients, more than 65% present with locally advanced or metastatic disease.[26] Despite treatment with platinum-based chemotherapy, the standard of care for first-line therapy, patients with metastatic NSCLC have a median survival of approximately 10 months and a 5-year survival rate of less than 5%,[27] and treatment options for epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) wild-type NSCLC are particularly limited after failure of front-line chemotherapy. Overall, this group of patients only has an OS of about 8 months after progression from platinum agents. Once resistance to tyrosine kinase inhibitors (TKIs) occurs, the patients who have EGFR mutations or ALK translocations often have a rapid disease progression.

Recently, nivolumab was approved for the management of advanced squamous and non-squamous NSCLC after there was demonstrable survival difference compared to chemotherapy.[28] However, the possibility that combining anti-PD-1 antibody with other agents could potentially lead to deeper and more durable long term responses in high PD-L1 expressing tumors and possibly even cures in this high unmet medical need population of patients with NSCLC provides additional rationale for evaluating novel combinations in this disease.

Carcinoma of the Cervix

Cervical cancer remains a considerable problem worldwide with 500,000 new cases and 250,000 deaths annually.[29] In 2014, in the US, an estimated 12,360 new cases were expected to be diagnosed, and 4,020 deaths are estimated to occur because of the disease.[30] Treatment for cervical cancer is typically surgery for Stages IA to IIA1 and concurrent chemoradiation for Stages IB2 to IVA. The 5-year survival rate for cervical cancer depends on stage and ranges from 93% for early stage disease (IA) to around 15% for Stages IVA and B.[31] Treatment of recurrent disease is typically with surgery for resectable disease or chemotherapy plus bevacizumab, which improved objective response rate (ORR), (48% vs. 36%) and mOS (17 vs. 13.3 months) compared to chemotherapy alone.[32] After first line chemotherapy, there is no standard of care that has demonstrated improved benefit over best supportive care.

Bladder Cancer

Bladder cancer is the ninth most common cancer in the world, with 430,000 newly diagnosed in 2012.[33] In the United States (US), approximately 77,000 new cases and 16,000 deaths occur each year due to bladder cancer.[34] In Europe, there were an estimated 118,000 cases and 52,000 deaths in 2012.[35] In developed regions such as North America and Europe, the histological phenotype is predominantly urothelial carcinoma.

From 1985 to 2005, the number of bladder cancers diagnosed in the US increased by more than 50%, while from 1975 to 1996, the five-year survival rate for those diagnosed with bladder cancer increased from 75% to 81%.[36] Mortality rates in several western European countries have shown similar downward trends over the last two decades but are still increasing in some eastern European countries.[36]

Many bladder cancer patients do not die of their disease but do experience multiple recurrences. As a consequence, there are a relatively large number of people alive with a history of bladder cancer. In middle-aged and elderly men, bladder cancer is the second most prevalent malignancy after prostate cancer.[37]

Squamous Cell Carcinoma Head and Neck

There are large geographic differences in the incidence and primary site of head and neck cancers. These likely reflect the prevalence of risk factors, such as tobacco and alcohol consumption, as well as ethnic and genetic differences among populations.

Although the highest rates of head and neck cancer are in older males, the incidence has been increasing in females as more women use tobacco, and in young non-smokers as human papillomavirus (HPV) plays an increasingly prominent role as an etiologic factor in the development of oropharyngeal head and neck cancer.

Tobacco (smoked and smokeless) is the most important known risk factor for the development of head and neck cancer. There is some evidence for a genetic predisposition to the carcinogenic effects of tobacco. In addition, tobacco and alcohol consumption appear to have a synergistic effect. The repeated exposure of the mucosa of the upper aerodigestive tract to the carcinogenic effects of tobacco, alcohol, or both appears to cause multiple primary and secondary tumors in this "condemned mucosa," a phenomenon described as "field cancerization."

HPV infection is a causative agent for head and neck cancer. HPV-associated head and neck cancers occur primarily in the oropharynx (tonsils and base of tongue), account for the younger age of patients with oropharyngeal squamous cell carcinoma, and define a subset of patients with improved treatment outcome. However, the use of HPV status in clinical decision making remains investigational at this time, and treatment is the same as for patients without an HPV-associated tumor.[38,39,40,41,42,43,44]

Ovarian Cancer

The term ovarian cancer (OC) includes not only epithelial OC but also primary peritoneal and fallopian tube cancer. The latter two are less common neoplasms, which, however, are managed in a similar manner to epithelial OC. Epithelial OC is the leading cause of death from gynecologic cancer in the US and is the country's fifth most common cause of cancer mortality in women. Nearly 75% of the patients present with advanced-stage OC.[45] According to the International Federation of Gynecology and Obstetrics, 5-year survival rates are approximately 46.7% for Stage IIIa, 41.5% for Stage IIIb, 32.5% for Stage IIIc, and 18.6% for Stage IV. Patients with platinum sensitive OC treated with platinum-based frontline therapy have high response rates of up to 81% and median progression free survival (mPFS) and mOS of 19.1 and 44.1 months, respectively.[46] However, patients with subsequent relapses, either platinum sensitive or resistant, have a significantly worse prognosis with mPFS between 10.2 and 4.1 months and mOS between 17.6 and 5.0 months, respectively,[47] Immunotherapy with weekly intraperitoneal IL 2 produced a ~17% complete pathologic response rate in patients with platinum-resistant OC.[48] A threefold prolongation of PFS was observed in patients treated with recombinant human IFN-γ combined with MTD cisplatin and cyclophosphamide chemotherapy, with minimal added toxicity.[49,50] The presence of tumor-infiltrating lymphocytes (TILs) in advanced-stage OC correlates with an improved outcome. Patients with Stage III and IV OC and the presence of TILs within the tumor had better disease free survival and OS ($P < 0.001$) than did patients with similar staged OC and absence of TILs.[51]

Hepatocellular Carcinoma

Hepatocellular carcinoma is the fifth most common cancer worldwide and the second leading cause of cancer-related death. The incidence of HCC varies geographically largely due to variations in hepatitis B and C virus infection.

HCC has the highest mortality-to-incidence rate ratio of 0.98, followed by lung (0.85) and esophageal (0.83) cancers.[52] The number of deaths is close to the number of new cases because most HCCs are detected at an advanced stage and occur in patients with underlying liver dysfunction, making HCC a highly lethal cancer. The prognosis is also poor because of the low effectiveness of available treatments. The 5-year HCC survival rate is approximately 5% to 6% compared with 72% and 22% for breast cancer stages III and IV, respectively.[53,54,55] Treatment of HCC is challenging because the disease is highly heterogeneous with different etiologies and because of varying approaches to diagnosis and treatment and variations in responses to therapy.[56]

Relatively few patients are eligible for curative treatment because of the late appearance of symptoms.[57] The majority of patients are diagnosed in the advanced stages of the disease when the disease is beyond resection and locoregional treatments are ineffective. The prognosis for these patients is poor.[58]

GITR: Immune Activation by T cell Costimulation and Regulatory T cell Suppression

GITR protein (also known as TNFRsf18) was first identified as a dexamethasone-inducible molecule on a murine T cell hybridoma.[59] GITR is a type I transmembrane protein belonging to the TNFRSF including OX40, CD27, and CD137. These receptors are costimulators of T cell activity and with T cell receptor engagement result in T cell activation.

GITR is expressed on naive murine T cells but shows little expression on naive human T cells.[60] GITR is expressed upon activation of CD8 and CD4 effector T (Teff) cells, but is constitutively expressed on regulatory T (Treg) cells. In normal human peripheral blood mononuclear cells (PBMCs), GITR expression on Treg cells is higher than on conventional T cells, and while expression on resting CD4+ T cells was low it markedly increased after activation.[61] It is also expressed on natural killer (NK) cells and at low levels on B cells, eosinophils, basophils, macrophages and dendritic cells, and can be upregulated by activation.[62,63,64,65,66,67,68] GITR ligand is found largely on APCs.[69]

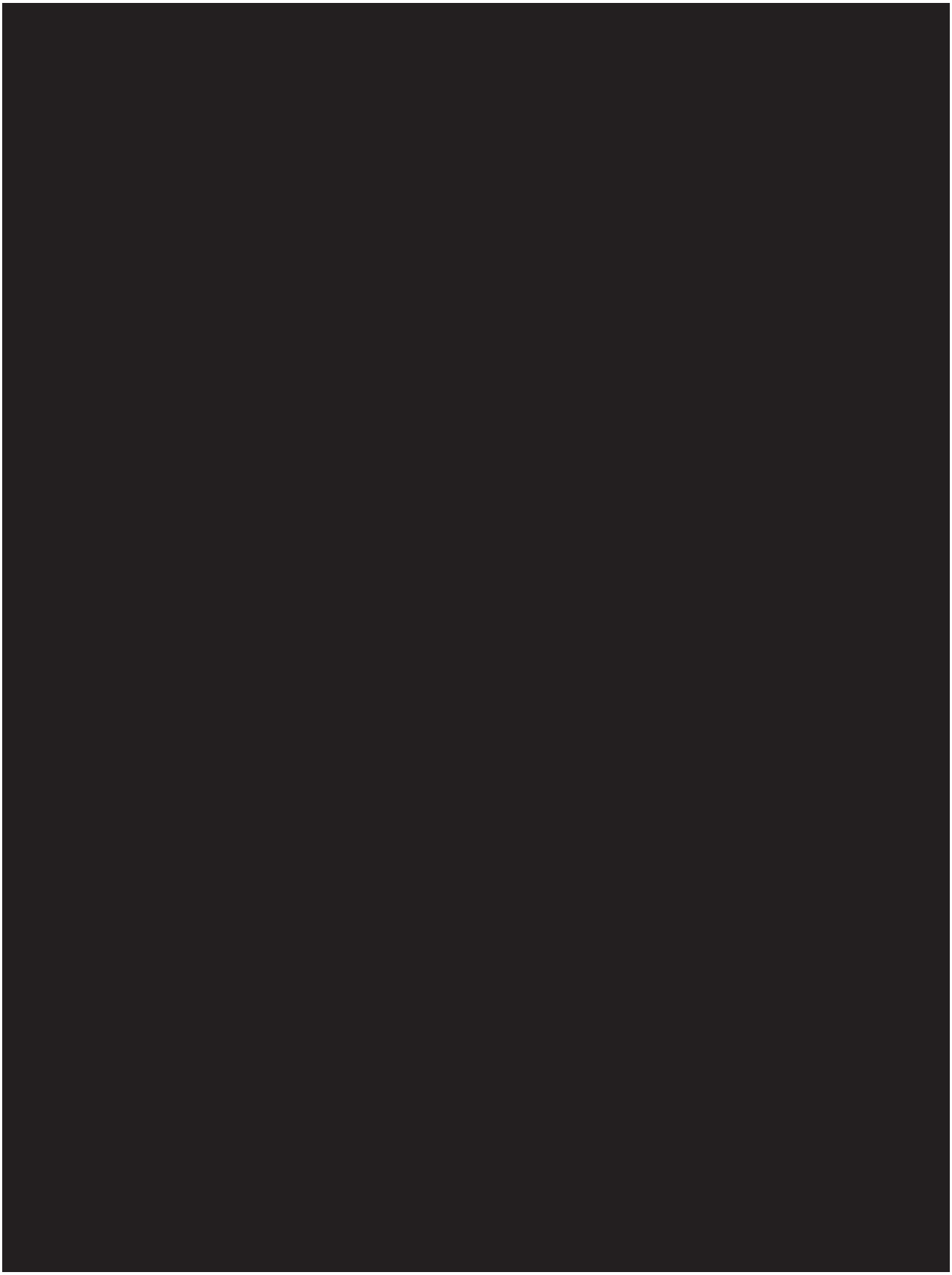
GITR engagement on CD8 T cells has been shown to have an intrinsic effect of potentiating CD8 T cell activity.[70,71] Additionally, GITR engagement has an intrinsic effect on CD8 T cell expansion.[72.] Consistent with its role in costimulation, GITR engagement promotes autoimmunity in autoimmune-prone mouse strains [73] similar to that observed upon blockade of the PD-1 pathway.[74] GITR signaling results in reduced T cell apoptosis and promotes T cell survival, at least in part by upregulating the expression of the Bcl-xL prosurvival molecule downstream of NFκB.[75]

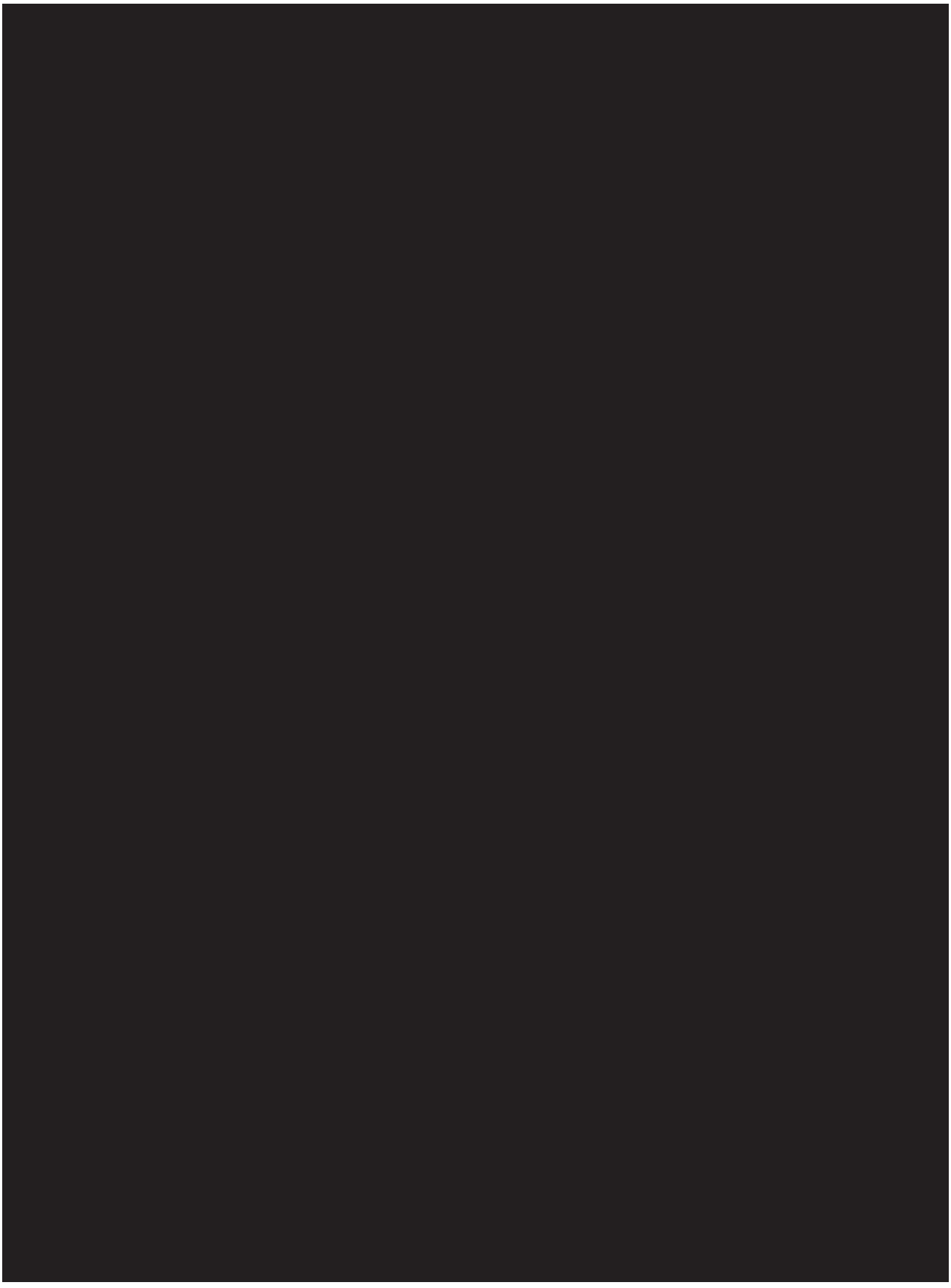
While Treg cells antagonize effector T cells, thereby limiting antitumor activity, engagement of GITR on Teff cells promotes increased T cell function by limiting the sensitivity of these cells to Treg suppression. Stephans et al mixed irradiated T-cell depleted splenocytes and anti-CD3, and Teff and Treg cells isolated from WT or GITR-deficient (GITR-/-) mice, showing that GITR agonism renders Teff cells resistant to Treg suppression.[76] In addition, in certain circumstances engagement of GITR on intratumoral Treg cell may result in diminished suppressor activity. NK cells also express low levels of GITR, which can be up regulated by interleukin (IL)-2 and IL-15.[77] The consequences of GITR engagement on NK cells in antitumor responses remains to be determined because of conflicting data as to whether engagement increase [78] or decreases NK cell activity.[79]

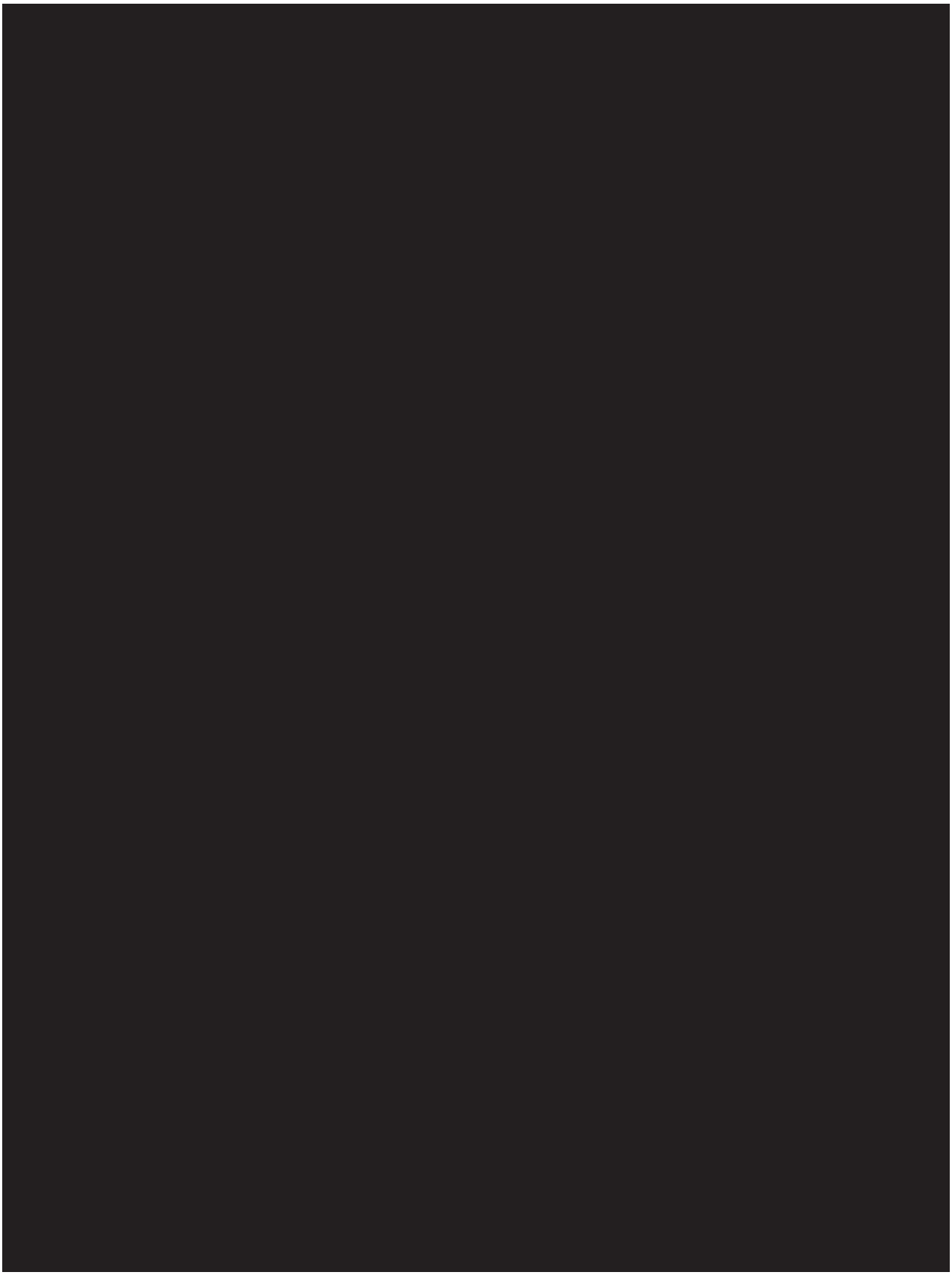
Rationale for BMS-986156 therapy

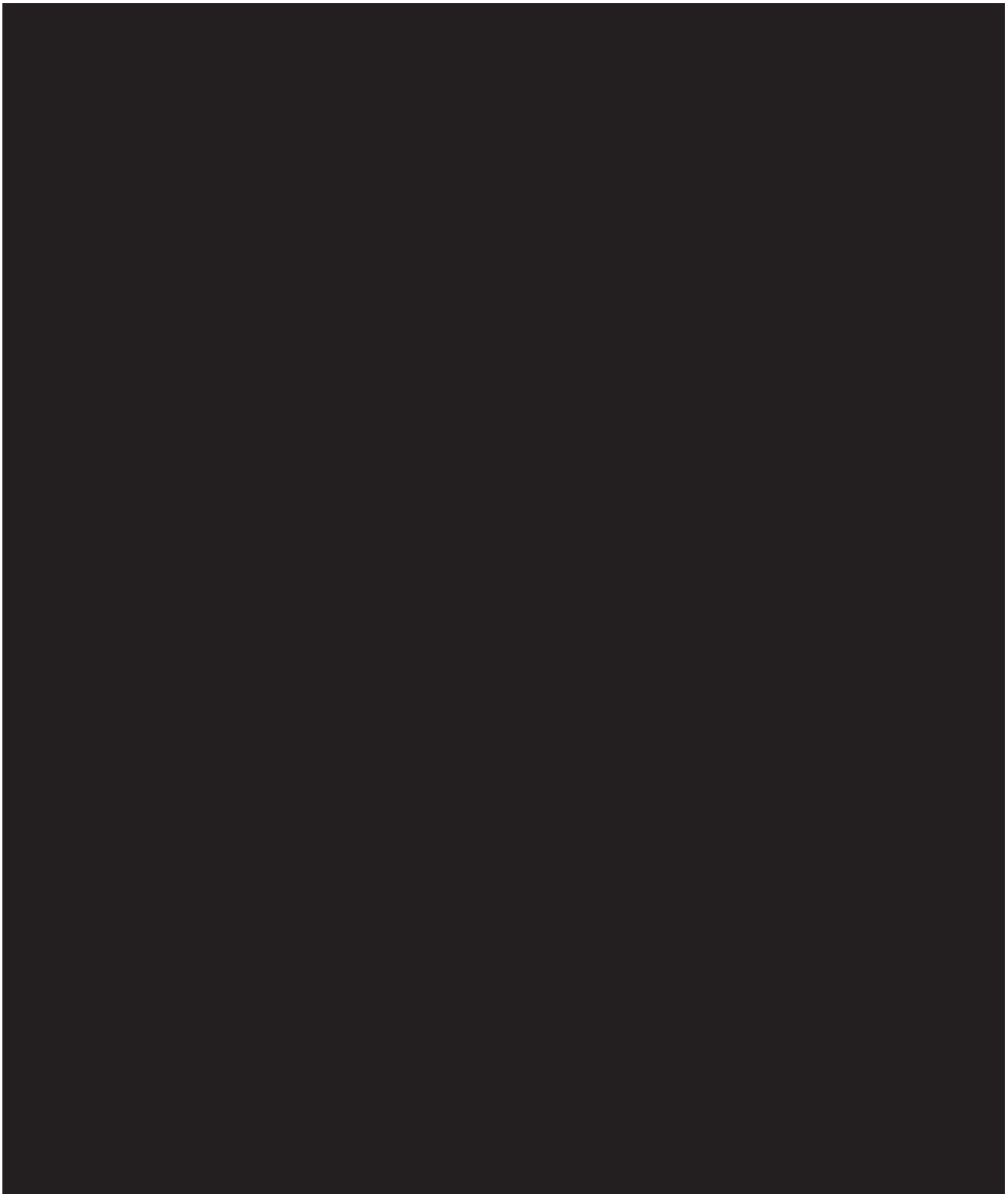
BMS-986156 is a fully human agonist antibody of the IgG1 isotype that binds with high affinity to the human GITR family related receptor. [redacted]

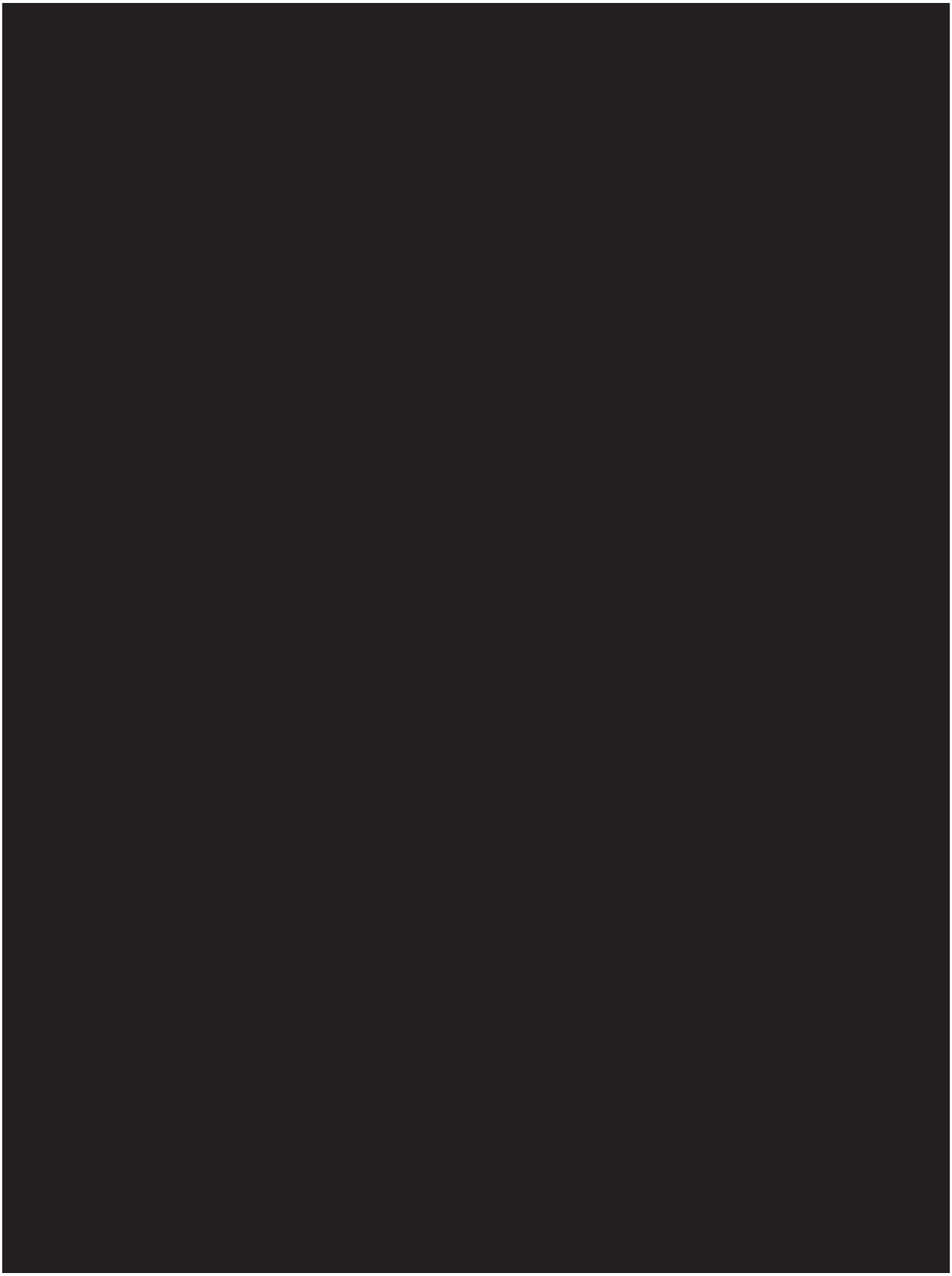
[redacted]

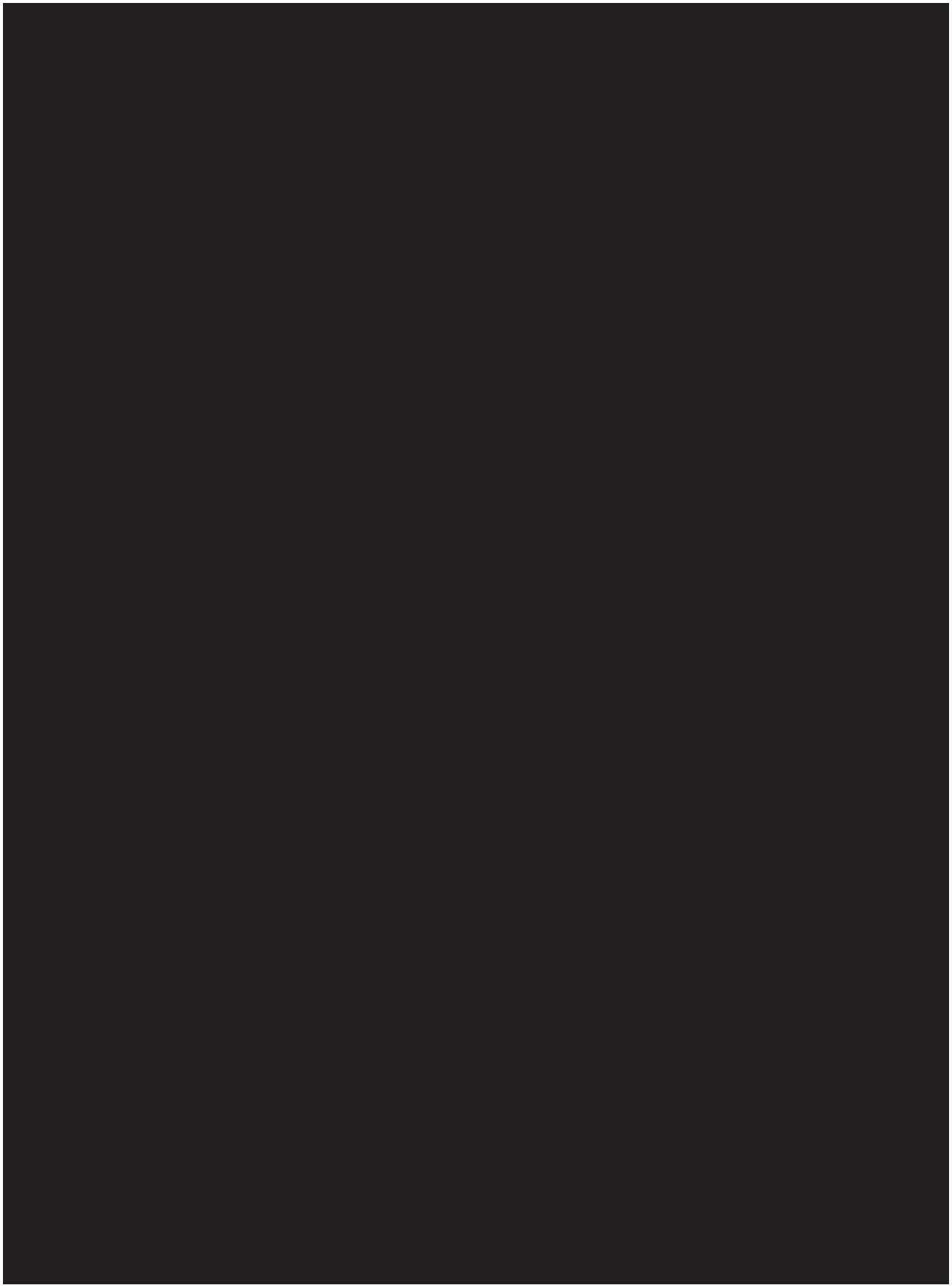


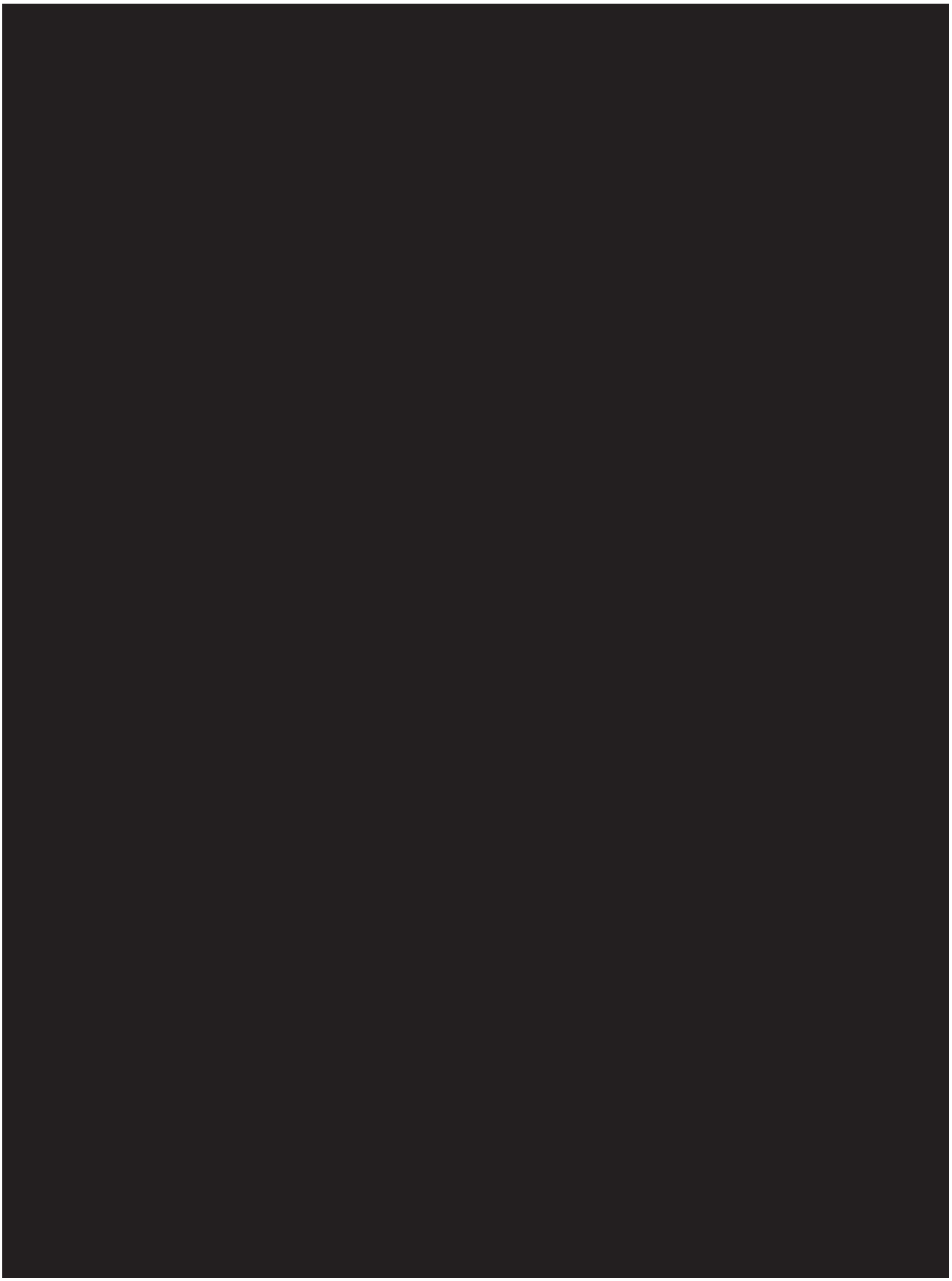


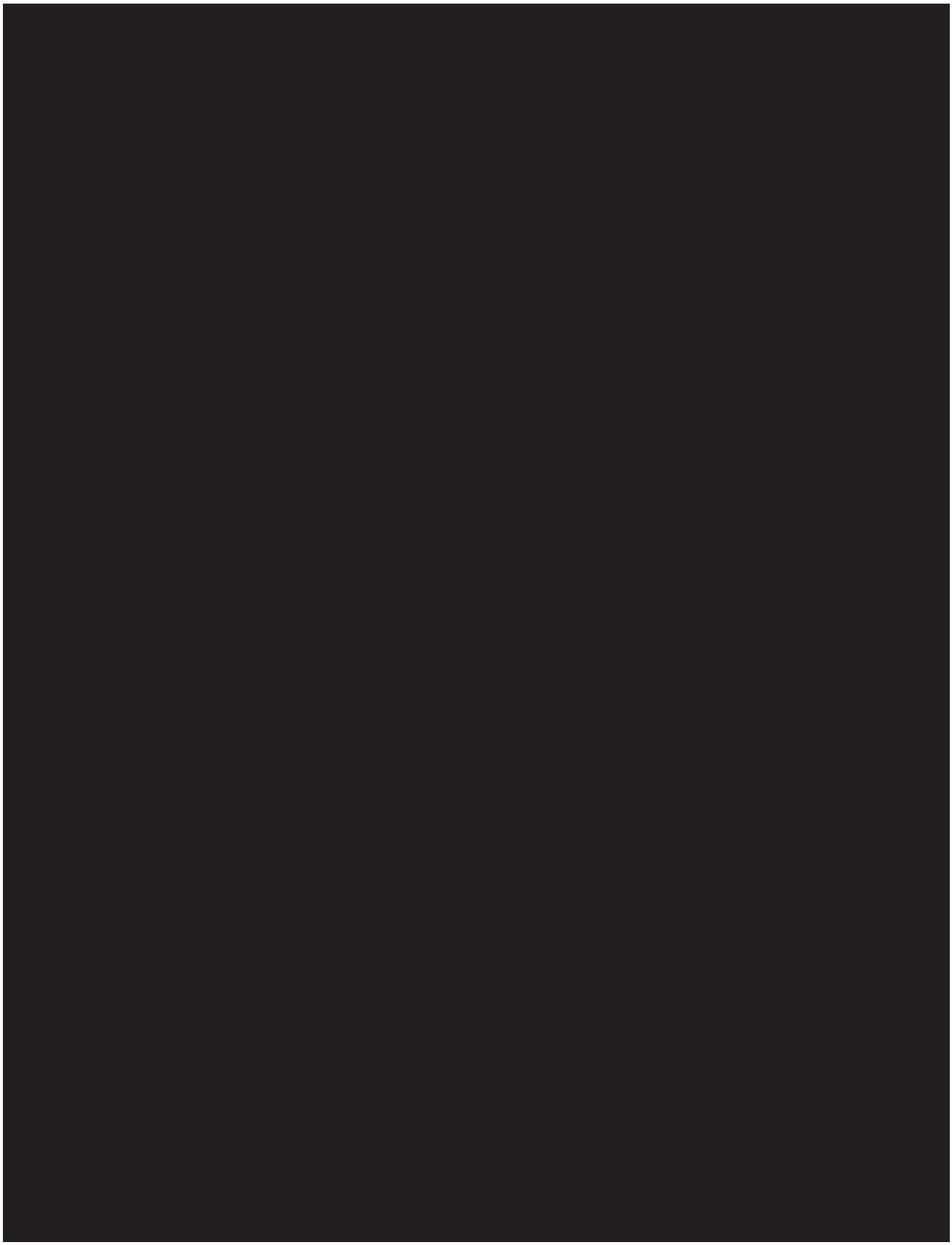


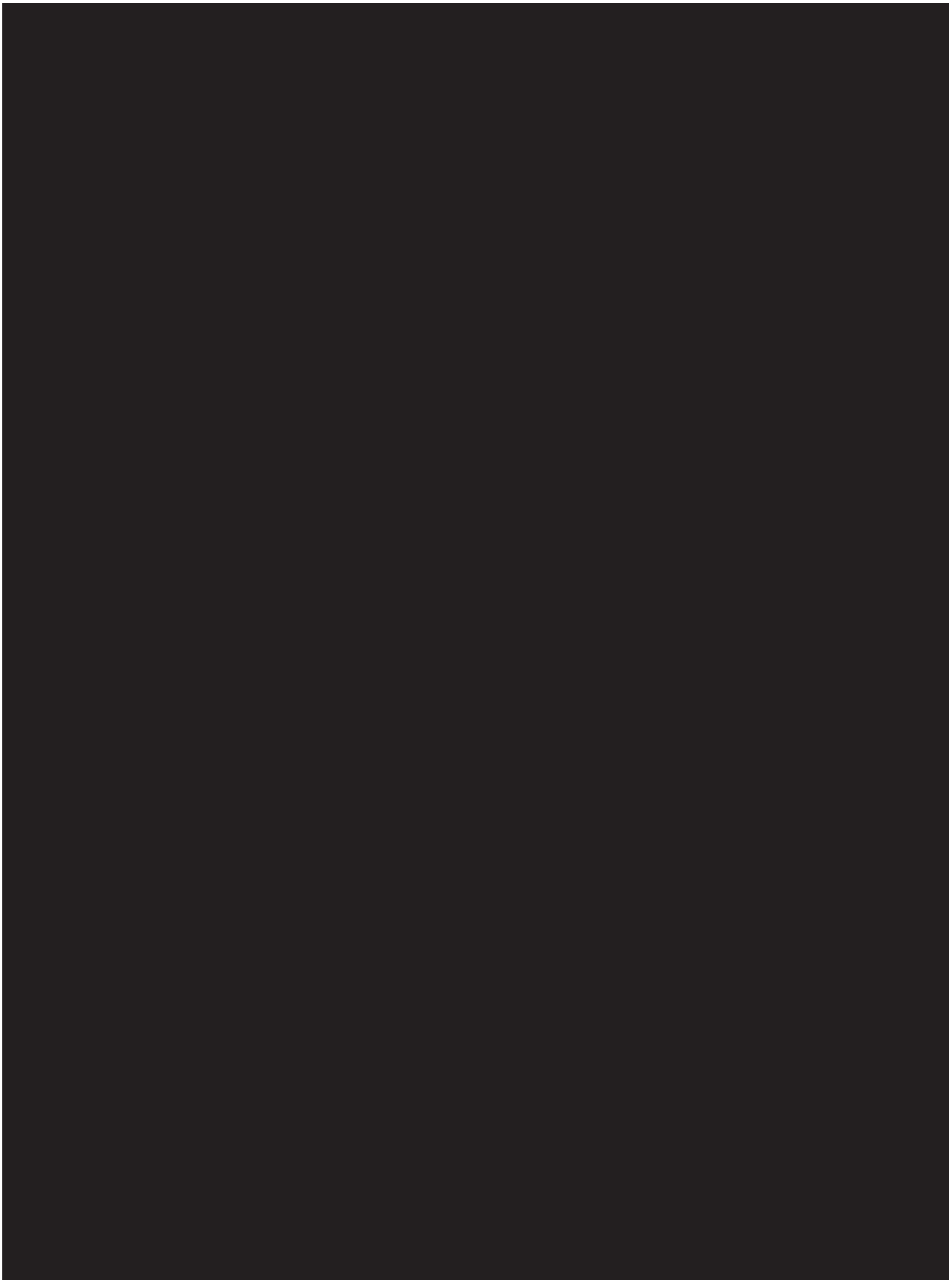


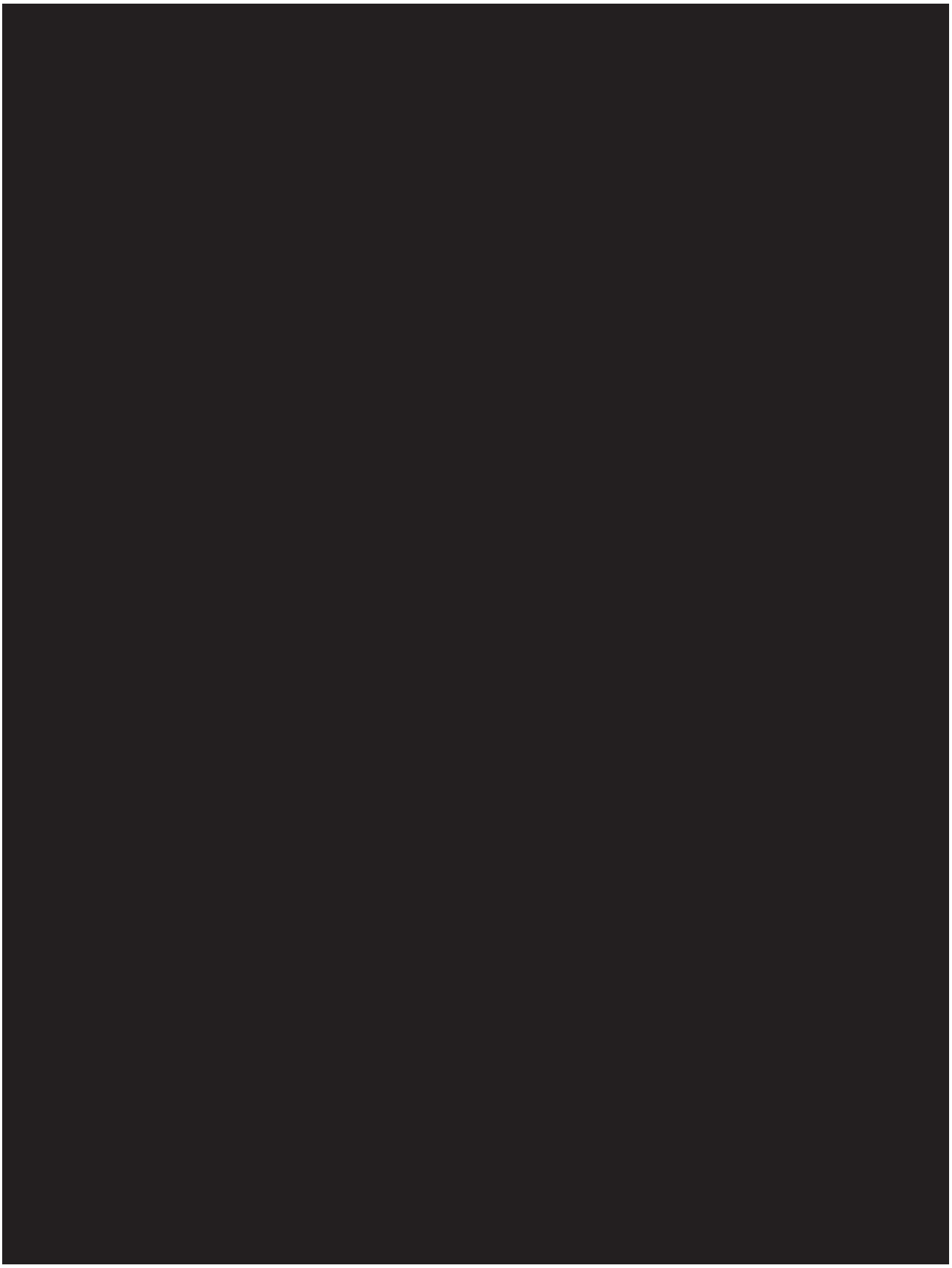


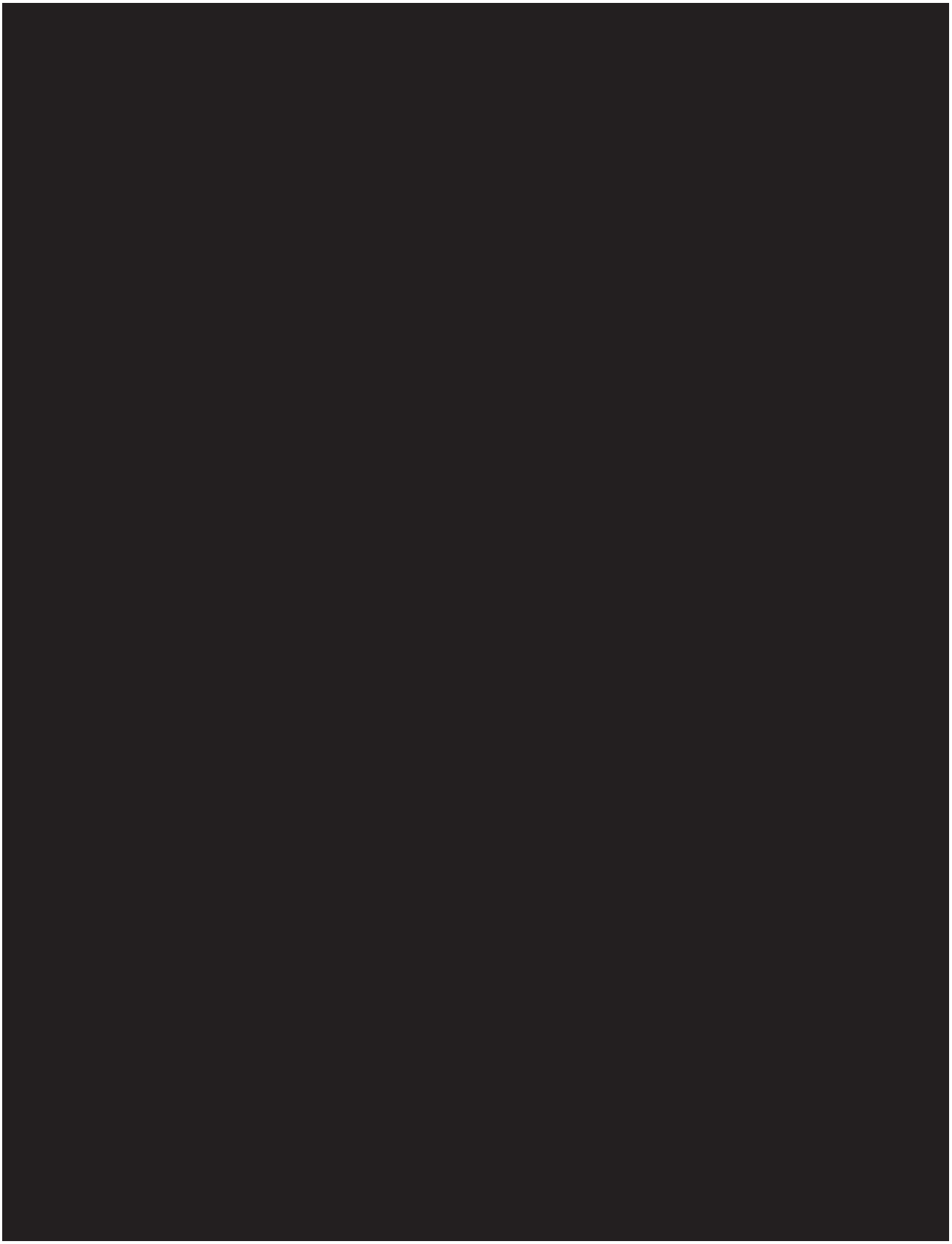












1.3 Research Hypothesis

It is anticipated that anti–GITR antibody (BMS-986156), administered as a single agent or in combination with nivolumab (BMS-936558, an anti–PD-1 antibody), 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.

1.4 Objectives(s)

1.4.1 Primary Objectives

The primary objective is to determine the safety, tolerability, dose-limiting toxicities (DLTs), and MTD/MAD/alternate dose(s) of BMS-986156 administered alone and in combination with nivolumab in subjects with advanced solid tumors.

1.4.2 Secondary Objectives

- To investigate the preliminary anti-tumor activity of BMS-986156 administered alone and in combination with nivolumab in subjects with advanced solid tumors
- To characterize the PK of BMS-986156 administered alone and in combination with nivolumab
- To characterize the immunogenicity of BMS-986156 administered alone and in combination with nivolumab, and the immunogenicity of nivolumab administered with BMS-986156

[redacted]

1.5 Product Development Background

1.5.1 Pharmacology

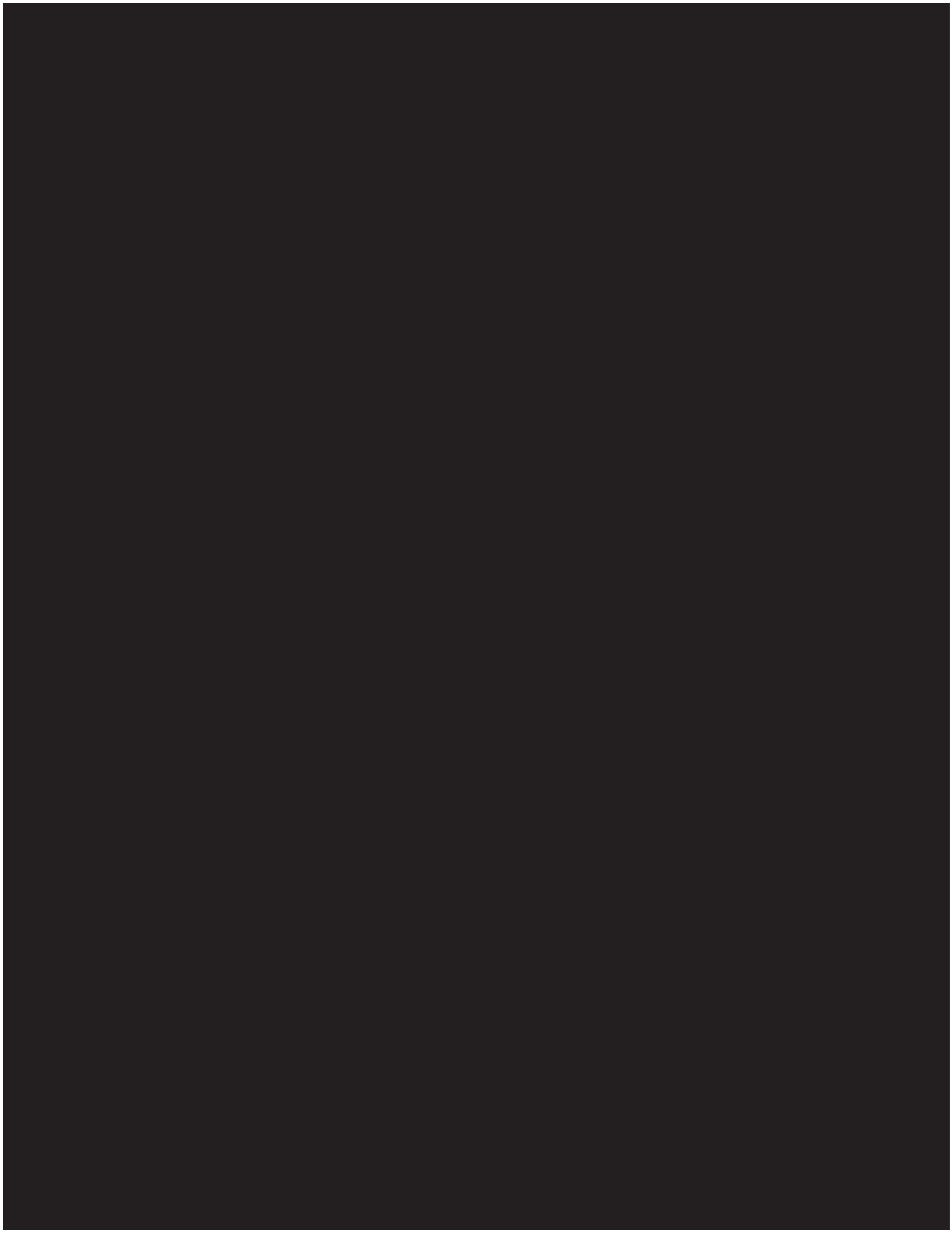
BMS-986156

BMS-986156 is an IgG1 agonist antibody that binds to activated human CD4+ and CD8+T cells with EC_{50}'s of 0.42-0.44 nM. EC_{50} values for binding of BMS-986156 to activated cynomolgus T cells (0.86-0.96 nM) were similar to those on human cells, being about 2-fold lower. [redacted]

[redacted]

[redacted]

[redacted]



1.5.4 Clinical Pharmacology and Safety

BMS-986156

Ongoing safety data as of 12-Dec-2016 from Study CA009002 are consistent with a manageable safety profile with no signals observed to date. Adverse events have been reported in 33 out of 34 (97.1%) subjects on monotherapy, and 39 out of 50 (78.0%) subjects on combination therapy of BMS-986156 with nivolumab (2 subjects on BMS-986156 30 mg/nivolumab 240 mg, 7 subjects on 100 mg BMS-986156/240 mg nivolumab, 20 subjects on 240 mg BMS-98156/240 mg nivolumab and 10 subjects on 800 mg BMS-98156/240 mg nivolumab). The AEs were mainly Grade 1 and Grade 2. The types of AEs (all grades, all causality) were similar among the BMS-986156 dose levels. One subject on 800 mg BMS 986156/240 mg nivolumab experienced a Grade 4 CPK elevation with myalgia event which was deemed related to study drug after the DLT window on day 29 of Cycle. Concomitantly the patient experienced increased liver values Grade 3 lasting 1 day. The patient was taken off study, treated with steroids, and then tapered off. He is clinically well and the CPK elevation is resolving to Grade 1 whereas the increased liver values lasted 1 day.

The most frequently reported AEs were nausea, vomiting, pyrexia, fatigue, abdominal pain, constipation, back pain, and headache. AEs for which no alternative cause other than study drug

could be identified, including infusion-related reactions (IRRs), were reported in 20 out of 34 (58.8%) subjects on monotherapy, and 28 out of 50 (56%) subjects on combination therapy.

Eleven subjects receiving BMS-986156 monotherapy died due to disease progression: 3 subjects on BMS-986156 10 mg, 4 subjects on BMS-986156 30 mg, 1 subject on BMS-986156 100 mg, and 3 on 240 mg BMS-986156 and 1 on 800 mg BMS-986156. One subject receiving BMS-986156 240 mg/nivolumab 240 mg died due to disease progression. One subject receiving BMS-986156 240 mg/nivolumab 240 mg died due to aspiration pneumonia. A total of 270 subjects reported serious adverse events (SAEs): Two SAE with no alternative cause other than study drug (Grade 2 pneumonitis identified, 800 mg Q2W and another subject Grade 4 blood creatine phosphokinase and Grade 3 hepatic enzyme elevation, 800 mg BMS 986156/ 240 mg nivolumab) and 25 SAEs considered not related to study drug. Nine subjects (2 on BMS-986156 10 mg, 2 on BMS-986156 30 mg, 1 BMS-986156 100 mg, 2 on BMS-986156 240 mg, and 2 on BMS-986156 240 mg/nivolumab 240 mg) discontinued from the study due to SAEs resulting from disease progression.

1.5.5 Nivolumab Clinical Safety and Activity

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

alone and, in some cases, both frequency and severity of AEs were greater than that observed with either agent alone. The safety profile of nivolumab + ipilimumab combination therapy was consistent with the mechanisms of action of nivolumab and ipilimumab. 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. For nivolumab monotherapy and combination therapy, most high-grade events were manageable with use of corticosteroids or hormone replacement therapy (HRT; endocrinopathies).

In several ongoing clinical trials, the safety of nivolumab in combination with other therapeutics such as ipilimumab, cytotoxic chemotherapy, anti-angiogenics, and targeted therapies is being explored. Most studies are ongoing and, as such, the safety profile of nivolumab combinations continues to evolve. Management algorithms including the use of immunosuppressive agents, such as corticosteroids, infliximab, etc., are provided in Appendix 4. Nivolumab should not be used in subjects with active autoimmune disease given the mechanism of action of the antibody. Updated overall clinical experience for nivolumab is available in the current version of the IB.[97]

1.6 Overall Risk/Benefit Assessment

[redacted]

[redacted]

BMS-986156 Starting Dose for Part A (Monotherapy)

The FIH dose for this study has been carefully selected based on a thorough review of all available nonclinical data [redacted]. Since BMS-986156 is an immune agonist and activates the T-cell mediated immune response, MABEL and HNSTD were considered in selecting the FIH starting dose.

To balance the potential for pharmacologic activity and need for reasonable safety in a cancer patient population vs. normal healthy volunteers, a dose of 10 mg was selected as the FIH safe starting dose. This dose is approximately 100-fold lower than the MRSD (992 mg) projected from the 1-month repeat-dose toxicity study in monkeys, is approximately 5-fold lower than the projected human efficacious dose (56 mg), and is within the derived MABEL dose range).[127] Thus the selected FIH starting dose of BMS-986156 appropriately balances regard for patient safety with the potential of exposing a higher number of patients with advanced cancer to non-pharmacologically active doses. Monotherapy dose escalation has cleared 800 mg without the MTD being reached.

BMS-986156 Starting Dose for Part B (Combination with Nivolumab)

The Sponsor decided to choose the 30 mg BMS-986156 in combination with 240 mg nivolumab based on the safety profile of the monotherapy dose escalation, Part A, of BMS-986156. No DLT nor any AE (greater than Grade 1) for which no other cause than the investigational drug could be identified had occurred. Starting dose of BMS-986156 in Part B (combination with nivolumab) is one dose level lower than a dose already tested and shown to be tolerated in ongoing monotherapy dose escalation in Part A [redacted]. At no point will the dose of BMS-986156 administered in combination with nivolumab in Part B exceed doses of BMS-986156 that have been demonstrated previously to be safe in the monotherapy dose escalation arm (Part A), nor at any point during Part B escalation will the BMS-986156 dose exceed the highest dose determined to be tolerated in Part A. Combination dose escalation has cleared 240 mg BMS-986156/240 mg nivolumab and has been initiated at 800 mg/240 mg without the MTD being reached.

Dose Escalation in Parts A and B

BLRM with overdose control (EWOC) principle[144] will be employed to ensure that safety is not compromised during dose escalation. In addition, following the completion of one dose level, dose selection for next cohort/dose level will be made in conjunction with the data available on all previously dosed subjects, (including clinical and laboratory safety assessments, PK, [redacted] data),

will not allow escalation by more than one dose level, and will be made after discussion and agreement between Investigators and Medical Monitor.

Safety Monitoring on Study Therapy (Parts A-F)

In the absence of a pre-clinically defined safety signal, safety monitoring, by way of complete blood counts and chemistry (including liver enzyme) tests will be carried out prior to administration of study therapy, on a weekly basis for the first cycle and bi-weekly thereafter. In addition, complete physical examinations (PEs) will be conducted on Day 1 of each new cycle, along with bi-weekly symptom-directed targeted PEs prior to each administration of study drug. [redacted]

In a pre-clinical mouse study in which a rat anti-GITR antibody was repeatedly administered anaphylactoid reactions were observed due to the development of IgE antibodies.[145] As noted in the nonclinical studies [redacted], BMS-986156 repeatedly administered to cynomolgus monkeys did not induce infusion-related or anaphylactoid reactions. However, because of the as yet unknown potential of infusion reactions with the administration of BMS-986156 in humans, all subjects receiving first 2 doses of BMS-986156 monotherapy and in combination with nivolumab, will be closely monitored until 120 minutes post infusion for potential infusion reactions that could occur after either first administration, or from repeat dosing of a novel monoclonal antibody. In addition, detail guidance management and algorithms for IRRs are provided in the protocol and the administration of BMS-986156 as monotherapy or in combination with nivolumab will occur at sites with medical monitoring and capability to manage infusion reaction or anaphylaxis.

Due to the potential risk of amplification of antigen-specific T-cell responses and exaggerated inflammatory response, subjects with auto-immune disorders who are at risk for flare of auto-immunity, as well as those with viral infection (human immunodeficiency virus [HIV], Hepatitis B or C) at risk for exaggerated anti-viral inflammatory response will be excluded (see Section 3.9.2).

Safety assessments will also be carried out by the Sponsor/Medical Monitor and Investigators throughout the study to determine whether dose modification, additional safety measures, or termination of the study, as pertaining to administration of BMS-986156 as monotherapy or in combination with nivolumab, is required at any time. In addition, AEs and SAEs will be reviewed regularly by the Medical Monitor/Study Director and the Pharmacovigilance group to look for trends and potential safety signals. Treatment of AEs will follow Institutional guidelines and recommended management algorithms as listed in the nivolumab prescribing information and nivolumab IB,[97] and provided as appendices to the protocol.

Clinical Safety Update

Study CA009002 is ongoing and safety data from patients treated in Parts A and B as of 12-Dec-2016, is summarized below:

BMS-986156 Monotherapy (Part A)

As of 12 Dec-2016, 34 subjects have been treated with BMS-986156 as monotherapy. BMS-986156 monotherapy was evaluated during dose escalation phases at 10 mg (4 subjects), 30 mg (6 subjects), 100 mg (4 subjects), 240 mg (9 subjects), and 800 mg (11 subjects) of BMS-986156. Overall, the safety profile of BMS-986156 monotherapy is manageable with the MTD not being reached at 800 mg.

There was no pattern in the incidence, severity, or causality of AEs across the BMS-986156 dose levels studied. AEs were experienced by 97.1% (33/34) of subjects on monotherapy, with the most frequently reported AEs being nausea, vomiting, pyrexia, fatigue, abdominal pain, constipation, back pain, and headache. There were no DLTs and all SAEs were attributed to causes other than the study drug with the exception of a SAE of Grade 2 pneumonitis in a single subject at the 800 mg dose level. All AEs leading to discontinuation are attributed to causes other than study drug. AEs for which no alternative cause besides BMS-986156 can be identified, including IRRs, were reported in 58.8% (20/34) of subjects with the most frequently reported AEs being nausea, pyrexia, and chills, all of which were Grade 1 or Grade 2. The 12 subjects for which no alternative cause besides BMS-986156 can be identified include:

- 9 subjects at the 240 mg dose level: 3 of these subjects experienced pyrexia
- 11 subjects at the 800 mg dose level: pain, paresthesia, cough and pneumonitis in 1 subject; chills, fever, nausea and vomiting in 1 subject; and cases of headache, fever, malaise, flu like symptoms, vomiting and IRR, each experienced in different single subjects. The IRR which occurred twice at Grade 2 occurred in a single subject. With full premedication (acetaminophen, diphenhydramine, and steroids) and a prolonged infusion time of 2 hours, the Grade 2 infusion reaction did not recur.

The Grade 2 pneumonitis case occurred [redacted] This subject received 2 doses of BMS-986156, 800 mg IV Q2W. Following the second dose, [redacted] complained of coughing and increasing dyspnea. On evaluation [redacted] was afebrile and had an oxygen saturation of 96%. Computed tomography of the chest showed lower lobe infiltrates that were consistent with pneumonitis, a left sided pleural effusion and increase in the size and number of pulmonary metastases. [redacted] was treated with IV methylprednisolone (80 mg) and was admitted overnight for observation. The steroid dose was continuously decreased and symptoms improved. The subject did not resume BMS-986156 dosing as [redacted] experienced disease progression and thus came off study.

The monotherapy safety profile supported initiation of the combination dosing at dose level 2 (30 mg GITR).

BMS-986156 in Combination with Nivolumab (Part B)

As of 12-Dec-2016, 50 subjects have been treated with the combination of BMS-986156 and nivolumab: 3 subjects at 30 mg BMS-986156/240 mg nivolumab, 9 subjects at 100 mg BMS-986156/240 mg nivolumab, 27 subjects at 240 mg BMS-986156/240 mg nivolumab and 800 mg BMS-986156/240 mg nivolumab. Overall, the safety profile of BMS-986156 combination therapy is manageable with no MTD reached.

There was no pattern in the incidence, severity, or causality of AEs to BMS-986156 across these dose levels. Adverse events were experienced by 78% (39/50) of subjects: 2 of 3 subjects on 30 mg BMS-986156/240 mg nivolumab, 7 of 9 subjects at 100 mg BMS-986156/240 mg nivolumab, 20 of 27 subjects BMS-98156 240 mg/nivolumab 240 mg and 10 of 11 BMS-98156 800 mg/nivolumab 240 mg. All SAEs reported were attributed to causes other than study drug.

In all 10 patients who experienced these AEs for which no alternative cause other than study drug could be identified, the nature of the AEs were as follows:

- 2 subjects on 30 mg BMS-986156/240 mg nivolumab: pyrexia and pruritus in 1 subject and pyrexia, hypomagnesemia, arthralgia, and appetite decreased in 1 subject, all Grade 1.
- 6 subjects on 100 mg BMS-986156 /nivolumab 240 mg: Grade 1 pyrexia, rigors, IRR, and elevated lipase. One subject experienced Grade 2 nausea, vomiting, and weight loss. One subject experienced Grade 3 elevated lipase, elevated amylase, myalgia and dry mouth all Grade 1. One patient experienced arthralgia, grade 2. One subject experienced a Grade 3 lung infection
- 13 subjects on 240 mg BMS-986156/240 mg nivolumab: Grade 1 pyrexia, headache, chills malaise, arthralgia, fatigue, myalgia diarrhea, dry mouth, hypertension, Grade 2, fatigue, cough, myalgia, decrease neutrophil count and peripheral sensory neuropathy.. Grade 3, fatigue.

Each subject treated with 30 mg BMS-986156 and 240 mg nivolumab experienced Grade 1-related IRRs (fever/pyrexia, rigors, chills, nausea, night sweats) following the first dose administered within 24 hours of the infusion. These events resolved with the oral administration of acetaminophen 500 mg. The IRRs did not recur upon subsequent dosing apart form in exception of 1 subject that experienced an additional related Grade 1 IRR after the third dose was administered (also resolved with acetaminophen 500 mg).

Two of the 9 subjects dosed with 100 mg BMS-986156/240 mg nivolumab experienced an IRR following the first dose administered within 24 hours of the infusion. These events resolved with the oral administration of acetaminophen 500 mg. These IRRs did not recur upon subsequent dosing. Six of the 27 subjects on 240 mg BMS-986156/240 mg nivolumab experienced an IRR following the first dose administered within 24 hours of the infusion. This event resolved with the oral administration of acetaminophen 500 mg. 6 of the 34 subjects (17.6%) on monotherapy experienced IRR, (1 subject on 100 mg BMS 986156, 3 on 240 mg BMS 986156 and 3 on 800 mg BMS 986156). 14 of the 50 subjects on combination therapy (28%) experienced IRR (2 on 30 mg BMS 986156/nivolumab 240 mg, 2 on 100 mg/nivolumab 240 mg, 6 on 240 mg BMS 986156/nivolumab 240 mg and 4 on 800 mg BMS 986156/nivolumab 240 mg).

Adequate monitoring and safety assessments as outlined in Section 5.3 of the study protocol is in place for mitigating the risk of cytokine release should it occur at any point in the trial. A specific study of cytokine release potential in pre-clinical models for the combination is at this time unnecessary given the clinical safety profile.

Overall Risk/Benefit for Combination with Nivolumab

Nivolumab has demonstrated clinical activity in subjects with advanced NSCLC, RCC, melanoma and lymphomas among other tumors and has been recently approved in the treatment of second line melanoma following Yervoy and BRAF inhibitors for BRAFV600 mutant positive tumors, and second line squamous NSCLC.[121]

Nivolumab has demonstrated a manageable safety profile. The overall safety experience with nivolumab, as a monotherapy or in combination with other therapeutics, is based on experience in approximately 8,700 subjects treated to date.[97] There is no pattern in the incidence, severity, or causality of AEs to nivolumab dose level. The most common AEs included fatigue, rash, pruritus, diarrhea, and nausea. Side effects of nivolumab therapy may include those associated with immune-mediated activation, such as pneumonitis, thyroiditis, and transaminitis. Most of these events resolved with immunomodulating medication (e.g. < 1% subjects who developed pneumonitis (5/ 691) treated subjects have died.[121] To mitigate risk from serious immune-mediated AEs, subject management algorithms for nivolumab-related AEs from prior collective nivolumab experience have been included (Appendix 4). For nivolumab monotherapy, the safety profile is similar across tumor types. The only exception is pulmonary inflammation AE), which may be numerically greater in subjects with NSCLC, because in some cases, it can be difficult to distinguish between nivolumab-related and unrelated causes of pulmonary symptoms and radiographic changes. The nonclinical findings of increased late-stage pregnancy loss and early infant deaths/euthanasia in nivolumab-exposed pregnant monkeys [redacted] suggest a potential risk to human pregnancy if there is continued treatment with nivolumab during pregnancy. However, nivolumab exposure during human pregnancy has not been permitted in clinical trials, and is not permitted in this protocol.

The combination of nivolumab and BMS-986156 has the potential for increased benefit compared to nivolumab monotherapy. In general, the combination of nivolumab with other therapeutic agents results in a safety profile with similar types of AEs as either agent alone, but in some cases, with a greater frequency. In several ongoing clinical trials, the safety of nivolumab in combination with other therapeutics such as ipilimumab, cytotoxic chemotherapy, anti-angiogenics, and targeted therapies is being explored. Most studies are ongoing and, as such, the safety profile of nivolumab combinations continues to evolve. Thus far, the combination of both agents results in a safety profile with similar types of AEs as either agent alone, but in some cases with a greater frequency.

Summary

An urgent need exists for new therapies for subjects with advanced cancer that has progressed or not responded to other treatments. Substantial nonclinical efficacy profile and evidence of single

agent as well as combination activity with mouse surrogates of anti-GTIR and anti-PD-1 antibodies has been noted in a variety of mouse tumor models (See Section 1). These pre-clinical results taken together with the emerging role of combination immunomodulating therapies in producing deep and durable responses in well-designed clinical trials, [146] the lack of a safety signal in pre-clinical toxicology studies in mice and cynomolgus monkeys, the careful consideration for safety in study design, and clinical data observed to date, support the expectation of favorable benefit to risk for evaluation of BMS-986156 as monotherapy or in combination with nivolumab.

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

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

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

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

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

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (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 IB or product labeling information to be provided to subjects and any updates.

The Investigator or BMS should provide the IRB/IEC with reports, updates and other information (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 (as per country guidelines) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the subject volunteers to participate.

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

Investigators must:

- Provide a copy of the consent form(s) and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be 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 ICF 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 ICF and, in the US, the subjects' signed Health Insurance Portability and Accountability Act Authorization.

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

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

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

This is a Phase 1/2a, open-label study of BMS-986156 administered as a single agent and in combination with nivolumab in subjects with advanced solid tumors.

The study will be conducted in 5 parts. Parts A and B will consist of dose escalation with BMS-986156 administered as a single agent (Part A) or in combination with nivolumab (Part B) in subjects with advanced solid tumors. Starting dose selection of BMS-986156 for Part B (combination with nivolumab) was determined using all available safety (clinical and laboratory), PK, [redacted] and modeling recommendations within Bayesian hierarchical modeling framework by incorporating single agent toxicity profiles of both BMS-986156 (Part A) and nivolumab (data from CA209003 study, a phase 1 nivolumab monotherapy data in advanced solid tumors) and will be one dose level lower than a dose already tested and shown to be tolerated in ongoing monotherapy dose escalation in Part A [redacted]. Subsequently, escalation in the 2 parts will proceed in parallel.

A dose -1 cohort of 3 mg has also been included and will only be explored in the event 10 mg dose of BMS-986156 is determined to exceed the MTD in monotherapy or in combination with nivolumab (Table 3.4.1-1).

At no point will the dose of BMS-986156 administered in combination with nivolumab in Part B exceed doses of BMS-986156 that have been demonstrated previously to be safe in the monotherapy dose escalation arm (Part A), nor at any point during Part B escalation will the BMS-986156 dose exceed the highest dose determined to be tolerated in Part A.

Nivolumab will be administered as a dose of 240 mg every 2 weeks for combination dose cohorts (Parts B and D).

Nivolumab will be administered as a dose of 480 mg every 4 weeks for combination dose cohorts Part E

Part C consists of cohort expansion with BMS-986156 monotherapy in 2 disease-restricted populations, NSCLC with progressive or recurrent disease (per RECIST v1.1) during or after anti-PD-1 or anti-PD-L1 therapy following prior platinum doublet-based chemotherapy, and persistent, recurrent, or metastatic cervical cancer, of approximately 40 subjects each.

Part D consists of cohort expansion with BMS-986156 administered in combination with nivolumab in disease-restricted populations as follow: (i) NSCLC, (ii) cervical, (iii) bladder cancer, (iv) squamous cell carcinoma head and neck, (v) ovarian cancer, and (vi) HCC, of approximately 40 subjects each.

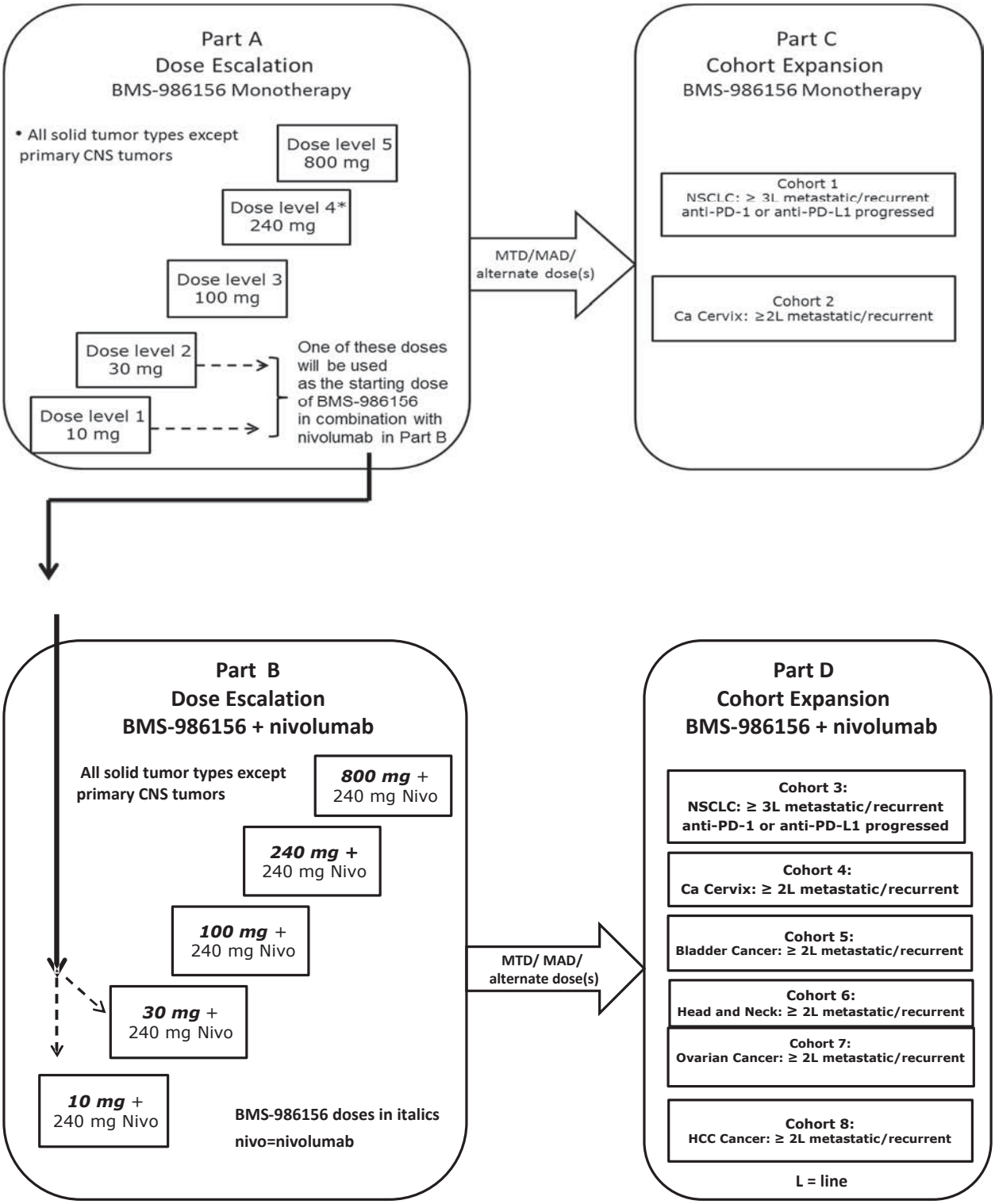
Part E consists of cohort expansion with BMS 986156 administered in combination with nivolumab in cervical cancer (cohort 9) and other tumor types (Cohort 10). Each cohort will contain approximately 40 subjects each. Patients who discontinue for reasons other than disease progression, death, or treatment-related toxicity may be replaced.

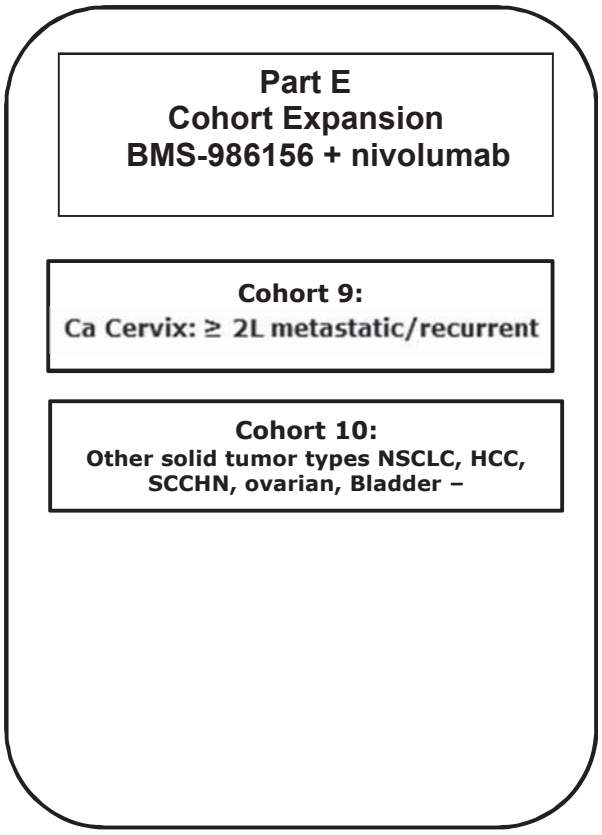
No more than 5 subjects previously found to be "rapid progressors" on anti-PD-1 or anti-PD-L1 therapy will be enrolled per cohort. Rapid progressors are defined as subjects who have progressed as of their first response assessment while on prior PD-1/PD-L1 therapy (if applicable).

Cohort expansion arm in part C will consist of approximately 25 subjects. Cohorts in Part D and Part E will contain approximately 40 subjects. Patients who discontinue for reasons other than disease progression, death, or treatment-related toxicity may be replaced. Treatment in Parts C and D will be initiated when the MTD/MAD/alternate dose(s) for monotherapy and combination with nivolumab have each been determined based on evaluation of the totality of available clinical safety, PK, [redacted] and modeling data for Parts A and B, respectively. The doses selected for Parts C D, and E will not exceed the MTD or MAD determined in Parts A and B. Part D may begin while Part B continues to explore higher dose levels.

A schematic of the study is provided in Figure 3.1-1.

Figure 3.1-1: Study Schematic





Subjects will complete up to 3 phases of the study: Screening, Treatment, and Safety follow-up, as described below:

Screening

The screening phase will last for up to 28 days. Screening phase begins by establishing the subject's initial eligibility and signing of the ICF. Subjects will be enrolled using the Interactive Voice Response System (IVRS).

Treatment Phase

The treatment phase consists of up to three 8-week treatment cycles. In Parts A and C, each treatment cycle comprises 4 doses of BMS-986156 administered every 2 weeks on Days 1, 15, 29, and 43 of the treatment cycle. In Parts B and D, each treatment cycle comprises 4 doses of BMS-986156 (administered on Days 1, 15, 29 and 43) in combination with 4 doses of nivolumab administered on Days 1, 15, 29, and 43 of the treatment cycle. In Parts B and D and E when both study drugs are given, nivolumab will be given first followed by BMS-986156 at least 30 minutes after completion of the infusion of nivolumab. In Part E, the cohort of 480 mg/480 mg each treatment cycle comprises 2 doses of BMS-986156 (administered on Days 1 and 29) in combination with 2 doses of nivolumab administered on Days 1 and 29 of the treatment cycle.

Following each treatment cycle, the decision to treat a subject with additional cycles of study therapy, up to a maximum of 13 treatment cycles, will be based on tumor assessment (evaluation performed between Days 49 and 56 of each cycle and completed before the first dose in the next cycle). Tumor progression or response endpoints will be assessed using Response Evaluation Criteria in Solid Tumor (RECIST) v1.1 criteria for solid tumors (Appendix 3).

Treatment beyond progression may be allowed in select subjects with initial RECIST v1.1-defined progressive disease (PD) after discussion and agreement with the BMS Medical Monitor that the benefit/risk assessment favors continued administration of study therapy (e.g., subjects are continuing to experience clinical benefit as assessed by the Investigator, tolerating treatment, and meeting other criteria specified in Section 3.11.1.1).

Subjects with a response of unconfirmed PD, SD, partial response (PR), or complete response (CR) at the end of a given cycle will continue to the next treatment cycle. Subjects will generally be allowed to continue study therapy until the first occurrence of either: 1) completion of the maximum number of cycles, 2) confirmed PD, 3) clinical deterioration suggesting that no further benefit from treatment is likely, 4) intolerability to therapy; or 5) the subject meets criteria for discontinuation of study therapy as outlined in protocol Section 3.11. Individual subjects with confirmed CR will be given the option to discontinue study therapy on a case by case basis after specific consultation and agreement between the Investigator and BMS Medical Monitor in settings where benefit/risk justify discontinuation of study therapy.

3.2 Treatment with Additional Cycles Beyond 24 Weeks

All subjects will be treated for 24 weeks (up to 3 cycles) of monotherapy (Parts A or C) or combination therapy (Parts B or D) unless criteria for study drug discontinuation are met earlier (Section 3.11). All subjects completing approximately 24 weeks of treatment with ongoing disease

control (CR, PR or SD) or unconfirmed PD, may be eligible for an additional 3 cycles of study therapy in both monotherapy (Parts A and C) and combination therapy (Parts B D and E) beyond the initial 24 weeks, on a case-by-case basis, after careful evaluation and discussion with the BMS Medical Monitor to determine whether the risk/benefit ratio supports administration of further study therapy. All subjects completing approximately 48 weeks of treatment with ongoing disease control (CR, PR or SD) or unconfirmed PD, may be eligible for an additional 7 cycles of study therapy in combination therapy (Parts D and E) beyond the initial 48 weeks, on a case-by-case basis, after careful evaluation and discussion with the BMS Medical Monitor to determine whether the risk/benefit ratio supports administration of further study therapy. For patients who present with PD for the first time at the end of cycle 6, please contact the Medical Monitor for discussion. Upon completion of 3 cycles of study therapy (or up to a maximum of 13 cycles if applicable), all subjects will enter safety follow-up period.

3.3 Follow-up

3.3.1 Safety Follow-up

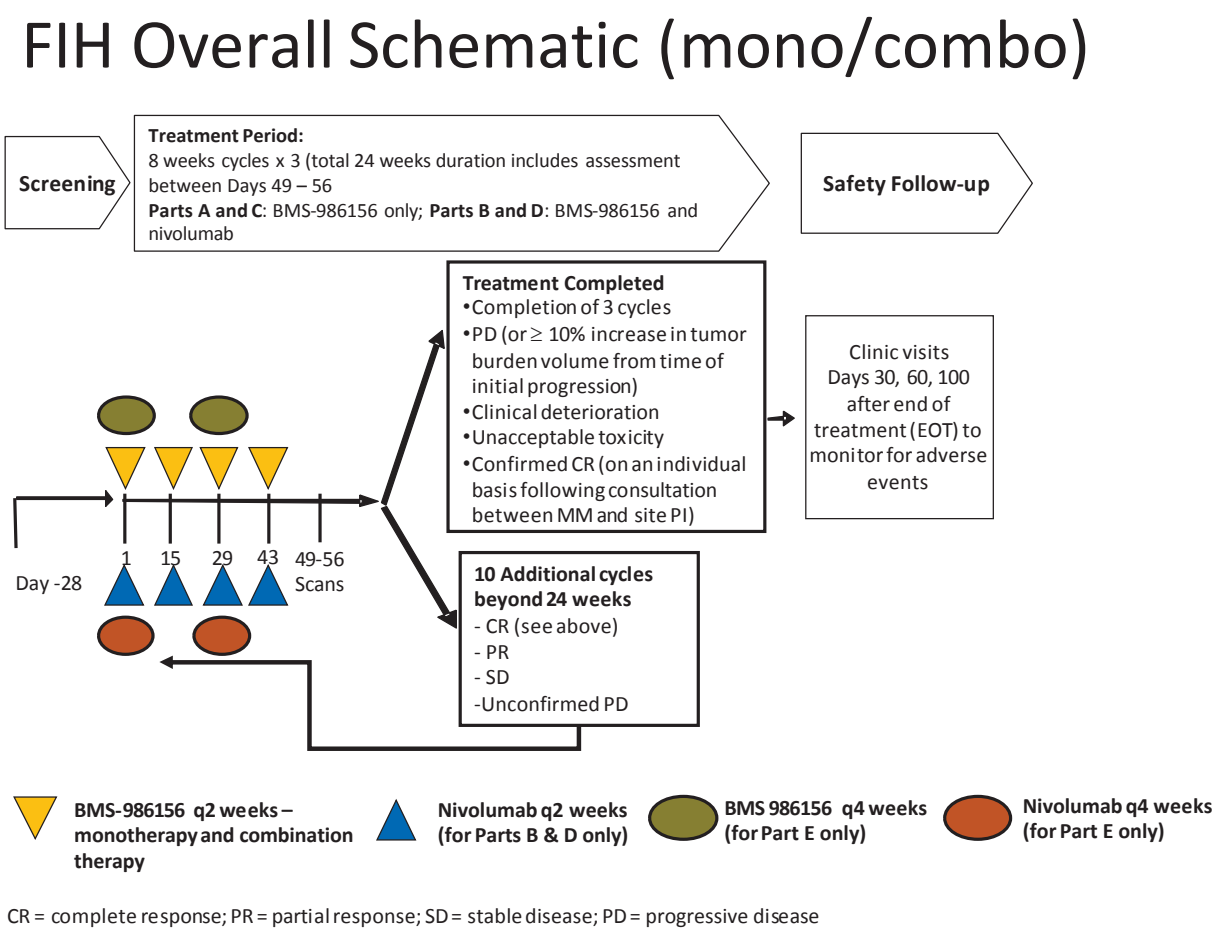
Upon completion of 3 cycles of study therapy (or up to a maximum of 6 cycles if applicable), all subjects will enter safety follow-up period once the decision is made to discontinue the subject from treatment (e.g., at end of treatment [EOT]).

For subjects that complete all scheduled cycles of therapy, EOT visit will be the same as the last scheduled and completed on-treatment visit, and the start of week 1 safety follow up visit. For subjects that do not complete all scheduled cycles of therapy, EOT visit will be the most recent on-treatment visit (with all available safety and response data) and does not need to be repeated, and will be considered the start of week 1 safety follow up visit.

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

The study design schematic is presented in Figure 3.3.1-1.

Figure 3.3.1-1: Study Schematic



CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease

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 will be collected for up to 29 days at specified times (Section 5.5) after study drug administration for PK analysis.

3.4 Dose Escalation

3.4.1 Parts A and B

The dose-escalation phase of the study will evaluate the MTD/MAD/alternate dose(s) of BMS-986156 alone or in combination with nivolumab based on DLTs using a BLRM-Copula model, where the BLRM is designed to guide BMS-986156 monotherapy dose escalation and BLRM-Copula is for the dose escalation of BMS-986156 in combination with nivolumab. The Bayesian model will be used for recommendation of next dose level to be investigated. BLRM (-Copula) with overdose control (EWOC) principle[144] will be employed to ensure that safety is not compromised during dose escalation.

The initial dose level of BMS-986156 in Part A will be a flat dose of 10 mg as an IV infusion over 60 minutes every 2 weeks. Expected dose levels for dose escalation (determined by half log increments from starting dose)[147] are provided in Table 3.4.1-1.

Starting dose selection of BMS-986156 for Part B will be determined using data available from all doses evaluated in Part A, including clinical and safety laboratory, PK, [redacted] and modeling recommendations within Bayesian hierarchical modeling framework by incorporating single agent toxicity profiles of both BMS-986156 (Part A) and nivolumab (CA209003, a Phase 1 nivolumab monotherapy data in advanced solid tumors); starting dose will be one dose level lower than a dose already tested and shown to be tolerated in ongoing monotherapy dose escalation in Part A [redacted]. A dose -1 cohort of 3 mg has been included and will only be explored in the event 10 mg dose of BMS-986156 is determined to exceed the MTD in monotherapy or in combination with nivolumab (Table 3.4.1-1).

Dose levels to be considered for the next cohort will be based on evaluating three potential recommendations by BLRM (-Copula): escalate, de-escalate, or stay at same dose level. Final dose selection for next cohort/dose level will be made in conjunction with the data available on all dosed subjects, including clinical and laboratory safety assessments, PK, [redacted] data, will not allow escalation by more than one dose level and will be made after discussion and agreement between Investigators and Medical Monitor. Accordingly, intermediate or lower doses, or less frequent dosing of BMS-986156 may be tested if none of the planned doses/schedules is found to be tolerated as monotherapy or in combination with nivolumab. Up to an additional 9 subjects may be enrolled in an already DLT cleared cohort to collect additional PK, [redacted] and safety data to better understand any dose response relationship.

Approximately 30 subjects each will be treated in each dose escalation phases in monotherapy (Part A) and combination therapy (Part B).

During dose escalation phase, once a dose level has been decided, a set of approximately 3 subjects will be treated at that specified dose level. Cohort tolerability assessment and subsequent dose recommendation will occur according to BLRM (-Copula) recommendation and after at least 2 subjects complete the 4 week DLT observation period. If the potential DLT occurring in the 3rd evaluable subject regarding the specific dose level does not influence the dose recommendation by BLRM (-Copula), the BLRM (-Copula) recommended next dose level may proceed without waiting for the 3rd subject to complete the corresponding DLT observation period, after discussion and agreement between Sponsor and Investigators.

Subjects must be observed for a total of 28 days following the first therapy dose to be considered evaluable for DLT. Subjects discontinued during DLT observation period due to DLT are also considered as evaluable for DLT. Continuous re-assessment of dose recommendation by BLRM (-Copula) will also be carried out at each dose levels.

The MTD/MAD/alternate dose(s) of BMS-986156 selected for cohort expansion in Parts C and D will be based on evaluating the recommendation from BLRM and a synthesis of all available data, including clinical and laboratory safety assessments, PK, [redacted] and efficacy data, from all treated patients at each dose level up to the MTD/MAD.

No intra-subject dose escalation or reduction is allowed.

Sentinel Subject (Parts A and B only): During dose escalation, a staggered dosing (sentinel subject) approach will be used for the first subject in the first dose level of both monotherapy and combination cohorts. Only applicable to the lowest dose level: The first subjects at the lowest dose levels in both Part A and Part B will receive Cycle 1 Day 1 dose (e.g., the first dose of study drugs) and be observed for 5 days before additional subjects in the cohort receive study drug (e.g., subject two onward are dosed). The first subjects to be dosed in subsequent cohorts will not be required to observe the 5-day interval between treatment start dates.

Table 3.4.1-1: Dose Escalation Schedule for Parts A and B[a,b,c]

Dose Level	BMS-986156 Part A and Part B	Nivolumab Only Part B
-1	3 mg	240 mg IV Q2W
1	10 mg	240 mg IV Q2W
2	30 mg	240 mg IV Q2W
3	100 mg	240 mg IV Q2W
4	240 mg	240 mg IV Q2W
5	800 mg	240 mg IV Q2W

Abbreviations: IV, intravenous; MAD, maximum administered dose; MTD, maximum tolerated dose; PK, pharmacokinetics; Q2W, every 2 weeks.

[a] Additional subjects may be added for a total of up to 12 subjects per selected dose levels to provide additional safety, tolerability and PK data. This information will be incorporated into final recommendation for MAD/MTD/alternate dose(s) of BMS-986156

[b] Dose -1 (3 mg) will be evaluated if 10 mg (dose level 1) exceeds MTD

[c] Starting dose for Part B will be one dose level lower than a dose already tested and shown to be tolerated in ongoing monotherapy dose escalation in Part A [redacted]

3.5 Cohort Expansion (Parts C, D, and E)

The purpose of cohort expansion is to gather additional safety, tolerability, preliminary efficacy, PK, [redacted] information regarding BMS-986156 as monotherapy or in combination with nivolumab.

Part C consists of cohort expansions with BMS-986156 monotherapy in 2 disease-restricted populations: (i) NSCLC subjects with progressive or recurrent disease (per RECIST v1.1) during or after anti-PD-1 or anti-PD-L1 therapy following prior platinum doublet-based chemotherapy and (ii) persistent, recurrent or metastatic cervical cancer.

Part D consists of cohort expansion with BMS-986156 administered in combination with nivolumab in disease-restricted populations: (i) NSCLC, (ii) cervical, (iii) bladder cancer, (iv) squamous cell carcinoma head and neck, (v) ovarian cancer, and (vi) HCC.

No more than 5 subjects previously found to be "rapid progressors" on anti-PD-1 or anti-PD-L1 therapy will be enrolled per cohort (see definition of "rapid progressors" in Section 3.1).

Each of the cohort in cohort expansion phase will contain approximately 40 subjects. (Please refer to more details in Section 8.1.2).

Parts E includes two cohorts with one as cervical and another for other solid tumors for signal seeking and exploration of Q4W dosing respectively. Due to the purpose of signal confirming in cervical cancer and heterogeneity of response rates of the other solid tumors cohort (I-O experienced NSCLC, ovarian cancer, bladder cancer, SCCHN, and HCC), approximately 40 subjects are planned for each cohort in part E. For initial safety evaluation of 480 mg BMS-986156/480 mg nivolumab Q4W 6 subjects for a safety lead-in will be enrolled and followed for a minimum of two weeks (refer to Section 3.6 for the rationale for two week period) prior to opening full enrollment of Part E.

Table 3.5-1: Expansion Cohorts

Cohorts		Total Subjects (Approximate Number)
Part C: BMS-986156		
1	NSCLC	25
2	Cervical Cancer	25
Part D: BMS-986156 + Nivolumab		
3	NSCLC	40
4	Cervical cancer	40
5	Bladder	40
6	Squamous cell carcinoma head and neck	40
7	Ovarian Cancer	40
8	Hepatocellular	40
Part E: BMS-986156 + Nivolumab		
9	Cervical	40
10	Multiple solid tumor types	40

Abbreviation: NSCLC, non-small cell lung cancer.

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 across all cohorts treated within monotherapy and combination therapy phases at the same dose, the findings will be discussed and further enrollment may be interrupted. Depending on the nature and grade of the toxicity and after

assessing the risk/benefit ratio, a new dose(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.

3.6 Dose-limiting Toxicities

For the purpose of guiding dose escalation, DLTs will be defined based on the incidence and grade of AEs for which no alternate cause can be identified (Section 4.3.1). The incidence of DLTs which occur within 4 weeks following the start of study therapy will guide dose escalation decisions. AEs will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v4.03). For the purposes of subject management, drug-related AEs occurring at any time which meet the DLT definition will lead to dose interruption and/or permanent discontinuation of study drug as defined in Section 4.3.6.

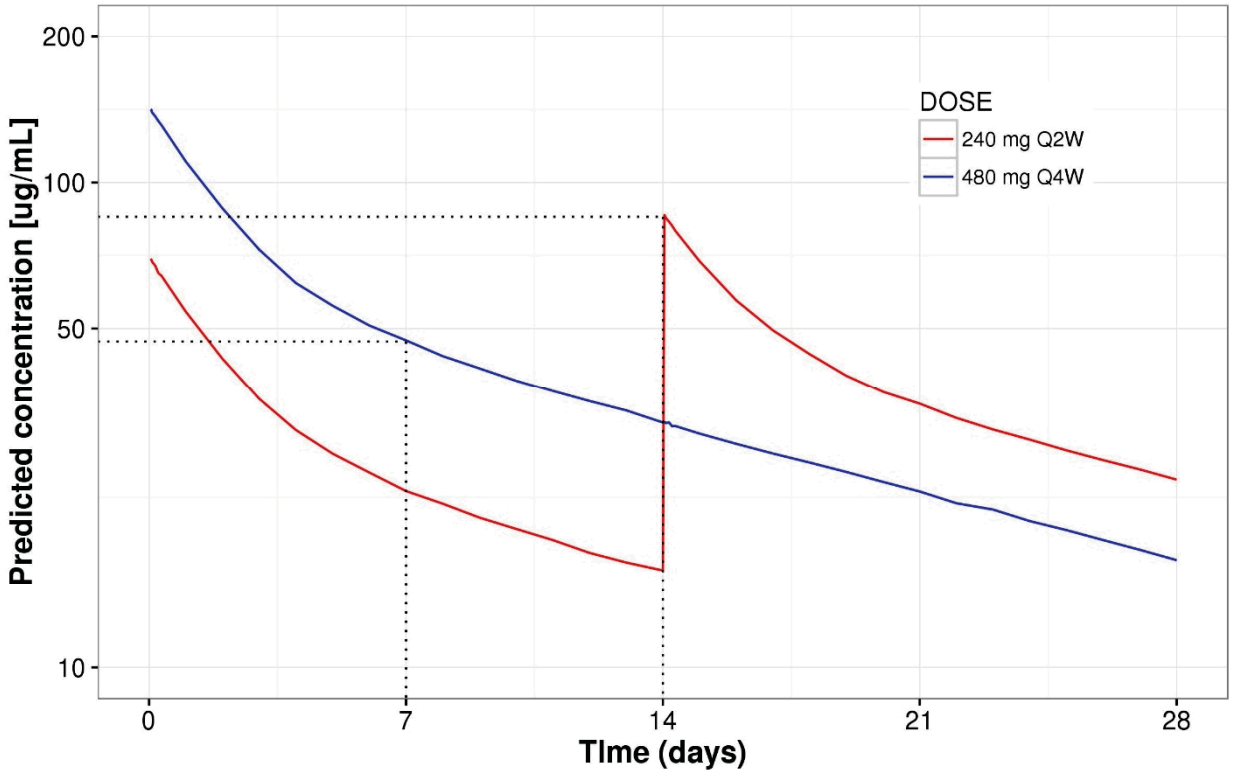
The DLT evaluation interval begins on the first day of treatment and continues for 4 weeks, that is, through Day 28 of the first cycle in both Parts A and B. Subjects discontinued during DLT observation period due to DLT are also considered as DLT evaluable. Based on the predicted human T-HALF of BMS-986156 of 2 weeks, this interval is expected to cover the anticipated time frame for the occurrence of clinically significant immediate and early onset AEs related to (i) single dose BMS-986156 monotherapy or first combination dose with nivolumab and, (ii) repeat dosing of monotherapy BMS-986156 as well as combination dose with nivolumab.

3.6.1 Safety observation time for Q4W dosing

Part E will consist of an initial safety lead in period of up to 12 subjects. Six subjects need to complete the 14 day observation period before the full expansion cohorts, of up to 40 subjects, are opened. Patients who discontinue for reasons other than disease progression, death, or treatment-related toxicity may be replaced. An observation period of 14 days has been chosen based on pharmacokinetic (PK) modeling and simulation for BMS-986156, based on PK parameters derived from preclinical studies. [redacted]

In part E, BMS-986156 will be evaluated at a dose of 480 mg every 4 weeks (Q4W) with nivolumab 480 mg Q4W. The BMS-986156 480 mg Q4W dose is much lower than the already assessed safe dose of 800 mg Q2W dose (given as monotherapy and combination with nivolumab 240 mg Q2W). Additionally, PK predictions indicate that BMS-986156 concentrations during the first 2 weeks after treatment with 480 mg Q4W will be higher than those achieved by first 240 mg Q2W dose of BMS-986156 Figure 3.6.1-1. However, BMS-986156 levels after first 480 mg dose will be markedly lower than the Cmax achieved after 1st or 2nd dose of 240 mg BMS-986156 within 7 days, as indicated by the dotted lines below in Figure 3.6.1-1. A similar trend is expected for nivolumab 480 mg Q4W when compared with nivolumab 240 mg Q2W. Although levels of BMS-986156 and nivolumab with 480 mg Q4W dosing regimens are predicted to be lower than the concentrations achieved after 2nd dose with Q2W dosing within 7 days, an additional 7 day safety margin was included to give a 14 day safety observation period was chosen. This measure ensures that nivolumab concentrations will be well below the Cmax seen with the tested 240 mg nivolumab plus BMS-986156 combination dose evaluated in part D [redacted]. A strict safety monitoring in patients will continue throughout the study.

Figure 3.6.1-1: Predicted BMS-986156 concentrations with Q2W and Q4W dosing using a preliminary pharmacokinetic model



3.7 Stopping Rules During Cohort Expansions

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 across all cohorts treated within monotherapy and combination therapy phases at the same dose, the findings will be discussed and further enrollment may be interrupted. If an expansion cohort is discontinued due to toxicity, a new cohort at a previously tested lower dose level, or an alternate treatment regimen (see Table 3.4.1-1) may be considered based on the aggregate safety experience and in consultation and agreement between Investigators and Sponsor.

All safety signals throughout the conduct of the study will be reviewed by the BMS-986156 Medical Surveillance Team (MST). If unexpected safety findings are identified between scheduled MST meetings, an ad hoc meeting will be convened as appropriate.

Efficacy and safety will be continuously monitored and go/no go decision will be made by discussion with sponsor based on totality of data after assessing benefit/risk ratio in combination with clinical judgement.

3.8 Post Study Access to Therapy

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

3.9 Study Population

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

3.9.1 Inclusion Criteria

1) Signed Written Informed Consent

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

[redacted]

2) Target Population

a) Subjects must be at least 18 years old and have histologic or cytologic confirmation of a malignancy that is advanced (metastatic and/or unresectable) with measureable disease per RECIST v1.1 (See Appendix 3).

b) **Dose Escalation**: Parts A and B

1) 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. Subjects who refuse or are ineligible for standard therapy will be allowed to enroll provided their refusal/ineligibility is documented in medical records.

2) All solid tumor histologies will be permitted except for subjects with primary central nervous system (CNS) tumors, or with CNS metastases as the only site of active disease.

c) **Cohort Expansion: Parts C, D and E**

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

2) Subjects with prior exposure to therapy with any agent specifically targeting checkpoint pathway inhibition (such as anti-PD-1, anti-PD-L1, anti-PDL-2, anti-LAG-3, anti-CTLA 4 antibody) are permitted after a washout period of any time greater than 4 weeks from the last treatment.

Note:

(*i*) *Subjects who experienced prior Grade 1 to 2 checkpoint therapy-related immune-mediated AEs must have confirmed recovery from these events at the*

time of study entry, other than endocrinopathies treated with supplementation, as documented by resolution of all related clinical symptoms, abnormal findings on PE, and/or associated laboratory abnormalities. Where applicable, these subjects must also have completed steroid tapers for treatment of these AEs by a minimum of 14 days prior to commencing treatment with study therapy.

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

(iii) In an effort to limit confounding factors, for all cohorts where applicable, no more than 5 subjects previously found to be "rapid progressors" on anti-PD-1 or anti-PD-L1 therapy will be enrolled per cohort.

d) **Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1**

e) Subjects with prior therapy with any agent specifically targeting T-cell co-stimulation pathways except such as anti-GITR antibody, anti- CD137, anti-OX40 antibody, are permitted after a washout period of any time greater than 4 weeks from the last treatment.

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

[redacted]

The following tumor types will be explored:

i. NSCLC Cohort 1 (Part C) and Cohort 3 (Part D): Cohort 10 (Part E)

1) Not applicable per Revised Protocol 2
2) All subjects with non-squamous histology must have known EGFR and ALK status.
3) Subjects with an activating EGFR mutation must have received an EGFR TKI.
4) Subjects with an ALK translocation must have received an ALK inhibitor.
5) NSCLC subjects with progressive or recurrent disease (per RECIST v1.1) during or after anti-PD-1 or anti-PD-L1 therapy following prior platinum doublet-based chemotherapy

ii. Cervical Cancer Cohort 2 (Part C) ,Cohort 4 (Part D) and Cohort 9 Part E

1) Persistent, recurrent or metastatic cervical cancer with documented disease progression
2) Squamous, adenosquamous or adenocarcinoma histology - confirmation of the original primary tumor is required
3) Must have had at least one prior platinum based regimen
4) Confirmation of tumor HPV status: Prior testing results are acceptable if known. If tumor HPV status is unknown, subjects must consent to allow their submitted archived tumor tissue sample in the form of block or unstained slides to be tested for confirmation of tumor HPV status. Both HPV positive and negative subjects are eligible to enroll.

iii. Bladder Cancer - Cohort 5

1) Histological or cytological evidence of metastatic or surgically unresectable transitional urothelium involving the bladder, urethra, ureter, or renal pelvis.
2) Minor histologic variants (< 50% overall) are acceptable.
3) Subjects must have metastatic or surgically unresectable disease.
4) Subjects must have progression or recurrence after treatment:
   - With at least 1 platinum-containing chemotherapy regimen for metastatic or surgically-unresectable locally advanced urothelial cancer
   - Within 12 months of peri-operative (neo-adjuvant or adjuvant) treatment with a platinum agent in the setting of cystectomy for localized muscle-invasive urothelial cancer

iv. SCCHN (oral cavity, pharynx, larynx) -Cohort 6

1) Documentation of p16-is sufficient to determine human papillomavirus (HPV) status of tumor for SCCHN of the oropharynx. Note: If results are not available, then a sample (tissue on microscopic slides, tissue block or a fresh tissue biopsy in formalin) should be sent to the central laboratory for analysis
2) Patients must have had treatment with a platinum containing regimen and evidence of progression or recurrence within six months of last dose of platinum therapy.
3) Radiation therapy must have been completed at least 4 weeks prior to study drug administration.
4) Histologically confirmed incurable locally advanced, recurrent, or metastatic squamous cell carcinoma head and neck (oral cavity, pharynx, larynx), stage III/IV and not amenable to local therapy with curative intent (surgery or radiation therapy with or without chemotherapy).
5) Not applicable in revised protocol 03.

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

7) Not applicable per Revised Protocol 2

v. Ovarian Cancer - Cohort 7 (including epithelial OC, primary peritoneal, or fallopian tube carcinoma)

1) Histologically- or cytologically-confirmed OC (including epithelial OC, primary peritoneal, or fallopian tube carcinoma) with documented disease progression

2) Documented BRCA mutation status, if known. However, if unknown, subjects must consent to allow their submitted archived tumor tissue sample (block or unstained slides) to be tested. Patients can enroll regardless of BRCA mutation status.

3) Prior therapy requirement: Subjects must have received and then progressed or have been intolerant or refractory to at least 1 standard systemic therapy (eg, platinum-based chemotherapy) for metastatic and/or unresectable disease. Subjects who are sensitive to platinum must have received at least 2 prior platinum-containing lines of treatment.

vi. Hepatocellular Carcinoma - Cohort 8

1) Subjects must have progressive disease, or been intolerant to, at least one line of therapy or refuse treatment with sorafenib.

2) Child-Pugh score of 6 points or less and must not have encephalopathy and total bilirubin $\leq 1.5 \times$ upper limit of normal (ULN; ie, Child Pugh A)

3) Subjects must have testing for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody, hepatitis B core antibody, hepatitis B DNA polymerase chain reaction (PCR), hepatitis C antibody, or hepatitis C RNA PCR.

4) Subjects with hepatitis B infection must have hepatitis B DNA viral load < 100 IU/mL and must be on anti-viral therapy per institutional guidelines.

5) Subjects with hepatitis B infection must not have co-infection with hepatitis C or hepatitis D (must obtain hepatitis D antibody testing).

6) Subjects must not have clinically significant ascites or clinically significant variceal bleeding.

vii. Solid tumors types as listed in part D are a part of Cohort 10, Part E

1) Subjects with NSCLC (prior I/O therapy), bladder, SCCHN, ovarian cancer and hepatocellular cancer. Must meet inclusion criteria listed in part D. Must not meet exclusion criteria

2) 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 must meet inclusion criteria as stated above. Subjects who refuse or are

ineligible for standard therapy will be allowed to enroll provided their refusal/ineligibility is documented in medical records

h) Conditions for all tumor types

[redacted]

2) Not applicable for revised protocol 03
3) Subjects must have ≤ 5 prior treatment regimens. The following are not considered separate lines of treatment: addition of a compound to an on-going regimen, re-starting the same regimen after a drug holiday, or switching from IV to oral therapy.

[redacted]

Parts A-E:

Not applicable as of revised protocol 03.

Adequate organ function for subjects with solid tumor histologies, which is defined as follows:

1) White blood cell ≥ 2000/μL (stable off any growth factor within 4 weeks of first study drug administration)
2) Neutrophils ≥ 1500/μL (stable off any growth factor within 4 weeks of first study drug administration)
3) Platelets ≥ 100 x 10^3/μL (transfusion to achieve this level is not permitted within 2 weeks of first study drug administration) subjects with hepatocellular cancer≥ 60 x 10^3/μL
4) Hemoglobin ≥ 8.5 g/dL (transfusion to achieve this level is not permitted within 2 weeks of first study drug administration)
5) Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3x ULN subjects with hepatocellular cancer ≤ 5x ULN

6) Total bilirubin ≤ 1.5x ULN (except subjects with Gilbert's Syndrome who must have normal direct bilirubin) subjects with hepatocellular cancer Bilirubin < 3 mg/dL

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

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

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

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

9) Albumin > 2.8 mg/dL

10) Ability to comply with treatment, PK [redacted] sample collection, and required study follow-up.

11) Subject Re-enrollment: This study permits the re-enrollment of a subject that has discontinued the study as a pre-treatment failure (e.g., subject has not been treated). If re-enrolled, the subject must be re-consented.

3) Age and Reproductive Status

a) Men and women, ages ≥ 18 years at the time of informed consent

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

c) Women must not be breastfeeding.

d) WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug (s) plus 5 half-lives of study drug plus 30 days (duration of ovulatory cycle) for a total of 23 weeks post-treatment completion.

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug (s) plus 5 half-lives of study drug (s) plus 90 days (duration of sperm turnover) for a total of 31 weeks post treatment completion.

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

Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise 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% when used consistently and correctly.

At a minimum, subjects must agree to the use of two methods of contraception, with one method being highly effective and the other method being either highly effective or less effective as listed below:

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly. WOCBP and female partners of male subjects who are WOCBP are expected to use one of the highly effective methods of contraception (listed below). Local laws and regulations may require use of alternative and/or additional contraception methods. Male subjects must inform their female partners who are WOCBP of the contraceptive requirements of the protocol and are expected to adhere to using contraception with their partner. Male subjects are expected to use a condom, in addition to a highly effective method as noted in the list below

1) Progestogen only hormonal contraception associated with inhibition of ovulation
2) Hormonal methods of contraception including oral contraceptive pills containing combined estrogen and progesterone, vaginal ring, injectables, implants, and intrauterine devices (IUDs), such as Mirena®
4) Nonhormonal IUDs, such as ParaGard®
5) Bilateral tubal occlusion
6) Vasectomized partner with documented azoospermia 90 days after procedure
    - Vasectomy is a highly effective birth control method provided that the partner is the sole sexual partner of the WOCBP study participant and that the vasectomized partner has received medical assessment of the surgical success.
7) Intrauterine hormone-releasing system
8) Complete abstinence
    - Complete abstinence is defined as the complete avoidance of heterosexual intercourse (refer to Glossary of Terms, Section 10)
    - Complete abstinence is an acceptable form of contraception for all study drugs and must be used throughout the duration of the study treatment (plus 5 half-lives of the study drug(s) plus 30 days).
    - It is not necessary to use any other method of contraception when complete abstinence is elected.
    - Subjects who choose complete abstinence must continue to have pregnancy tests, as specified in Section 5.1.
    - Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.
    - The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the subject.
9) Use a condom in male subjects with female partners.

UNACCEPTABLE METHODS OF CONTRACEPTION

1) Periodic abstinence (calendar, symptothermal, and/or post-ovulation methods)
2) Withdrawal (coitus interruptus)

3) Spermicide only
4) Lactation amenorrhea method
5) Diaphragm with spermicide
6) Cervical cap with spermicide
7) Vaginal sponge with spermicide
8) Male or female condom with or without spermicide*
9) Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action.

3.9.2 Exclusion Criteria

1. Target Disease Exceptions
   a) Subjects with known or suspected central nervous system (CNS) metastases, untreated CNS metastases, or with the CNS as the only site of disease are excluded. However, subjects with controlled brain metastases will be allowed to enroll. Controlled brain metastases are defined as no radiographic progression for at least 4 weeks following radiation and/or surgical treatment (or 4 weeks of observation if no intervention is clinically indicated), and off of steroids for at least 2 weeks, and no new or progressive neurological signs and symptoms.
   b) Subjects with carcinomatous meningitis
2. Medical History and Concurrent Diseases
   a) Subjects with a prior malignancy are excluded (except non-melanoma skin cancers, and in situ cancers such as the following: bladder, colon, cervical/dysplasia, melanoma, or breast). Subjects with other second malignancies diagnosed more than 2 years ago who have received therapy with curative intent with no evidence of disease during the interval who are considered by the Investigator to present a low risk for recurrence will be eligible.
   b) Other active malignancy requiring concurrent intervention
   c) Prior organ allograft
   d) Any anti-cancer therapy (e.g., chemotherapy, biologics, vaccines, or hormonal treatment) including investigational drugs within 4 weeks prior to the first dose of study drug administration, with the exception of GnRH agonist therapy for subjects with prostate cancer and anti-cancer therapies with T-HALF < 4 weeks (e.g. prior use of EGFR TKI (completed at least two weeks prior to first dose of study drug is acceptable).
   e) Prior therapy with T-cell stimulatory anti-GITR antibody
   f) Subjects with active, known or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, euthyroid patients with a history of Grave's disease (subjects with suspected autoimmune thyroid disorders must be negative for thyroglobulin and thyroid peroxidase antibodies and thyroid stimulating immunoglobulin prior to first dose of study drug), psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

g) Subjects with interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity, including subjects with pneumonitis

h) Chronic Obstructive Pulmonary Disease requiring recurrent steroids bursts or chronic steroids at doses greater than 10 mg/day of prednisone or the equivalent

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

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

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

   ii) uncontrolled angina within the past 3 months

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

   iv) QTcF prolongation > 480 msec

   v) history of other clinically significant heart disease (e.g., cardiomyopathy, congestive heart failure with New York Heart Association functional classification III-IV, pericarditis, significant pericardial effusion)

   vi) requirement for daily supplemental oxygen therapy

   vii) Subjects with history of myocarditis, regardless of etiology

k) History of any chronic hepatitis as evidenced by:

   i) Positive test for HBsAg

   ii) Positive test for qualitative hepatitis C viral load (by PCR)

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

   b.) Criteria k) do not apply to subjects with hepatocellular cancer, (see section 3.9.1)

l) Evidence of active infection ≤ 7 days prior to initiation of study drug therapy (does not apply to viral infections that are presumed to be associated with the underlying tumor type required for study entry).

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

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

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

p) All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have resolved to Grade 1 (NCI CTCAE version 4.03) or baseline before administration of study drug. Subjects with toxicities attributed to prior anti-cancer therapy which are not expected to resolve and result in long lasting sequelae, such as neuropathy after platinum based therapy, are permitted to enroll.

q) Use of non-oncology vaccines containing live virus for prevention of infectious diseases within 12 weeks prior to study drug. The use of inactivated seasonal influenza vaccines e.g. Fluzone® will be permitted on study without restriction.

r) Use of pRBC or platelet transfusion within 2 weeks prior to the first dose of study drug.

s) A known or underlying medical condition that, in the opinion of the Investigator or Sponsor, could make the administration of study drug hazardous to the subjects, or could adversely affect the ability of the subject to comply with or tolerate the study.

3. Physical and Laboratory Test Findings

   a) Positive tests for hepatitis B virus surface antigen, hepatitis B core antibody, or hepatitis C RNA (Subjects with positive hepatitis C antibody and negative quantitative hepatitis C by PCR are eligible.) Additional testing or substitute testing per institutional guidelines to rule out infection is permitted

4. Allergies and Adverse Drug Reaction

   a) History of allergy to nivolumab

   b) History of any significant drug allergy (such as anaphylaxis or hepatotoxicity) to prior anti-cancer immune modulating therapies (e.g. checkpoint inhibitors, T cell co-stimulatory antibodies)

5. 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/treatments as listed in Section 3.10.1

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.

3.9.3 Women of Childbearing Potential

Women of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 in the absence of other biological or physiological causes. In addition,

females under the age of 55 years must have a documented serum follicle stimulating hormone, (FSH) level > 40 mIU/mL to confirm menopause.

Females treated with 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.

3.10 Concomitant Treatments

3.10.1 Prohibited and/or Restricted Treatments

a) Immunosuppressive agents (except as stated in Section 3.10.3), unless they are utilized to treat an AE.

b) Concomitant therapies are allowed but must be recorded on the case report form (CRF).

c) Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids, and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.

d) Herbal remedies which are not approved in writing by the PI

3.10.2 Other Restrictions and Precautions

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. Magnetic resonance imaging (MRI) contrast should not be given to subjects with severe renal insufficiency (e.g., estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2) because of increased risk of nephrogenic systemic fibrosis in this subject population. In these patients, alternative imaging tests, or MRI without gadolinium should be considered. In addition, subjects are excluded from MRI if they have tattoos, metallic implants, pacemakers, etc.

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

3.10.3 Permitted Therapy

Subjects are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Systemic treatment with a short course of steroids (< 5 days) up to 7 days prior to initiating study drug is permitted. A brief course of systemic corticosteroids for prophylaxis (e.g., contrast dye allergy) or for treatment of non-autoimmune conditions (e.g., delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.

- Systemic immunosuppressive agents and the use of systemic corticosteroids are permitted in the context of treating AEs. Subjects receiving corticosteroids for treatment of drug-related AEs must be at < 10 mg/day prednisone or equivalent prior to re-initiation of study therapy for ≤7 days. Subjects may continue to receive HRT.
- Subjects are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption).

3.10.4 Palliative Local Therapy

- Palliative and supportive care for disease related symptoms may be offered to all subjects on the trial after the DLT evaluation period. Limited radiation therapy or surgery to control isolated lesions is permitted for subjects who have investigator assessed clinical benefit following consultation with the BMS Medical Monitor.
- Subjects should not receive study treatment during radiation as the potential for overlapping toxicities with radiotherapy and BMS-986156, or combination of BMS-986156 and nivolumab currently is not known. Anecdotal data suggest that radiotherapy administered to subjects while receiving nivolumab therapy is tolerable. However, because concurrent radiotherapy and immunotherapies in cancer have not been formally evaluated, in cases where palliative radiotherapy is required for a tumor lesion, then BMS-986156 alone or BMS-986156 in combination with nivolumab should be withheld for at least 1 week before, during, and 1 week after radiation. Subjects should be closely monitored for any potential toxicity during and after receiving radiotherapy, and AEs related to radiotherapy should resolve to Grade 1 prior to resuming study therapy.
- Subjects who have received palliative local therapy will be documented as having had disease progression for the purpose of efficacy analyses.

3.11 Discontinuation of Subjects Following Any Treatment with Study Drug

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

- Subject's request to stop study treatment and/or participation in the study
- Any clinical AE, laboratory abnormality or intercurrent illness which, in the opinion of the Investigator, indicates that continued participation in the study is not in the best interest of the subject
- Termination of the study by BMS
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness
- Pregnancy

- Documented and confirmed disease progression as defined by RECIST (see Appendix 3) unless subject meets criteria for treatment beyond progression (Section 3.11.1)
- Clinical deterioration while receiving active study therapy that in the opinion of the Investigator indicates that continued participation in the study is not in the best interest of the subject
- Discretion of the Investigator
- Inability to comply with the protocol requirements
- Protocol defined reasons for discontinuation (see Section 4.3.6).

In the case of pregnancy, the Investigator must immediately notify the BMS Medical Monitor/Designee of this event. In most cases, the study drug will be permanently discontinued in an appropriate manner. If the Investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug, a discussion between the Investigator and the BMS Medical Monitor/Designee must occur.

All subjects who discontinue IP should comply with protocol specified follow-up procedures as outlined in Section 3.3. 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 (e.g., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

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

3.11.1 Treatment Beyond Disease Progression

As described in Section 1.1.3 accumulating evidence indicates a minority of subjects with solid tumors treated with immunotherapy may derive clinical benefit despite initial evidence of PD. Subjects will be permitted to continue on treatment beyond initial RECIST v1.1 (see Appendix 3) defined PD, as long as they meet the following criteria:

- Investigator-assessed clinical benefit, and do not have rapid disease progression
- Continue to meet all other study protocol eligibility criteria
- Tolerance of study drug
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases)
- Subject provides written informed consent prior to receiving any additional nivolumab or BMS-986156 treatment, using an ICF describing any reasonably foreseeable risks or discomforts, or other alternative treatment options
- Absence of signs or symptoms indicating disease progression

The assessment of clinical benefit should take into account whether the subject is clinically deteriorating and unlikely to receive further benefit from continued treatment. All decisions to continue treatment beyond initial progression must be discussed with the BMS Medical Monitor

and an assessment of the risk/benefit of continuing with study therapy must be documented in the study records. Subjects will be re-consented to explain the rationale for this ongoing treatment.

3.11.1.1 Discontinuation Due to Further Progression (Confirmed Progression)

Subjects should discontinue study therapy upon further evidence of further progression, defined as an additional 10% or greater increase in tumor burden volume from time of initial progression (including all target lesions and new measurable lesions).

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

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

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

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

3.11.1.2 Assessment Schedule for Subjects with Post-progression Treatment

Subjects should continue to receive monitoring according to the On-Treatment Assessments in Section 5.3. Radiographic assessment by computerized tomography (CT; preferred) or MRI described in Section 5 is required when subjects continue post-progression treatment. For subjects that discontinue post-progression treatment with study therapy, no additional radiographic assessments will be required.

3.12 Post Study Drug Follow up

Post-study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study drug must continue to be followed per the Safety Follow-up (approximately 100 days).

3.12.1 Withdrawal of Consent

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

3.12.2 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 three 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 third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the Investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the Investigator should be reported and documented in the subject's medical records.

4 TREATMENTS

All protocol-specified investigational and non-IPs 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: Study Drugs for CA009002

Product Description Class and Dosage Form	Potency	IP/Non-IP	Blinded or Open Label	Packaging/Appearance	Storage Conditions (per Label)
BMS-986156 injection	100 mg/vial (10 mg/mL)	IP	Open	Clear to opalescent colorless to pale yellow liquid. May contain particles	2 to 8°C. Protect from light
Nivolumab injection	100 mg/vial (10 mg/mL)	IP	Open	Clear to opalescent colorless to pale yellow liquid. May contain particles	2 to 8°C. Protect from light and freezing

Abbreviation: IP, investigational product

4.1.1 Investigational Product

An IP, also known as investigational medicinal product in some regions, is defined 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 IP should be stored in a secure area according to local regulations. It is the responsibility of the Investigator to ensure that IP is only dispensed to study subjects. The IP must be dispensed only from official study sites by authorized personnel according to local regulations.

In this protocol, IPs are: BMS-986156 and nivolumab.

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-IPs.

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

4.1.3 Storage and Dispensing

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

Non-study drug not supplied by BMS will be stored in accordance with the package insert.

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

For non-IP, if marketed product is utilized, it should be stored in accordance with the package insert, SmPC, or similar.

For treatment visits where both BMS-986156 and nivolumab are administered, nivolumab will be administered first for 30 minutes followed by BMS-986156 at least 30 minutes after completion of the nivolumab infusion. 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-labeled study. All subjects must be assigned a subject number upon providing signed written informed consent. During the Screening visit, the investigative site will call into the enrollment option of the 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 [redacted]. The patient

identification number (PID) will ultimately be comprised of the site number and subject number. For example, the first subject screened (e.g., enrolled) at site number 1, will have a PID [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 following the Screening visit, the investigative site will call the IVRS within 3 days prior to the first study drug administration for the subject to be either:

- Assigned to a part (Part A or Part B) and dose cohort in the dose escalation portion of the study
- Assigned to a part (Part C, D, or E F) and dose cohort in the dose expansion portion of the study.

During dose escalation, all subjects will be assigned to Part A until the decision is made to start the combination with nivolumab at n-1 dose level. 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 (Part A and Part 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.

Subjects in expansion cohorts in Parts C and D and E may be added if adequate paired pre-treatment and on-treatment biopsy specimens are not obtained. The replacement subject will receive the same treatment as the subject being replaced but a new subject number will be assigned.

Escalation and expansion may be open in parallel. Once expansion is open subjects eligible for parts C and D and E based on tumor type, may be assigned to any open cohort.

4.3 Selection and Timing of Dose for Each Subject

Each subject will be assigned to a specific dose level as listed in Section 4.2 in sequential order during dose escalation. Subjects in cohort expansion will be treated at the MTD, the MAD, or at an alternate dose(s), as agreed upon by the Investigators and the Sponsor.

Nivolumab will be administered as flat doses in cohorts B and D at 240 mg and in cohort E, at 480 mg. There will be no dose escalations or reductions of nivolumab allowed once assigned. Subjects may be dosed no less than 12 days from the previous dose. There are no pre-medications recommended for nivolumab on the first cycle. If an acute infusion reaction is noted, the subjects should be managed according to Section 4.3.7.

BMS-986156 will be administered as flat dosing at the doses listed in Section 1.1.1.

4.3.1 Dose-limiting Toxicities

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

Non-hematologic Dose-limiting Toxicity (DLT)

A. Hepatic Non-hematologic DLT

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

- Any Grade ≥ 3 elevation of AST, ALT, or total bilirubin
- Grade 2 AST or ALT with symptomatic liver inflammation (e.g., right upper quadrant tenderness, jaundice, pruritus)
- AST or ALT > 3 x ULN and concurrent total bilirubin > 2 x ULN without initial findings of cholestasis (elevated serum ALP (e.g., findings consistent with Hy's law or FDA definition of potential drug-induced liver injury or pDILI). Note that this special category of DLT uses ULN rather than CTC Grade for definition

B. Non-hepatic Non-hematologic DLT

Any of the following events will be considered a Non-Hepatic Non-Hematologic DLT:

- Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity ≤2 weeks OR requires systemic treatment
- Grade 3 drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
- Any Grade 3 or greater non-dermatologic, non-hepatic non-hematologic study drug-related toxicity will be considered a dose-limiting toxicity with the following specific EXCEPTIONS:
  - Grade 3 or grade 4 electrolyte abnormalities that are not complicated by associated clinical adverse experiences, last ≤48 hours and either resolve spontaneously or respond to conventional medical intervention
  - Grade 3 nausea, vomiting or diarrhea that lasts less than 48 hours, and either resolves spontaneously or responds to conventional medical intervention
  - Isolated Grade 3 elevation of amylase or lipase not associated with clinical or radiographic evidence of pancreatitis
  - Isolated Grade 3 fever not associated with hemodynamic compromise (eg, hypotension, clinical or laboratory evidence of impaired end-organ perfusion)
  - Grade 3 endocrinopathy that is well controlled by hormone replacement
  - Grade 3 tumor flare (defined as pain, irritation, or rash that localizes to sites of known or suspected tumor)
  - Grade 3 fatigue for ≤7 days
  - Grade 3 infusion reaction that returns to Grade 1 in ≤ 6 hours

C. Dermatologic DLT

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

D. Hematologic DLT (Study Drug-related)

- Grade 4 neutropenia ≥ 5 days in duration
- Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with clinically significant bleeding, or any requirement for platelet transfusion
- Grade 4 anemia not explained by underlying disease
- Grade 4 febrile neutropenia
- Grade 3 febrile neutropenia that lasts > 48 hours
- Grade ≥ 3 hemolysis (ie, requiring transfusion or medical intervention such as steroids)

4.3.2 Management Algorithms for Immuno-oncology Agents

Immuno-oncology (I-O) agents are associated with AEs that can differ in severity and duration from AEs caused by other therapeutic classes. Nivolumab and BMS-986156 are considered I-O agents in this protocol. Early recognition and management of AEs associated with I-O agents may mitigate severe toxicity. Management algorithms that have been developed from extensive experience with nivolumab to assist Investigators in assessing and managing the following groups of AEs:

- Gastrointestinal
- Renal
- Pulmonary
- Hepatic
- Endocrinopathies
- Skin
- Neurological
- The clinical nature of AEs noted with BMS-986156 will determine the role of the above algorithms for use in toxicities related to its use in this study.

The algorithms recommended for utilization in this protocol are included in Appendix 4.

4.3.3 Guidelines for Dose Modification

Intra-subject dose escalation or reduction of BMS-986156 or nivolumab is not permitted in this study in order to allow better evaluation of extended safety and efficacy at individual dose levels and schedules.

4.3.4 Dose Delays Due to Toxicity

Subjects who experience a DLT must have study drug held. Subjects who are required to permanently discontinue both study drugs are listed in Section 4.3.6. In addition, all Grade 2 hepatic, pulmonary, renal, gastrointestinal, and neurological AEs should be evaluated and managed per the toxicity management algorithms (Appendix 4). Subjects not meeting guidelines for permanent discontinuation will be permitted to resume therapy based on the criteria specified below in Section 4.3.5. Subjects eligible to resume study therapy will resume study therapy at the treatment visit following their last received study medication dose.

In Parts A and C, if there is a delay in dosing of BMS-986156 of between 1 -12 days, the procedures at the original scheduled visit should be performed as soon as possible. If the delay is more than

12 days, the visit and dose will be considered missed; the procedures at the next scheduled visit should be performed, and subsequent BMS-986156 doses will follow every 2 weeks.

In Parts B, D and E depending on the dosing schedule (See Table 5.1-2), if there is a delay in dosing of combination dose (same day dose of BMS-986156 and nivolumab) of between 1 -12 days, If the delay is more than 12 days, the visit and dose will be considered missed; the procedures at the next scheduled visit should be performed, and subsequent combination doses will follow after 2 weeks.

Extensions to the period of dose delays may be granted for individual subjects on a case by case basis after specific consultation and agreement between the Investigator and BMS Medical Monitor in settings where benefit/risk may justify continued study therapy (e.g., subject deriving clinical benefit who requires prolonged steroid taper for management of non-DLT drug-related AEs, or experiences delays for management of a non drug related AE).

The end of cycle tumor assessments (i.e., CT/MRI, positron emission tomography, etc) will continue on an every 8 weeks schedule relative to the subject's 1st dose regardless of any treatment delay incurred.

4.3.5 Criteria to Resume Treatment

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

Subjects experiencing AEs not meeting criteria for permanent discontinuation as outlined in Section 4.3.6 may resume treatment with study medication under the following criteria:

- Subjects may resume treatment with study drug when the drug-related AE(s) resolve to Grade ≤ 1 or baseline value with the following exceptions:
  - Subjects may resume treatment in the presence of Grade 2 fatigue;
  - Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity;
  - Subjects with Grade 2 uveitis or eye pain or blurred vision not meeting DLT criteria (Section 4.3.1) must resolve to baseline prior to resuming study therapy;
  - Drug-related pulmonary toxicity, diarrhea, or colitis, must have resolved to baseline before treatment is resumed;
  - Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment.

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

The consideration to re-initiate study therapy under these exceptions will 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. Any AE with clinical risk will be assessed on a case by case basis with the Investigator and the BMS Medical Monitor to determine the risks and benefits of continuing on therapy following resolution versus discontinuing therapy permanently.

If treatment with study medication is delayed > 6 weeks, the subject must be permanently discontinued from study therapy, except as specified in Section 4.3.6.

4.3.6 Guidelines for Permanent Discontinuation

Subjects will be required to permanently discontinue both study drugs for the following AEs:

- Any drug related AE occurring at any time that meets DLT criteria as outlined in Section 4.3.1 will require permanent discontinuation with the following **exceptions**:
  a) Grade 3 diarrhea, nausea, vomiting, or abdominal pain that returns to grade 1 or baseline within 3 days with medical intervention;
  b) Grade 3 pruritus or rash that returns to grade 1 or baseline within 7 days or baseline with medical intervention;
  c) Grade 4 electrolyte abnormalities that ≤ 72 hours in duration;
  d) Grade 4 neutropenia ≤ 5 days in duration;
  e) Grade 4 increase in amylase or lipase that is not associated with clinical or radiographic evidence of pancreatitis;
  f) Grade 4 lymphopenia ≤ 5 days in duration.
- Any dosing delay lasting > 6 weeks will be cause for permanent discontinuation. Extensions to the period of dose delays may be granted for individual subjects on a case by case basis after specific consultation and agreement between the Investigator and BMS Medical Monitor in settings where benefit/risk may justify continued study therapy (e.g., subject deriving clinical benefit who requires prolonged steroid taper for management of non-DLT irAEs, or experiences delays for management of a non-drug-related AE).
- Accordingly, dosing delays to allow for prolonged steroid tapers to manage drug-related AEs are allowed. Additionally, dosing delays > 6 weeks 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.

All subjects who discontinue IP should comply with protocol specified follow-up procedures as outlined in Section 3.3. 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 (e.g., 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 CRF page.

4.3.7 Treatment of Drug-related Infusion Reactions

Since BMS-986156 and nivolumab contain only human immunoglobulin protein sequences, it is 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, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion

reactions should be reported within 24 hours to the BMS Medical Monitor and reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE v4.03 guidelines.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines as appropriate:

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

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

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

- Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); monitor subject until resolution of symptoms.
- Bronchodilator or corticosteroid therapy may also be administered as appropriate.
- The infusion may be restarted at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely.
- The amount of study drug infused must be recorded on the CRF.
- If symptoms recur, then no further nivolumab, as the case may be, will be administered at that visit.
- The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional nivolumab administrations. If necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent) may be used.

Late-occurring symptoms: In the 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 (eg, oral antihistamine, or corticosteroids).

For Grade 3 or Grade 4 symptoms (Severe reaction, Grade 3: prolonged [e.g., 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]; Grade 4: life-threatening; pressor or ventilatory support indicated).

Immediately discontinue study drug infusion. Begin an IV infusion of normal saline, and treat the subject as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or

equivalent), as needed. Subject should be monitored until the Investigator is comfortable that the symptoms will not recur. Study drug will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms. In the 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).

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-986156 and nivolumab administration in subjects' medical records and CRF.

4.6 Destruction of Study Drug

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

Any unused study drugs can only be destroyed after being inspected and reconciled by the responsible BMS Study Monitor unless study drug containers must be immediately destroyed as required for safety, or to meet local regulations (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 systems and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

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.

4.7 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 BMS. The return of study drug will be arranged by the responsible 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.

Arrangements for the return of study drug will be made by the responsible Study Monitor.

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 (CA009002)

Procedure	Screening Visit (Day -28 to -1)	Day -14 to -1 Visit	Day -3 to -1 Visit	Notes
Eligibility Assessments				
Informed consent	X			A subject is considered enrolled only when a protocol specific informed consent is signed. Obtain subject number from IVRS.
Inclusion/Exclusion criteria	X			
Medical history	X			Include any toxicities or allergy related to previous treatments.
Prior systemic therapies	X			
Tobacco history/status	X			Document subject's history and current status of tobacco use.
[redacted]				
Safety Assessments				
PE	X			If the screening PE is performed within 1 day of dosing on C1D1, then a single exam may count as both the screening and pre-dose evaluation.
Physical measurements	X			Includes height, weight
ECOG performance status	X			See Appendix 2
Vital signs	X			Includes body temperature, respiratory rate, seated blood pressure and heart rate. Blood pressure, respiratory rate and heart rate should be measured after the subject has been resting quietly for at least 5 minutes.

Table 5.1-1: Screening Procedural Outline (CA009002)

Procedure	Screening Visit (Day -28 to -1)	Day -14 to -1 Visit	Day -3 to -1 Visit	Notes
Oxygen saturation	X			Pulse oximetry collected at rest. Oxygen levels will be used in combination with clinical signs and symptoms and radiographic images to evaluate pulmonary/respiratory status. Changes in O_2 levels will not be used in isolation to document or diagnosis pulmonary toxicity.
ECGs	X			12-lead ECGs should be recorded after the subject has been supine for at least 5 minutes.
Laboratory Tests				***Laboratory tests listed below must be completed within 2 weeks of Day 1 unless otherwise noted.***
Chemistry (excluding LFTs)		X		Includes assessments for sodium, potassium, chloride, total serum calcium, magnesium, carbon dioxide, phosphorus, BUN, creatinine, creatinine kinase, CrCl, fasting glucose, total protein, albumin, amylase, lipase, CRP, uric acid, and LDH.
Complete blood count (differential & platelets)		X		
LFT assessments		X		Includes AST, ALT, total bilirubin, direct bilirubin (only if total bilirubin is elevated) ALP and GGT (only when ALP increases to ≥ grade 2).
Urinalysis		X		Urine to be checked for protein, glucose, blood, leukocyte esterase, specific gravity and pH. Microscopic examination of sediment if blood, protein, or leukocyte esterase positive on dipstick.
Thyroid function tests		X		TSH with free T3 and free T4.
Mutational and viral status	X			Document EGFR and ALK mutation status for all subjects with NSCLC non-squamous cell histology. Cervical cancer only: Sites must submit and document prior HPV status within 28 days of dosing. For subjects with unknown status, tumor tissue will be required, per inclusion criteria. Subjects must consent to HPV testing.
Serology tests	X			Within 28 days of dosing: hepatitis B surface antigen, hepatitis C antibody (if is positive reflex to hepatitis C RNA) or hepatitis C RNA. **Note**: Testing for HIV-1, HIV-2 must be performed at sites where mandated by local requirements.
Pregnancy test			X	WOCBP only at screening and within 24 hours prior to dosing. The serum pregnancy test may be completed on the first day of treatment provided the results are available

Table 5.1-1: Screening Procedural Outline (CA009002)

Procedure	Screening Visit (Day -28 to -1)	Day -14 to -1 Visit	Day -3 to -1 Visit	Notes
				before the start of study therapy. If performed within 24 hours of dosing on C1D1, then C1D1 pregnancy test is not required.
FSH	X			If needed to document post-menopausal status as defined in Section 3.9.3.
Concomitant medications		X		Collected during the 2 weeks prior to C1D1.
Clinical complaints		X		Collected during the 2 weeks prior to C1D1.
Adverse Event Reporting				
Monitor for SAEs	X			All SAEs must be collected from the date of subject's written consent until 100 days post discontinuation of dosing or subject's participation in the study if the last scheduled visit occurs at a later time. eSAEs should be approved in the electronic capture system within 5 business days of entry.
Efficacy Assessments				
Tumor assessments	X			CT with contrast is the preferred modality (MRI if CT is not feasible). Assessment should include the chest/abdomen/pelvis at a minimum; and should include other anatomic regions as indicated by individual subject disease histories.
Brain imaging	X			Brain imaging (CT/MRI) for subjects with history or symptoms of brain metastases and who have not had brain imaging within 30 days of anticipated first study drug administration
Bone scan	X			As clinical indicated (e.g., subjects with history or symptoms of bone metastases), Bone scans will not be considered a modality for assessment for measurable disease.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; C1D1, cycle 1 day 1; CrCl; creatinine clearance; CRP, C-reactive protein; CT, computerized tomography; ECG, electrocardiogram; EGFR, epidermal growth factor receptor; ECOG, Eastern Cooperative Oncology Group; FFPE, formalin-fixed paraffin-embedded; FSH, follicle-stimulating hormone; GGT, gamma-glutamyl transferase, HPV, human papillomavirus; HIV, human immunodeficiency virus; IVRS, Interactive Voice Response System; LDH, lactate dehydrogenase; LFT, liver function test; MRI, magnetic resonance imaging; PE, physical examination; SAE, serious adverse event; T3, triiodothyronine; T4, thyroxine;; TSH, thyroid-stimulating hormone; WOCBP, women of childbearing potential.

Table 5.1-2: On-Treatment Procedural Outline

Procedure	Cycles 1 -13						
	Day 1 (± 2 days)	Day 15 (± 2 days)	Day 29 (± 2 days)	Day 43 (± 2 days)	Day 49-56	EOT[a,b]	Notes
IVRS Assignment							
IVRS assignment	X						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							
PE	X						
Symptom-directed PE		X	X	X		X[c]	
ECOG performance status	X	X	X	X		X	ECOG score (Appendix 2)
Vital signs	X	X	X	X		X	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. For BMS-986156, vital signs will be obtained before the infusion and then every 15 minutes (± 5 minutes) until 60 minutes after completion of the infusion except for Cycle 1 Day 1 and Cycle 1 Day 15 (where it will be obtained for until 120 minutes post infusion). From cycle 4-13, as long as the patient has not had previous IRRs, vital signs will be obtained before the infusion, after the infusion and at 60 minutes after the completion of the infusion.. If the patient has experienced any IRR, obtain vital signs every 15 minutes (± 5 minutes) until 60 minutes after completion of the infusion. For nivolumab, vital signs will be obtained before the infusion and then every 30 minutes (±10 minutes) until the start of BMS-986156 infusion or per institution guidelines for administration of nivolumab. The 30-minute post nivolumab

Table 5.1-2: On-Treatment Procedural Outline

Procedure	Cycles 1 -13					EOT[a,b]	Notes
	Day 1 (± 2 days)	Day 15 (± 2 days)	Day 29 (± 2 days)	Day 43 (± 2 days)	Day 49-56		
							infusion vital signs may correspond to those pre-infusion BMS-986156 vital signs. In the event BMS-986156 administration is delayed, nivolumab vital signs will be obtained until 60 minutes after completion of the infusion. If any vital sign is abnormal (based upon clinician assessment) at the final check, the subject must be observed further for a period of time, as clinically indicated.
12-lead ECG	X						All ECG tests will be in performed in triplicates (e.g., 1 ECG test equals 3 consecutive individual 12 lead ECGs performed 5 minutes apart). [redacted]
Laboratory Tests	**On study labs (including pregnancy testing) to be done on site/local. Within 72 hrs prior to dosing** ***All labs will be done weekly for Cycle 1 only. Starting Cycle 2, all of the labs will be done bi-weekly**						
Chemistry (excluding LFTs)*	X	X	X	X		X	Includes assessments for sodium, potassium, chloride, total serum calcium, magnesium, carbon dioxide, phosphorus, BUN, creatinine, creatinine kinase, glucose, total protein, albumin, amylase, lipase, CRP, LDH.
Complete blood count (differential & platelets)*	X	X	X	X		X	
LFT assessments*	X	X	X	X		X	Includes AST, ALT, total bilirubin, direct bilirubin (only if total bilirubin is elevated) ALP and GGT (only when ALP is abnormal).
Thyroid function tests*	X	X	X	X		X	To include TSH with reflex testing (free T3 and free T4) if applicable. Results should be examined by the Investigator or appropriate designee within 48 hours of dose administration.

Table 5.1-2: On-Treatment Procedural Outline

Procedure	Cycles 1 -13					EOT[a,b]	Notes
	Day 1 (± 2 days)	Day 15 (± 2 days)	Day 29 (± 2 days)	Day 43 (± 2 days)	Day 49-56		
Urinalysis *	X	X	X	X		X	Urine to be checked for protein, glucose, blood, leukocyte esterase, specific gravity and pH. Microscopic examination of sediment if blood, protein, or leukocyte esterase positive on dipstick.
Pregnancy test (WOCBP)	X	X	X	X		X	Serum/urine pregnancy test must be performed (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG) within 24 hours prior to administration of study drug. If the pregnancy test is positive, hold all study drugs and perform confirmatory testing. If pregnancy is confirmed, permanently discontinue all study drug and immediately notify Sponsor per Section 6.4.
Adverse Event Reporting & Concomitant Medication Assessments[d]							
Concomitant medication assessments	X	X	X	X	X	X	Review prior to dosing
Monitor for non-serious AEs	X	X	X	X	X	X	Non-serious AEs will be collected starting with the first dose of study medication and through 100 days after discontinuation of dosing.
Monitor for SAEs	X	X	X	X	X	X	All SAEs must be collected from the date of subject's written consent until 100 days post discontinuation of dosing or subject's participation in the study if the last scheduled visit occurs at a later time. eSAEs should be approved in in the electronic capture system within 5 business days of entry.
Sample Collection							
PK assessments	See Section 5.5 and Table 5.5.1-1						Performed in all subjects.
[redacted]							
Immunogenicity assessments	See Table 5.5.1-1						Performed in all subjects.

Table 5.1-2: On-Treatment Procedural Outline

Procedure	Cycles 1 -13						
	Day 1 (± 2 days)	Day 15 (± 2 days)	Day 29 (± 2 days)	Day 43 (± 2 days)	Day 49-56	EOT[a,b]	Notes
[redacted]							
Efficacy Assessments							
Tumor/Response assessment					X	X	By methods used at baseline. Same modality/scanner should be used for all assessments. Assessed by RECIST v1.1 (Appendix 3). Assessment must be performed prior to initiating the next cycle of treatment.
Brain imaging					X		As clinically indicated.
Bone scan					X		As clinically indicated.

Table 5.1-2: On-Treatment Procedural Outline

Procedure	Cycles 1 -13						
	Day 1 (± 2 days)	Day 15 (± 2 days)	Day 29 (± 2 days)	Day 43 (± 2 days)	Day 49-56	EOT[a,b]	Notes
Study Drug Administration							Details regarding preparation and administration are provided in site training materials.
Parts A, B, C, and D: BMS-986156 administration	X	X	X	X			Use vials assigned per IVRS.
Part E: BMS-986156 administration	X		X				Use vials assigned per IVRS
Parts B and D ONLY: nivolumab administration	X	X	X	X			Use vials assigned per IVRS. Nivolumab is administered ONLY for those subjects enrolled in Part B (dose escalation, combination therapy) and Part D (cohort expansion, combination therapy).
Part E ONLY: nivolumab administration	X		X				Use vials assigned per IVRS, for subjects enrolled in Part E

Abbreviations: AE, adverse event, ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CRP, C-reactive protein; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EOT, end of treatment GGT, gamma-glutamyl transferase; hCG, human chorionic gonadotropin; IVRS, Interactive Voice Response System; LDH, lactate dehydrogenase; LFT, liver function test; [redacted] PE, physical examination; PK, pharmacokinetics; RECIST, Response Evaluation Criteria in Solid Tumor; SAE, serious adverse event; T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone; WOCBP, women of childbearing potential.

[a] EOT is defined as the visit where decision is made to discontinue the subject from treatment.

[b] For subject who complete all scheduled cycles of therapy, EOT visit will be the same as the last scheduled and completed on treatment visit (e.g., Cycle 3 Day 43), and the start of week 1 safety follow-up visit.

[c] For subjects that do not complete all scheduled cycles of therapy, EOT visit will be the most recent on-treatment visit (with all available safety and response data) and does not need to be repeated, and will be considered the start of week 1 safety follow up visit.

[d] If there is a safety concern (e.g. Grade 3 or 4 AE, SAE, etc.), ad hoc PK and ADA sample collection would be permissible (using an Unscheduled Visit Form).

Table 5.1-3: Follow-up Procedural Outline (CA009002)

Procedure	Safety Follow-up			
	FU 1 30 days[a] (± 7 days)	**FU 2 60 days (± 7 days)**	**FU 3 100 days (± 7 days)**	**Notes**
Safety Assessments				
PE	X	X	X	Symptom directed only.
ECOG performance status	X	X	X	ECOG score (Appendix 2).
Vital signs	X	X	X	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.
Laboratory Tests				
Chemistry (excluding LFTs)	X	X	X	Includes assessments for sodium, potassium, chloride, total serum calcium, magnesium, carbon dioxide, phosphorus, BUN, creatinine, creatinine kinase, glucose, total protein, albumin, amylase, lipase, CRP, and LDH.
Complete blood count (differential & platelets)	X	X	X	
LFT assessment	Weekly for 8 weeks following last dose of BMS-986156 (if applicable and at 30 Day, 60 Day, 100 Day follow-up.			LFTs will be monitored weekly for 8 weeks following the last dose of BMS-986156. Includes AST, ALT, total bilirubin, Direct bilirubin (only if Total Bilirubin is elevated) ALP and GGT (only when ALP is abnormal).
Thyroid function tests	X	X	X	To include TSH with reflex testing (free T3 and free T4).
Urinalysis	X	X	X	Urine to be checked for protein, glucose, blood, leukocyte esterase, specific gravity

Table 5.1-3: Follow-up Procedural Outline (CA009002)

Procedure	Safety Follow-up			
	FU 1 30 days[a] (± 7 days)	**FU 2 60 days (± 7 days)**	**FU 3 100 days (± 7 days)**	**Notes**
				and pH. Microscopic examination of sediment if blood, protein, or leukocyte esterase positive on dipstick.
Pregnancy Test	X	X	X	For WOCBP; serum or urine pregnancy test may be performed (clinic urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG). If positive, perform confirmatory testing. If pregnancy is confirmed, immediately notify Sponsor per Section 6.4.
Adverse Event Reporting and Concomitant Medication Assessments				
Monitor for non-serious AEs	X	X	X	Non-serious AEs will be collected starting with the first dose of study medication and through 100 days after discontinuation of dosing.
Monitor for SAEs	X	X	X	All SAEs must be collected from the date of subject's written consent until 100 days post discontinuation of dosing or subject's participation in the study if the last scheduled visit occurs at a later time. eSAEs should be approved in in the electronic capture system within 5 business days of entry.
Concomitant medication assessments	X	X	X	
Sample Collection[b]				
PK assessments	See Table 5.5.1-1			

Table 5.1-3: Follow-up Procedural Outline (CA009002)

Procedure	Safety Follow-up			
	FU 1 30 days[a] (± 7 days)	**FU 2 60 days (± 7 days)**	**FU 3 100 days (± 7 days)**	**Notes**
[redacted] Immunogenicity (ADA) assessments	See Table 5.5.1-1			
Efficacy Assessments				
Tumor/Response assessments			X	Diagnostic imaging required by method used at baseline; an unconfirmed PR or unconfirmed CR must be confirmed ≥ 4 weeks after initial assessment. Same modality/scanner should be used for all assessments. Assessed by RECIST v1.1 (Appendix 3).
New anti-cancer therapies	X	X	X	Any new anti-cancer therapies (including surgery and radiotherapy) will be recorded.

Abbreviations: AE, adverse event, ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CR, complete response; CRP, C-reactive protein; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EOT, end of treatment; FU, follow up; GGT, gamma-glutamyl transferase; hCG, human chorionic gonadotropin IVRS, Interactive Voice Response System; LDH, lactate dehydrogenase; LFT, liver function test; [redacted] PE, physical examination; PK, pharmacokinetics; PR, partial response; Q12W, every 12 weeks; RECIST, Response Evaluation Criteria in Solid Tumor; SAE, serious adverse event; SD, stable disease; T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone; WOCBP, women of childbearing potential.

[a] Follow-up visits at Days 30, 60, and 100 (± 7 days) should occur after the last dose or coinciding with the date of discontinuation ±7 days if date of discontinuation is greater than 30 days after the last dose to monitor for AEs.

[b] If there is a safety concern (eg, Grade 3 or 4 AE, SAE, etc.), ad hoc PK and ADA sample collection would be permissible (using an Unscheduled Visit Form).

5.2 Study Materials

The site will provide all required materials for the tests performed locally (e.g., relevant clinical laboratory tests and urine drug screens). The site will have available a well-calibrated scale for recording body weight, a 12-lead ECG machine, and a calibrated sphygmomanometer and thermometer for vital signs assessments. A current and fully-stocked advanced cardiac life support cart will be immediately available on the premises. The site will have urine collection containers, a refrigerated centrifuge, a monitored and alarmed refrigerator, and freezer (-70°C or below), as well as containers and dry ice for shipment and storage of blood and urine samples. The site will provide all materials required for accurate source documentation of study activities and for housing the subjects during the study. The site will source marketed product from a single commercial lot.

BMS will provide a BMS-approved protocol and any amendments or administrative letters (if required), and IBs for BMS-986156 as well as nivolumab. Case report forms (electronic or hard copy) will be provided by BMS. The Central Laboratory will provide labels and tubes for the collection of blood samples for PK [redacted] and for genotyping analysis. Additionally, the IVRS manual and Pharmacy manual will also be provided.

5.3 Safety Assessments

Adverse events will be assessed continuously during the study and for 100 days after the last treatment. Adverse events will be evaluated according to the NCI CTCAE version 4.03 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. Subjects should be followed until all treatment related AEs have recovered to baseline or are deemed irreversible by the Investigator.

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

5.3.1 Imaging Assessment for the Study

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

5.3.2 Laboratory Test Assessments

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

Hematology

Complete blood count with differential and platelets
Hemoglobin
Hematocrit
Total leukocyte count, including differential
Platelet count

Serum Chemistry

AST
ALT
Total bilirubin
Direct Bilirubin (only if Total Bilirubin is elevated)
ALP
Lactate dehydrogenase
Creatinine
Blood Urea Nitrogen
Uric acid (for screening only)
Glucose (Fasting at screen visit)
Amlyase
Lipase
C-reactive Protein
Gamma-glutamyl transferase (only when ALP is abnormal)
Total Protein
Albumin
Sodium
Potassium
Chloride
Carbon dioxide
Calcium
Phosphorus
Magnesium
Creatine kinase
Creatinine Clearance - Screening only

Urinalysis

Protein
Glucose
Blood
Leukocyte esterase
Specific gravity
pH
Microscopic examination of the sediment if blood, protein or leukocytes esterase are positive on the dipstick

Serology

Serum for Hepatitis C Antibody (If Hepatitis C antibody is positive reflex to Hepatitis C RNA) or Hepatitis C RNA, HBsAg, HPV status, HIV-1, -2 antibody (Testing for HIV-1, HIV-2 must be performed at sites where mandated by local requirements).

Other Analyses

Pregnancy Test (WOCBP only)
Thyroid-stimulating hormone (TSH) with reflex to free T3 and free T4 as applicable
FSH (if needed to document post-menopausal status as defined in Section 3.9.3)

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 Laboratory Test Result Abnormalities).

5.4 Efficacy Assessments

Disease assessment with CT and/or MRI as appropriate will be performed at baseline and every 8 weeks during Treatment Phase until disease progression per RECIST v1.1 (see Appendix 3), or until confirmed disease progression for subjects treated beyond progression [defined as an additional 10% or greater increase in tumor burden volume from time of initial progression (including all target lesions and new measurable lesions)], discontinuation of treatment or withdrawal from study. Tumor assessments at other time points may be performed if the Investigator is concerned about tumor progression. Assessment of tumor response will be reported by the Investigator for appropriate populations of subjects as defined by RECIST v1.1[148] (see Appendix 3) for subjects with solid tumors. Same modality/scanner should be used for all assessments.

Changes in tumor measurements and tumor responses will be assessed by the Investigator using RECIST criteria. Investigators will also report the number and size of new lesions that appear while on-study. The time point tumor assessments will be reported on the CRF based on Investigators' assessment using RECIST criteria. Please refer to Appendix 3 for specifics of RECIST v1.1 criteria to be utilized in this study.

5.4.1 Primary Efficacy Assessment

Not applicable.

5.4.2 Secondary Efficacy Assessments

The efficacy assessments will include the ORR (e.g., PR + CR), DOR, and progression-free survival rate (PFSR) at time points (e.g., 24 weeks) based on assessment of tumor response using RECIST v1.1.

[redacted]

5.5 Pharmacokinetic and Immunogenicity Assessments

Samples for PK and immunogenicity assessments will be collected for all subjects receiving BMS-986156 and nivolumab as described in Table 5.5.1-1 and Table 5.5.1-2 . Pharmacokinetics of BMS-986156 will be characterized by noncompartmental analysis method. Immunogenicity samples will be analyzed for anti-BMS-986156 antibodies and/or anti-nivolumab antibodies by validated immunoassays (See Table 5.5.1-1 and Table 5.5.1-2).

The PK parameters to be assessed following Cycle 1 Day 1 and Cycle 3 Day 1 dose administrations, if data permit, include:

Cmax	Maximum observed concentration
Tmax	Time of maximum observed plasma concentration
AUC(0-T)	Area under the plasma concentration-time curve from time 0 to time of last quantifiable concentration
AUC(TAU)	Area under the concentration-time curve in 1 dosing interval

In addition, the PK parameters listed below may be assessed, if data permit, following Cycle 3 Day 1 dose administration:

Cmin	The minimum observed concentration within a dosing interval (e.g., occurring no matter when over the dosing interval)
CLT	Total body clearance
Css-avg	Average concentration over a dosing interval (AUC[TAU]/tau)
AI	Accumulation index; ratio of an exposure measure at steady-state (e.g., following Cycle 3 Day 1 dose) to that after the first dose (exposure measure includes AUC[TAU], Cmax, and concentrations at the end of dosing interval (Ctau).
T-HALF	Apparent terminal half-life in serum
T-HALFeff	Effective elimination half-life that explains the degree of accumulation observed for a specific exposure measure (exposure measure includes AUC[TAU], Cmax, and Ctau)

The following PK parameter will be reported as a separate listing, summary, and plot:

- Ctrough — Trough observed plasma concentrations (this includes predose concentrations and concentrations at the end of dosing interval (Ctau))

5.5.1 Pharmacokinetics and Immunogenicity Collection and Processing

Table 5.5.1-1 lists a detailed sampling schedule to be followed for the assessment of PK and immunogenicity for BMS-986156 as a monotherapy and in combination with nivolumab. All time points are relative to the start of BMS-986156 and nivolumab 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 (EOI; 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. If it is known that a dose is going to be delayed, then the pre-dose sample should be collected just prior to the delayed dose. However, if a pre-dose sample is collected but the dose is subsequently delayed, an additional pre-dose sample should not be collected.

Additional samples for immunogenicity assessments and serum concentration, referred to as "ADA Event Driven" samples, may be collected and justified in cases of Grade 3/4 infusion or hypersensitivity reactions (see Section 4.3.7). The immunogenicity (and corresponding serum concentration) data from these samples will be reported as part of a subject's overall immunogenicity assessment. Uniquely identified specimen collection kits and instructions for collection of "ADA Event Driven" samples will be provided by the central laboratory vendor.

Table 5.5.1-1: Pharmacokinetic and Anti-Drug Antibody Sampling Schedule for every 2 week (Q2W) dosing schedule of for BMS-986156 and Nivolumab(Parts A, B, C, and D)

Study Day of Sample Collection (Each Cycle = 8 weeks)	Event	Time (Relative to BMS-986156 Infusion) Hour: Min	BMS-986156 PK Sample (All Subjects)	[redacted]	BMS-986156 ADA Sample (All Subjects)	Nivolumab ADA Sample (Parts B and D only)
Cycle 1						
Cycle 1 Day 1 (C1D1)	Predose[a]	00:00[a]			X	X
	EOI[b]	01:00[b]				
C1D2		24:00	X			
C1D5[c]		96:00	X			
C1D8[d]		168:00	X			
C1D15	Predose[a]	00:00[a]			X	X
C1D15	EOI[b]	01:00[b]				
C1D29	Predose[a]	00:00[a]			X	X
Cycle 2						
C2D1	Predose[a]	00:00[a]			X	X
C2D29	Predose[a]	00:00[a]				
Cycle 3						
C3D1	Predose[a]	00:00[a]			X	X
	EOI[b]	01:00[b]				
C3D2		24:00	X			
C3D5[c]		96:00	X			
C3D8[d]		168:00	X			
C3D15	Predose[a]	00:00[a]				

Table 5.5.1-1: Pharmacokinetic and Anti-Drug Antibody Sampling Schedule for every 2 week (Q2W) dosing schedule of for BMS-986156 and Nivolumab(Parts A, B, C, and D)

Study Day of Sample Collection (Each Cycle = 8 weeks)	Event	Time (Relative to BMS-986156 Infusion) Hour: Min	BMS-986156 PK Sample (All Subjects)	[redacted]	BMS-986156 ADA Sample (All Subjects)	Nivolumab ADA Sample (Parts B and D only)
Subsequent Treatment Cycles (if applicable)						
C5D1	Predose[a]	00:00[a]		[redacted]	X	X
Adverse event						
Grade 3/4 hypersensitivity reaction[e] /Unscheduled[f]					X	X

Abbreviation: AE, adverse event; ADA, anti-drug antibody; EOI, end of infusion; Min, minutes; PK, pharmacokinetics

[a] Pre-dose: All pre-dose samples for nivolumab and BMS-986156 should be taken prior to the start of nivolumab infusion.

[b] EOI samples for both [redacted] BMS-986156 should be collected at the end of BMS-986156 infusion (preferably within 2 minutes prior to the end of BMS-986156 infusion). If the EOI 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 to 5 of a cycle.

[d] Day 8 sample may be taken during Days 7 to 9 of a cycle.

[e] PK and immunogenicity samples will be collected as directed drug-related AE or Grade 3/4 infusion or when hypersensitivity reaction is confirmed.

[f] If there is a safety concern (e.g. Grade 3 or 4 AE, SAE, etc.), ad hoc PK and ADA sample collection would be permissible (using an Unscheduled Visit Form).

Table 5.5.1-2: Pharmacokinetic and Anti-Drug Antibody Sampling Schedule for every 4 week (Q4W) dosing schedule of BMS-986156 and Nivolumab [Part E - cohort 9 and cohort 10]

Study Day of Sample Collection (Each Cycle = 8 weeks)	Event	Time (Relative to BMS-986156 Infusion) Hour: Min	BMS-986156 PK Sample (All Subjects)	[redacted]	BMS-986156 ADA Sample (All Subjects)	Nivolumab ADA Sample (Parts B, D and E only)
Cycle 1						
Cycle 1 Day 1 (C1D1)	Predose [a]	00:00[a]			X	X
	EOI[b]	01:00[b]				
C1D2		24:00	X			
C1D5[c]		96:00	X			
C1D8[d]		168:00	X			
C1D15		336:00	X		X	X
C1D29	Predose[a]	00:00[a]			X	X
C1D29	EOI[b]	01:00[b]				
Cycle 2						
C2D1	Predose[a]	00:00[a]			X	X
	EOI[b]	01:00[b]				
C2D29	Predose[a]	00:00[a]				
Cycle 3						
C3D1	Predose[a]	0:00 [a]			X	X
	EOI[b]	01:00[b]				
C3D2		24:00	X			
C1D5[c]		96:00	X			

Table 5.5.1-2: Pharmacokinetic and Anti-Drug Antibody Sampling Schedule for every 4 week (Q4W) dosing schedule of BMS-986156 and Nivolumab [Part E - cohort 9 and cohort 10]

Study Day of Sample Collection (Each Cycle = 8 weeks)	Event	Time (Relative to BMS-986156 Infusion) Hour: Min	BMS-986156 PK Sample (All Subjects)	[redacted]	BMS-986156 ADA Sample (All Subjects)	Nivolumab ADA Sample (Parts B, D and E only)
C3D8[d]		168:00	X			
C3D15		336:00	X			
C3D29	Predose[a]	00:00[a]				
Adverse event						
Grade 3/4 hypersensitivity reaction[e]/Unscheduled[f]					X	X

Abbreviation: AE, adverse event; ADA, anti-drug antibody; EOI, end of infusion; Min, minutes; PK, pharmacokinetics

[a] All pre-dose samples for nivolumab and BMS-986156 should be taken prior to the start of nivolumab infusion.

[b] EOI samples for both [redacted] BMS-986156 should be collected at the end of BMS-986156 infusion (preferably within 2 minutes prior to the end of BMS-986156 infusion). If the EOI 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 to 5 of a cycle.

[d] Day 8 sample may be taken during Days 7 to 9 of a cycle.

[e] PK and immunogenicity samples will be collected as directed drug-related AE or Grade 3/4 infusion or when hypersensitivity reaction is confirmed.

[f] If there is a safety concern (e.g. Grade 3 or 4 AE, SAE, etc.), ad hoc PK and ADA sample collection would be permissible (using an Unscheduled Visit Form).

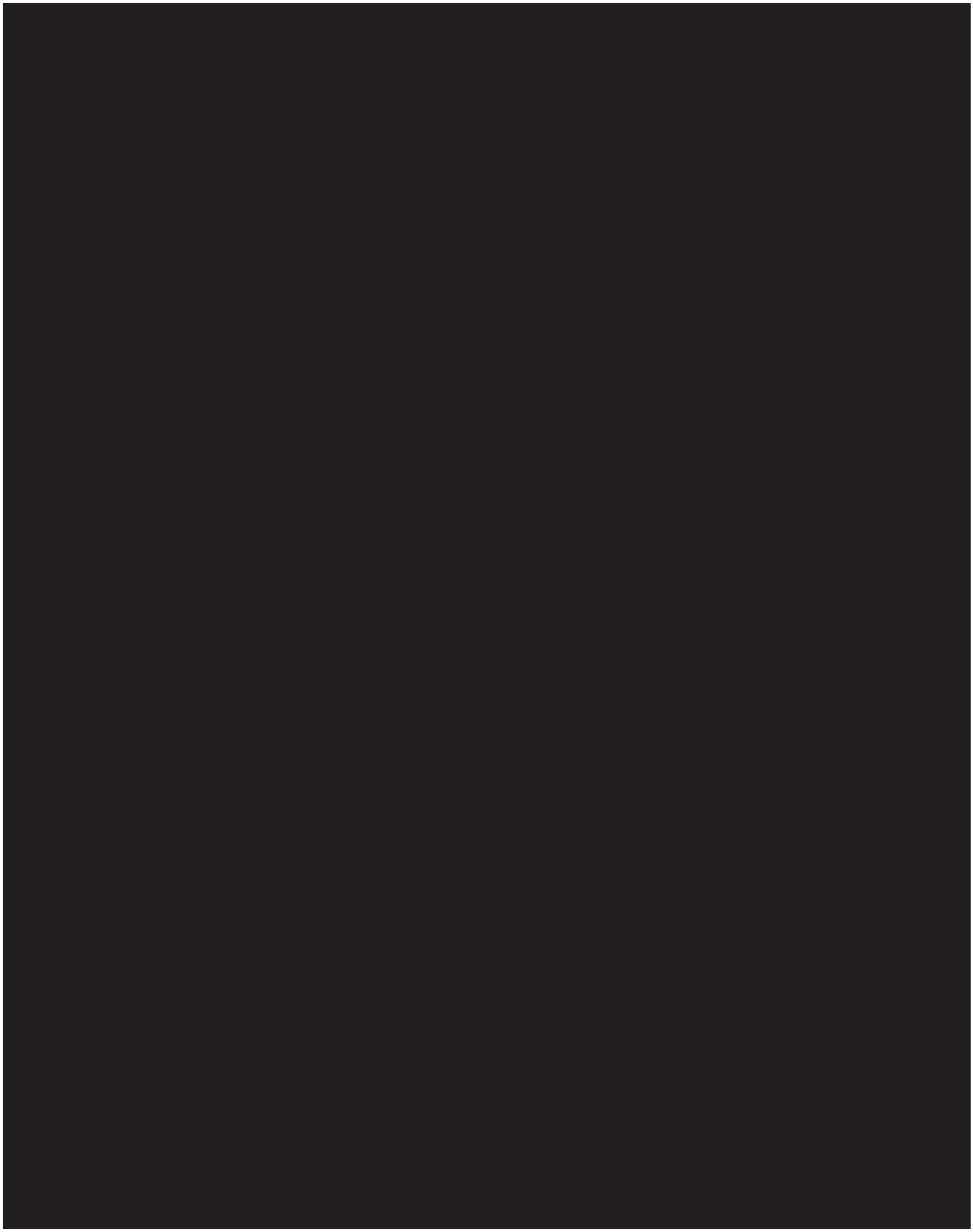
5.5.2 Pharmacokinetic and Immunogenicity Sample Analyses

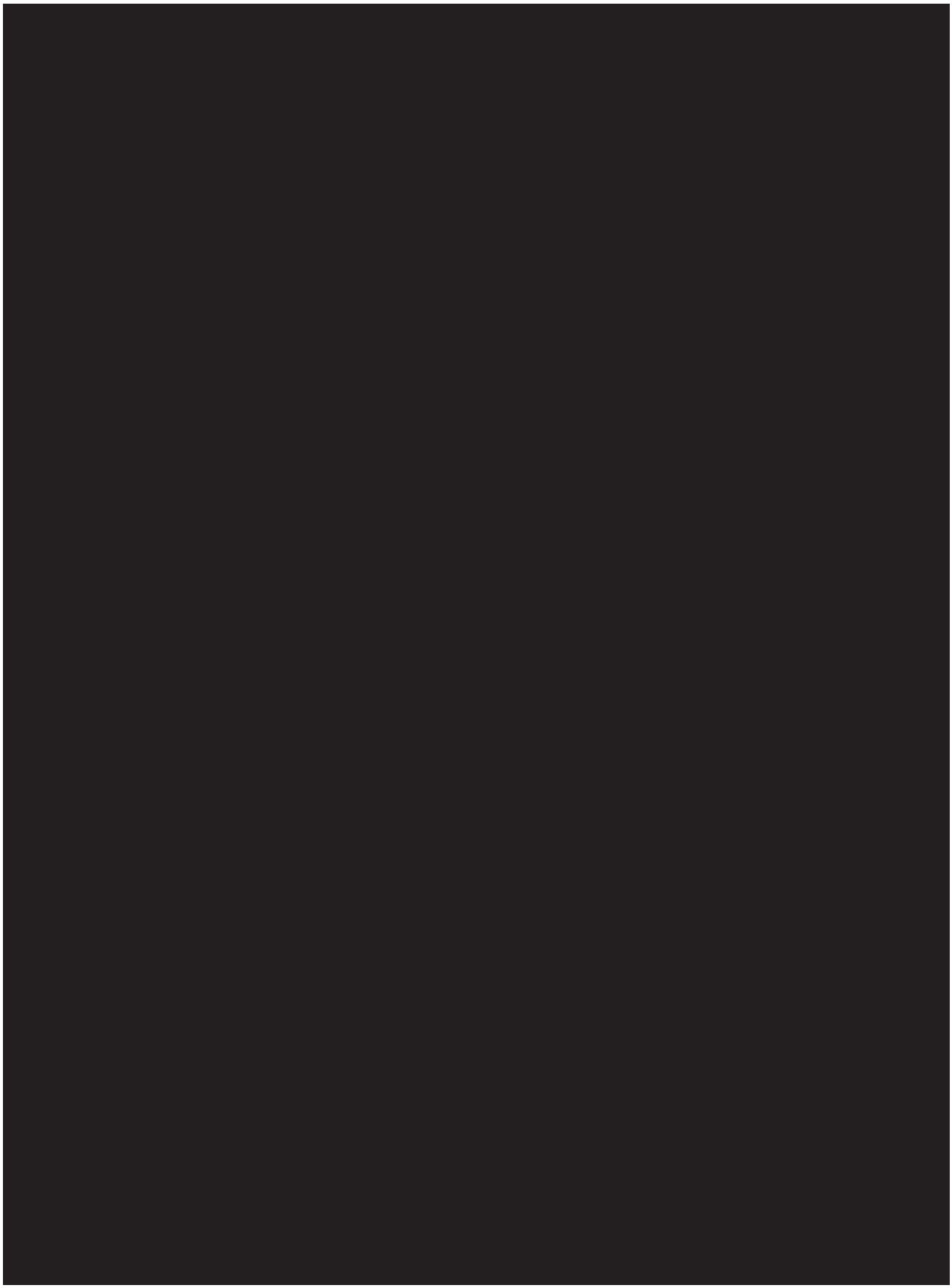
The serum samples will be analyzed for drug (BMS-986156 and/or nivolumab) and ADA (anti-BMS-986156 antibodies and/or anti-nivolumab antibodies) by validated immunoassays. In addition, selected serum samples may be analyzed by an exploratory method that measures BMS-986156 and nivolumab or detect anti-drug antibodies for technology exploration purposes; exploratory results will not be reported. Serum samples designated for PK [redacted] 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).

Labeling and Shipping of Biological Samples: Detailed instructions for the PK [redacted] blood collection, labeling, processing, storage, and shipping will be provided to the site in the procedure manual.

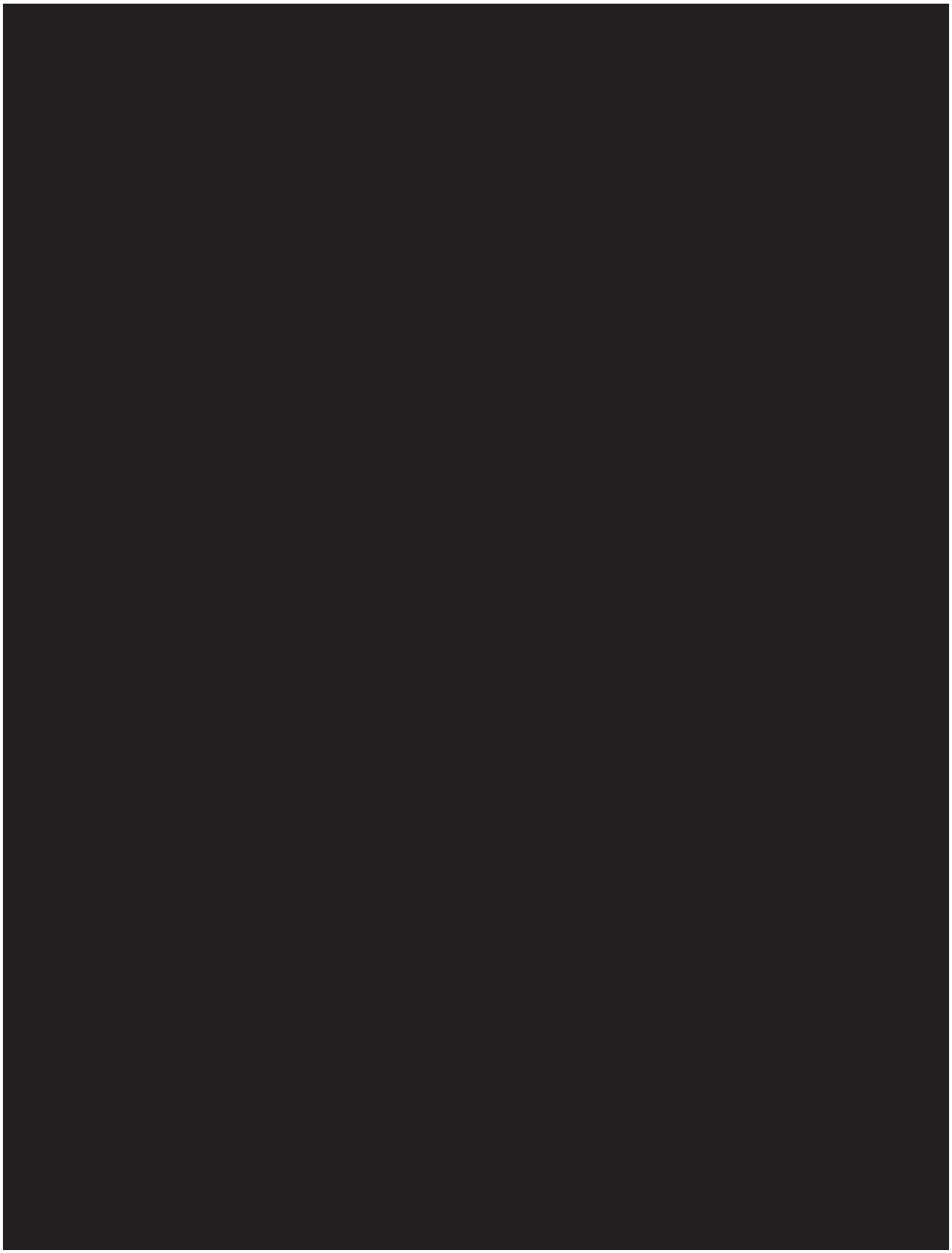
[redacted]

[redacted]





[redacted]



[redacted]

5.8 Outcomes Research Assessments

Not applicable.

5.9 Other Assessments

Not applicable.

[redacted]

6 ADVERSE EVENTS

An ***AE*** is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not considered related to the study drug.

The causal relationship to study drug is determined by a physician and should be used to assess all 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 that there is evidence to suggest a causal relationship.

AEs 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

An ***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 may not 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 (pDILI) is also considered an important medical event (see Section 6.6 for the definition of potential pDILI).

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

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

Any component of a study endpoint that is considered related to study therapy (eg, 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 (e.g., routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases.
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)
- admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)

6.1.1 Serious Adverse Event Collection and Reporting

Sections 5.6.1 and 5.6.2 in the IB[98] represent the Reference Safety Information to determine expectedness of SAEs for expedited reporting. Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening phase and within 100 days of discontinuation of dosing., except in cases where a study participant has started a new anti-neoplastic treatment.

However, any SAE occurring after the start of a new anti-neoplastic treatment that is suspected to be related to study treatment by the investigator should be reported.

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 for SAE data reporting collection is through the electronic (e)CRF. 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 that 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 Non-serious Adverse Events

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

6.2.1 Non-serious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug 100 days after discontinuation of dosing or until starting a new anti-neoplastic treatment (whichever occurs first) at the time points specified in the study assessments and procedures (Section 5). Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

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

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

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 (eg, anemia versus low hemoglobin value).

6.4 Pregnancy

If, following initiation of the IP, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half-lives after product administration, the Investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to 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 (eg, dose tapering if necessary for subject safety).

In the rare event that the benefit of continuing study drug is thought to outweigh the risk, after consultation with BMS, the pregnant subject may continue study drug after a thorough discussion of benefits and risk with the subject.

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, 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 (pDILI)

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

Potential drug induced liver injury is defined as:

1) Aminotransferase (ALT or AST) elevation > 3 times ULN,
2) Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum ALP), AND

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

6.7 Other Safety Considerations

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

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

Not applicable.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

8.1.1 Dose Escalation

As a Phase 1 dose-escalation trial, the sample size at each dose in these arms depends on observed toxicity and posterior inference. Approximately 60 subjects are expected to be treated during the dose-escalation phase (around 30 subjects for BMS-986156 monotherapy and around 30 subjects for BMS-986156 in combination with nivolumab). Initially approximately 3 subjects will be treated at the starting dose levels of BMS-986156 or BMS-986156 in combination with nivolumab. Additional subjects will be treated in recommended dose levels per BLRM (-Copula) during the dose-escalation phase. At most 12 DLT-evaluable subjects will be treated at each dose level.

Additional subjects may be treated at any dose level at or below the MTD or MAD (if no MTD is identified) for further evaluation of safety, [redacted]PK parameters as required. At most 12 DLT-evaluable subjects will be treated at each dose level.

8.1.2 Cohort Expansion

Part C contains 2 cohorts of 25 subjects each in monotherapy cohort expansion,. Each cohort in the combination cohort expansion phase (parts D and E) will contain approximately 40 subjects. Forty subjects in parts D and E are planned with the goal of achieving a width of approximately 20% in the 95% confidence interval for ORR, and to provide additional information on safety. Patients in any cohort who discontinue for reasons other than disease progression, death, or treatment-related toxicity may be replaced.

For initial safety evaluation of 480 mg BMS-986156/480 mg nivolumab Q4W in Part E, 6 subjects will be enrolled and followed for a minimum of 2 weeks (please refer to Section 3.6 for the rationale for 2 week period) prior to opening Part E to full enrollment.

If in a cohort of 40 subjects, 10 or 15 responses are observed, then the lower limit of the one-sided 90% CI for the ORR would be 16%, and 27% respectively. These calculations are made using the Clopper-Pearson method for exact confidence intervals. If the true ORR in a tumor type is 40%, then with 40 subjects there is 93% chance of observing at least 12 responses, and 87% chance of observing at least 13 responses, and there is 7% chance of observing 11 or fewer responses.

Continuous interim evaluations and monitoring of safety and efficacy based on the totality of data will be carried out throughout the expansion phase. Decisions regarding continuing enrollment based on these evaluations will be made through discussion between the Sponsor and investigators based on totality of data and overall clinical activity (such as but not limited to duration of response, quality of response, clinical assessment of response and/or SD and safety). The number of subjects receiving treatment of the planned sample size is approximate and may exceed the specified numbers due to unknown time to response and true recruitment rate (i.e additional participants may be enrolled to compensate the 25%-35% of the screening failure rate in combination with the non response evaluable rate to account for participants who may drop out of the study without being evaluable for response and/or true recruitment rate is much higher than anticipated and thus, Sponsor will examine on the totality of data to determine the benefit/risk ratio as well as overall clinical activity when making the final Go/no Go decision.

8.2 Populations for Analyses

- All Enrolled Subjects: All subjects who have signed an ICF and are registered into the IVRS.
- All Treated Subjects: All subjects who received at least one dose of study medication.
- The PK data set includes all available concentration-time data from the subjects who received any BMS-986156 [redacted].
- The Immunogenicity data set consists of all available immunogenicity data from the subjects who receive BMS-986156 or nivolumab and have a baseline and at least one post treatment immunogenicity measurement.

[redacted]

Analyses of safety, extent of exposure, [redacted] PK, efficacy and immunogenicity will be based on all treated subjects.

8.3 Endpoints

8.3.1 Primary Endpoint(s)

The primary objective of the study is to establish MTD/MAD/alternate dose(s). The assessment of safety will be based on the incidence of AEs, SAEs, AEs leading to discontinuation, and deaths. In addition clinical laboratory test abnormalities will be examined.

AEs and laboratory values will be graded according to the NCI CTCAE version 4.03.

8.3.2 Secondary Endpoint(s)

8.3.2.1 Pharmacokinetics

Pharmacokinetics of BMS-986156 will be characterized by estimation of PK parameters as defined in Section 5.5.

8.3.2.2 Efficacy

The second antitumor activity of BMS-986156 alone and BMS-986156 in combination with nivolumab will be measured by ORR and duration of response based on RECIST 1.1. Disease assessment with CT and/or MRI as appropriate will be performed at baseline and every 8 weeks during Treatment Phase until disease progression per RECIST v1.1, or until confirmed disease progression for subjects treated beyond progression [defined as an additional 10% or greater increase in tumor burden volume from time of initial progression (including all target lesions and new measurable lesions)], discontinuation of treatment or withdrawal from study. Subjects having received local palliative therapy will be documented as having had disease progression for the purpose of efficacy analyses.

- Best overall response (BOR): defined as the best response designation over the study as a whole, recorded between the dates of first dose until the last tumor assessment prior to subsequent therapy. BOR is assessed by investigator (BIRC) per RECIST 1.1 criteria.
- ORR is defined as the proportion of all treated subjects whose BOR is either a CR or PR.
- Duration of response, computed for all treated subjects with a BOR of CR or PR, is defined as the time between the date of first response and the date of disease progression or death, whichever occurs first.
- PFSR at 24 *Weeks*: The proportion of treated subjects remaining progression free and surviving at *24 weeks*. The proportion will be calculated by the K-M estimate which takes into account censored data.

8.3.2.3 Immunogenicity

The third secondary objective of immunogenicity will be assessed by the following endpoint:

- Frequency of positive ADA to BMS-986156 or nivolumab.

[redacted]

8.4 Analyses

8.4.1 Demographics and Baseline Characteristics

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

8.4.2 Safety Analyses

All recorded AEs will be listed and tabulated by system organ class, preferred term and treatment. Vital signs and clinical laboratory test results will be listed and summarized by treatment. Any significant PE findings and clinical laboratory results will be listed. ECG readings will be evaluated by the Investigator and abnormalities, if present, will be listed.

8.4.3 Efficacy Analyses

Listing of tumor measurements will be provided by subject and study day in each arm and dose level. Individual subject's BOR will be listed based on RECIST 1.1.
To describe the antitumor activity of BMS-986156 alone or in combination with nivolumab, ORR will be calculated. ORR and corresponding 2-sided exact 95% exact CI by the Clopper and Pearson method will be provided by treatment and dose level. Median duration of response and corresponding two-sided 95% CI will be reported by treatment and dose level. Duration of response will be analyzed using the Kaplan-Meier method.

In addition, PFSR, the probability of a subject remaining progression free or surviving to 24 weeks, will be estimated by the Kaplan-Meier methodology, by treatment and dose level. The corresponding 90% CI will be derived based on Greenwood formula. PFSR at month 12 will be estimated using the same method for the combination treatment BMS-986156 and nivolumab.

8.4.4 Pharmacokinetic Analyses

All individual PK parameters will be listed for each analyte including any exclusions and reasons for exclusion from summaries. Summary statistics will be tabulated for each PK parameters by treatment. Geometric means and coefficients of variation will be presented for Cmax, AUC, CLT, and AI. Medians and ranges will be presented for Tmax. Means and standard deviations will be presented for all other PK parameters.

Ctrough values will be listed and summarized by treatment and study day/week.

BMS-986156 dose dependency will be accessed in Part A and B. To describe the dependency on dose of BMS-986156, scatter plots of Cmax and AUC(TAU) versus dose may be provided for each day measured. Dose proportionality of BMS-986156 when administered alone or co-administered with nivolumab may also be assessed based on a power model. [redacted]

8.4.5 Immunogenicity Analyses

Immunogenicity analysis: A listing of all available immunogenicity data will be provided by treatment, dose and immunogenicity status. The frequency of subjects with a baseline and at least one positive ADA assessment of BMS-986156 or nivolumab will be summarized.

[redacted]

[redacted]

8.4.7 Outcomes Research Analyses

Not applicable.

8.4.8 Other Analyses

Not applicable.

8.5 Interim Analyses

Not applicable.

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

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

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

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

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

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

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

9.1.2 Monitoring

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

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

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

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

9.1.2.1 Source Documentation

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

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

9.1.3 Investigational Site Training

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

9.2 Records

9.2.1 Records Retention

The Investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS, whichever is longer. The Investigator must contact BMS prior to destroying any records associated with the study.

BMS will notify the Investigator when the study records are no longer needed.

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

9.2.2 Study Drug Records

It is the responsibility of the Investigator to ensure that a current disposition record of study drug (inventoried and dispensed) is maintained at the study site to include IP. 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
- non-study disposition (e.g., lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to BMS
- retain samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for IP 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 EDC 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 sub-investigator 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 EDC 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 EDC tool using the unique user account provided by BMS. User accounts are not to be shared or reassigned to other individuals.

9.3 Clinical Study Report and Publications

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

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

- Subject recruitment (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
Complete Abstinence	Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.
[redacted]	

11 LIST OF ABBREVIATIONS

Term	Definition
AE	adverse event
ACLS	advanced cardiac life support
ADA	anti-drug antibody
[redacted]	
AI	accumulation index
AIDS	acquired Immunodeficiency Syndrome
ALK	anaplastic Lymphoma Kinase
ALP	alkaline Phosphatase
ALT	alanine Aminotransferase
APC	antigen-presenting cells
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC(INF)	area under the concentration-time curve from time 0 extrapolated to infinite times
AUC(0-T)	area under the concentration-time curve from time 0 to the time of the last quantifiable concentration
AUC(TAU)	area under the concentration-time curve in one dosing interval
BLRM	Bayesian Logistic Regression Method
BMS	Bristol-Myers Squibb
BOR	best overall response
BUN	blood urea nitrogen
C1D1	cycle 1 day 1
CI	confidence interval
[redacted]	
CrCl	creatinine clearance
CLT	total body clearance
Cmax	maximum observed concentration
[redacted]	
Cmin	trough observed concentration
[redacted]	

Term	Definition
CNS	central nervous system
CR	complete response
CRF	Case Report Form, paper or electronic
CRP	C-reactive protein
[redacted]	
Css-avg	average concentration over a dosing interval (AUC [TAU]/tau)
CT	computerized tomography
CTA	Clinical Trial Agreement
CTCAE	Common Terminology Criteria for Adverse Events
CTLA	cytotoxic T-lymphocyte-associated antigen
Ctrough	trough observed plasma concentration
DLT	dose-limiting toxicity
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EGFR	epidermal growth factor receptor
EHR	electronic health records
EMR	electronic medical records
EOI	end of infusion
EOT	end of treatment
EWOC	escalation with overdose control
FDA	Food and Drug Administration
FFPE	formalin fixed paraffin embedded
FIH	first-in-human
FNR	false negative rate
FPR	false positive rate
FSH	follicle-stimulating hormone
FU	follow up
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase

Term	Definition
GITR	glucocorticoid induced tumor necrosis factor receptor
[redacted]	
HBsAg	hepatitis B surface antigen
HCC	hepatocellular carcinoma
hCG	human chorionic gonadotropin
HIV	human immunodeficiency virus
HIPAA	Health Insurance Portability and Accountability Act
HNSTD	highest non-severely toxic dose
HPV	Human papillomavirus
[redacted]	
HRT	hormone replacement therapy
I-O	immuno-oncology
IB	Investigator Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFN	interferon
[redacted]	
IP	investigational product
IRB	Institutional Review Board
IRR	infusion-related reaction
IUD	intrauterine device
IV	intravenous
IVRS	Interactive Voice Response System
LCM	Laser Capture Microdissection
LDH	lactate dehydrogenase
LFT	liver function test
MABEL	minimum anticipated biological effect level
MAD	maximum administered dose
MedDRA	Medical Dictionary for Regulatory Activities
MDSC	myeloid-derived suppressor cell
[redacted]	

Term	Definition
MRI	magnetic resonance imaging
MRSD	maximum recommended starting dose
MST	Medical Surveillance Team
MTD	maximum tolerated dose
NCI	National Cancer Institute
NK	natural killer
[redacted]	
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
OC	ovarian cancer
ORR	objective response rate
[redacted]	
PCR	polymerase chain reaction
[redacted]	
pDILI	potential drug-induced liver injury
PD-1	programmed death-1
PD-L1	programmed death-ligand 1
PD-L2	programmed death-ligand 2
PE	physical examination
PET	positron emission tomography
PFSR	progression-free survival rate
PK	pharmacokinetics
PPD	purified protein derivative
[redacted]	
PR	partial response
Q2W	every 2 weeks
Q12W	every 12 weeks
[redacted]	
RCC	renal cell cancer
RECIST	Response Evaluation Criteria in Solid Tumor
SAE	serious adverse event

Term	Definition
SD	stable disease
SmPC	summary of product characteristics
[redacted]	
T3	triiodothyronine
T4	thyroxine
Teff	effector T cells
T-HALF	half-life
TIA	transient ischemic attack
TIL	tumor-infiltrating lymphocyte
TKI	tyrosine kinase inhibitor
Tmax	time of maximum observed plasma concentration
TNFRsf	tumor necrosis factor receptor superfamily
Treg	regulatory T cells
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
[redacted]	
WBC	white blood cell
WOCBP	women of childbearing potential

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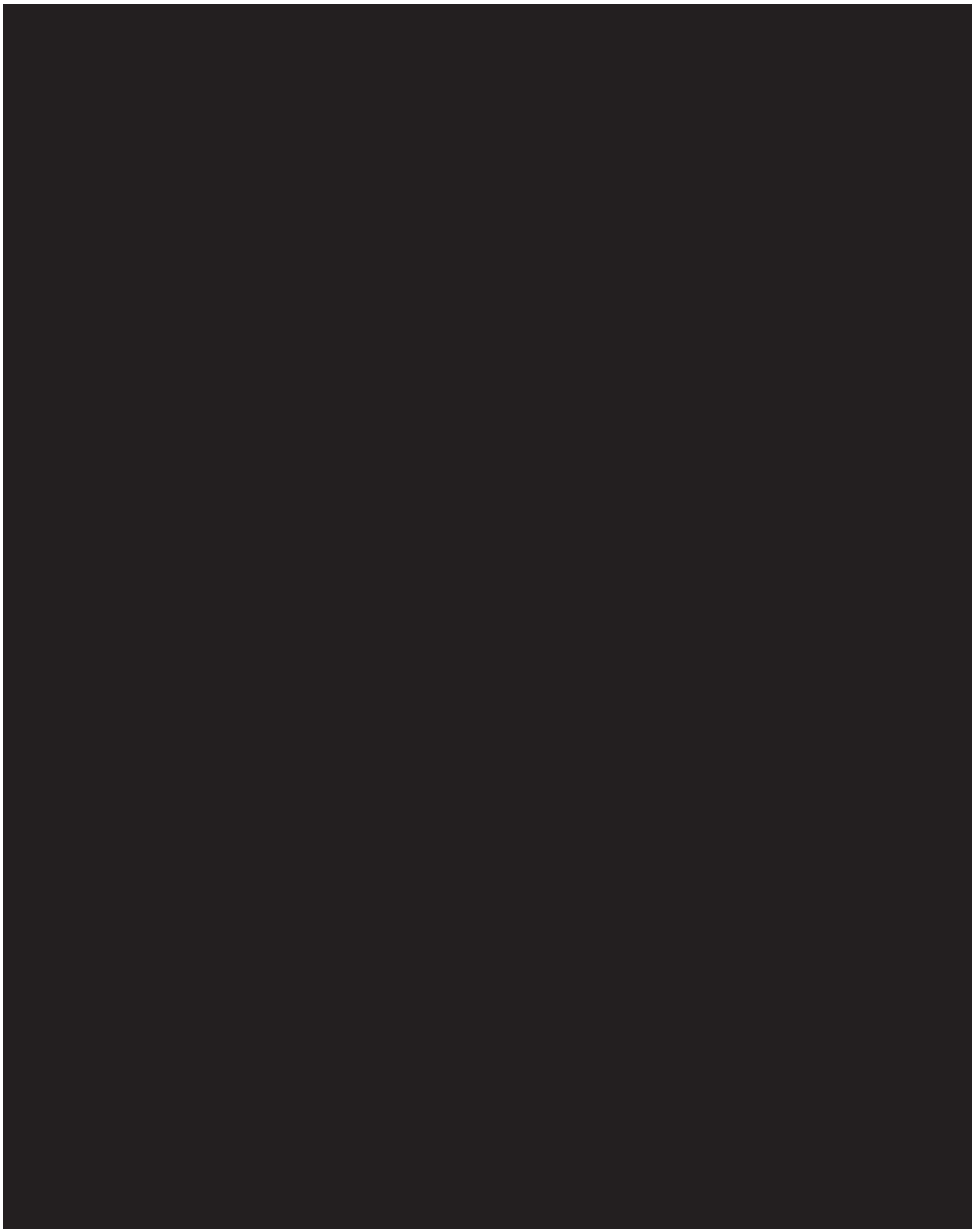

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APPENDIX 1 STATISTICAL METHODOLOGY

STATISTICAL DETAILS FOR BAYESIAN LOGISTIC REGRESSION MODEL (BLRM AND BLRM-COPULA) AND PRIORS FOR DOSE ESCALATION

1 MODEL SETUP FOR BMS-986156 MONOTHERAPY (PART A):

1.1 Monotherapy Methodology Description

An adaptive 2-parameter Bayesian Logistic Regression Model (BLRM) guided by the escalation with overdose control (EWOC) principle [1,2,3] will be used to guide the dose escalation of BMS-986156 in the monotherapy phase.

The BLRM will be fitted on the dose-limiting toxicity (DLT) data collected within the 28-day DLT period to model the dose-toxicity relationship of BMS-986156 in the monotherapy dose escalation phase.

The dose-toxicity relationship for BMS-986156 alone is assumed to follow a logistic model:

$$logit(p_i) = log(\alpha_1) + \beta_1 log(^{d_{1i}}/_{d_1^*})$$

where p_i is the probability of toxicity at dose level d_{1i}. Note that the α_1 and β_1 parameters are assumed positive, and d_1^* is the reference dose for BMS-986156 (α_1 and β_1 are defined in Section 1.2.1).

1.2 Prior Specification for BMS-986156 Monotherapy

The Bayesian approach requires the specification of prior distributions for model parameters which include parameters (α_1, β_1) for BMS-986156. The prior distributions for this single agent activity were derived using the meta-analytic-predictive (MAP) [3] approach based on CD137 agonist (BMS-663513) dose- DLT data.

Derivation of prior distribution of these parameters is provided in the following subsections.

1.2.1 Prior Derivation for BMS-986156 Parameters ($log(\alpha_1), log(\beta_1)$)

A mixture prior will be used for parameters (α_1, β_1) for BMS-986156. There are two bivariate normal components in generating this mixture prior:

- MAP component: Obtained from the dose-DLT data from CD137 agonist (study CA186001 and study CA186006) using the MAP approach.
- Weakly informative component: Reflecting the potential of different toxicity of BMS-986156 and allowing for considerable prior uncertainty.

[redacted]

[redacted]

2 MODEL SETUP FOR BMS-986156 AND NIVOLUMAB COMBINATION (PART B)

2.1 Methodology Description for Combination therapy

Toxicity profiles of both BMS-986156 monotherapy and nivolumab monotherapy will be incorporated to develop the combination model framework. A copula-type model will be used to cover all general combination cases, including additive and synergistic effects. The combination of the 2 treatments will be explored using a Bayesian hierarchical model by utilizing the toxicity profiles of both BMS-986156 (Part A) and nivolumab (CA209-003, Phase 1 nivolumab monotherapy data in advanced solid tumors). The following copula-type model[4] will be used to describe the probability p_{ij} of toxicity when dose level i of agent A and dose level j of agent B are administered in combination:

$$p_{ij} = 1 - exp(-\left[\{-log(1-p_i{}^m)\}^{1/\gamma_1} + \{-log(1-q_j{}^n)\}^{1/\gamma_1}\right]^{\gamma_1}),$$

where p_i is the prespecified best guess toxicity probability for agent A, q_j is the prespecified best guess toxicity probability for agent B, m and n characterize the individual drug effect, and γ_1 characterizes the drug-drug interactive effect.

The joint toxicity framework models the toxicity rates of both agents as well as their interaction effects in a 7-parameter hierarchical model, where each monotherapy dose-toxicity relationship will be characterized by a 2-parameter BLRM model (see Section 1.1). There are 3 additional parameters for the copula-type model, one for each agent (m and n) as well as one for the interaction term (γ_1). A dose-toxicity surface will be characterized for different dose combinations of these 2 agents.

As there are currently neither historical data nor prior knowledge to indicate how much information is to be borrowed for each of the single agents, parameters m and n are both set to be 1, meaning borrowing 100% of the information from the 2 agents. The above formula is then simplified into a 5-parameter model as follows:

$$p_{ij} = 1 - exp(-\left[\{-log(1-p_i)\}^{1/\gamma_1} + \{-log(1-q_j)\}^{1/\gamma_1}\right]^{\gamma_1}.$$

Since only a fixed nivolumab dose (240 mg) will be used in the BMS-986156 and nivolumab combination arm, this surface will be simplified into a 2-dimensional dose-toxicity curve. Posteriors for the corresponding 5 parameters (2 logistic regression parameters $[\alpha_1, \beta_1]$ for BMS-986156 and 2 logistic regression parameters $[\alpha_2, \beta_2]$ for nivolumab, as well as 1 interaction parameter for the copula-type model [γ_1, which will be discussed in detail in the following section]) will be fitted into the in-house developed model. The model implements the above-described theoretical setup.

2.2 Prior Specification for Combination Studies

2.2.1 Marginal Prior for BMS-986156

Posterior information on $\log(\alpha_1)$ and $\log(\beta_1)$ from the monotherapy part of the study will be used as marginal BMS-986156 prior for combination with nivolumab. This prior information will be continuously updated when additional toxicity (DLT) information from the monotherapy (Part A) is available. [redacted]

[redacted]

2.2.2 Marginal Prior Derivation for Nivolumab Parameters (log(α_2), log(β_2))

Similar to BMS-986156 monotherapy in the monotherapy phase, the logistic model for nivolumab is as follows:

$$logit(q_j) = log(\alpha_2) + \beta_2 log(^{d_{2j}}/_{d_2^*}),$$

where q_j is the probability of toxicity at dose level d_{2j}. Note that the α_2 and β_2 parameters are assumed positive, and d_2^* is the reference dose for nivolumab.

The toxicity profile of nivolumab has been evaluated in several studies. A bivariate normal prior for the nivolumab model parameters (log(α_2), log(β_2)) was obtained by extracting a posterior for nivolumab using DLT and safety data from the Study CA209003, which is used later as the meta-analytical-predictive (MAP) prior for nivolumab.

[redacted]

2.2.3 Prior for Interaction Parameters for Joint Toxicity of BMS-986156 and Nivolumab Combination

A gamma prior distribution for the interaction parameter γ_1 is derived to reflect the current lack of knowledge regarding the toxicity profile of the combination of BMS-986156 and nivolumab. Although no PK drug-drug interaction is expected, the possibility of a significant positive interaction between BMS-986156 and nivolumab cannot be totally excluded. The interaction parameter γ_1 was chosen accordingly but with a degree of uncertainty in order to allow for the possibility that the interaction may be positive or negative. Therefore, the following assumptions are made for the interaction parameter:

- γ_1 follows a gamma distribution and with a mean centered at 1.1, which means the combination of 2 agents is likely to have only a small synergistic effect.
- The standard deviation of γ_1 is 0.8, such that there is a 45% prior probability that γ is larger than 1.

This model assigns the highest probability to there being small synergistic interaction and also allows for the potential of larger synergism of the toxic profiles. It also does not completely ignore the possibility of antagonism because there is also a 55% prior probability that γ_1 is less than 1.

3 DECISION RULE FOR DOSE ESCALATION AND SIMULATION

3.1 Parameters for Dose Recommendation Decision for the Monotherapy and Combination Therapy

In Parts A and B, the BLRM and BLRM-Copula models will be utilized for dose recommendations after DLT information becomes available for each dose cohort and each dose level. Final dose selection for the next dose cohort will be based on BLRM (-Copula) dose recommendations in combination with the totality of data available on all dosed subjects, after discussion and agreement between investigators and the BMS Medical Monitor.

The Bayesian Logistic Regression Method (BLRM) with an overdose control principle (escalation with overdose control [EWOC]) was selected as an appropriate design for the dose escalation parts of this study for the monotherapy setting. For the combination setting, the BLRM-Copula model, which is an extension of the BLRM design, will be utilized. BLRM (-Copula) is similar to the rule-based method (ie, 3 + 3 design) in that the cohort size is approximately 3 subjects for each subject cohort and the toxicity boundaries are set at a minimum 16% (~ 1 in 6) dose-limiting toxicity (DLT) rate and a maximum 33% (~ 1 in 3) DLT rate. These boundaries were chosen in order to target a dose that has meaningful activity but not unacceptably high toxicity. A minimum 16% DLT rate ensures that the model does not guide to use of too low a dose and sacrifice opportunity for benefit without meaningful improvement in safety. The 33% maximum is chosen as this would be the maximum DLT rate where a positive benefit/risk ratio is likely to be demonstrated.

Compared with the rule-based method, when recommending the next dose level, BLRM offers more accuracy and efficiency in determining the true MTD by incorporating historical data and all previous on-study DLT data. The BLRM model also quantifies the benefit and risk during the dose level decision making process. When DLT data are incorporated into the model, the distribution of predicted DLT rates (based on posterior estimation) for a specific dose level will be updated accordingly. The predicted DLT rates will be categorized according to the following 3 categories:

- “under-dosing” defined as a predicted DLT rate between 0% and up to 16%
- “target dosing” defined as a predicted DLT rate between over 16% and up to 33%
- “overdosing” defined as a predicted DLT rate between over 33% and 100%

Following the principle of EWOC, after DLT information is obtained from each cohort, the candidate doses are those with less than 25% chance of excessive toxicity for monotherapy and with less than 35% chance of excessive toxicity for combination therapies. These two EWOC cutoffs are selected after examining various cutoffs in simulation studies by optimizing the chance of identifying the true MTDs under different scenarios. Only the candidate doses will be considered for dose decision by Investigators and BMS study personnel based on all relevant data available from all dose levels evaluated in the ongoing study.

For dose expansion, the final recommended maximum tolerated dose (MTD)/recommended Phase 2 dose (RP2D) of BMS-986156 alone and in combination with nivolumab will be based on the recommendation from the BLRM (-Copula) model and a synthesis of all the data available on all dosed subjects, including clinical and laboratory safety assessments, PK [redacted] data, and efficacy data from all treated patients at each dose level MTD/RP2D.

To examine the operating characteristics of BLRM (-Copula) method, simulations for BMS-986156 alone and in combination with nivolumab were conducted. Simulation details are shown in the following sections.

3.2 BLRM (-Copula) Dose Escalation Recommendation Rules and Tools

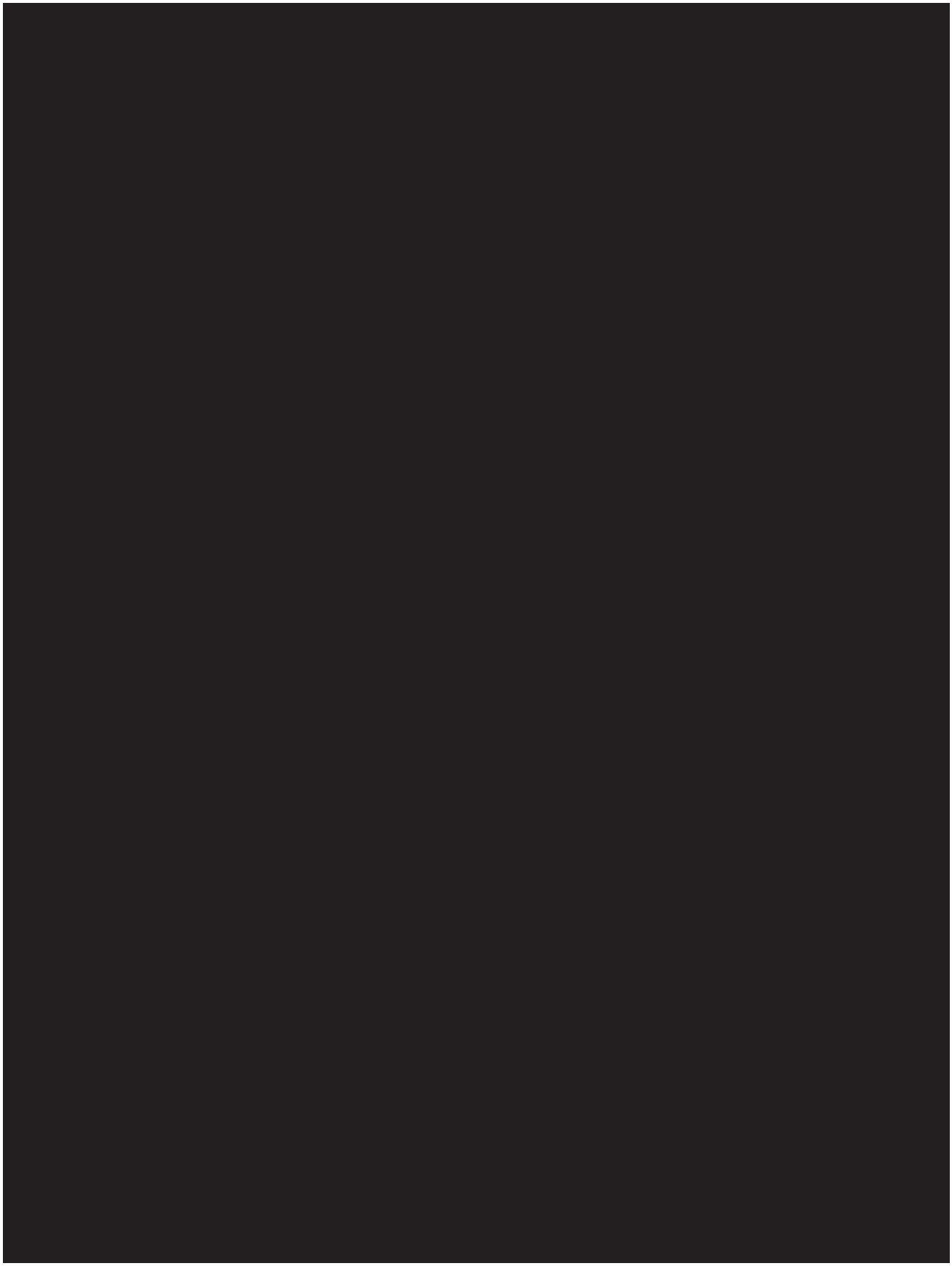
Recommendations for the next dose level will be provided by BLRM (-Copula) models (considering available DLT information) together with the following dose escalation rules for BMS-986156 alone and in combination with nivolumab:

- Dose levels for the next cohort will be based on evaluating 4 potential recommendations: escalate, de-escalate, stay at same dose level, or stop and select a new dose other than pre-specified doses.
- Escalation by more than 1 dose level (dose skipping) is not permitted in real trial conduction.
- Based on model suggestions and a review of the available safety, PK, and PD data in combination with clinical recommendation, lower doses of BMS-986156 may be tested if none of the planned doses are found to be tolerated as monotherapy or in combination with nivolumab. Such decisions will be made after discussion and agreement between the investigators and the BMS Medical Monitor.
- No intra-subject dose escalation of BMS-986156 is allowed at any dose level.
- Dose de-escalation can be recommended by the model, and the final decision will be made based on clinical recommendation.

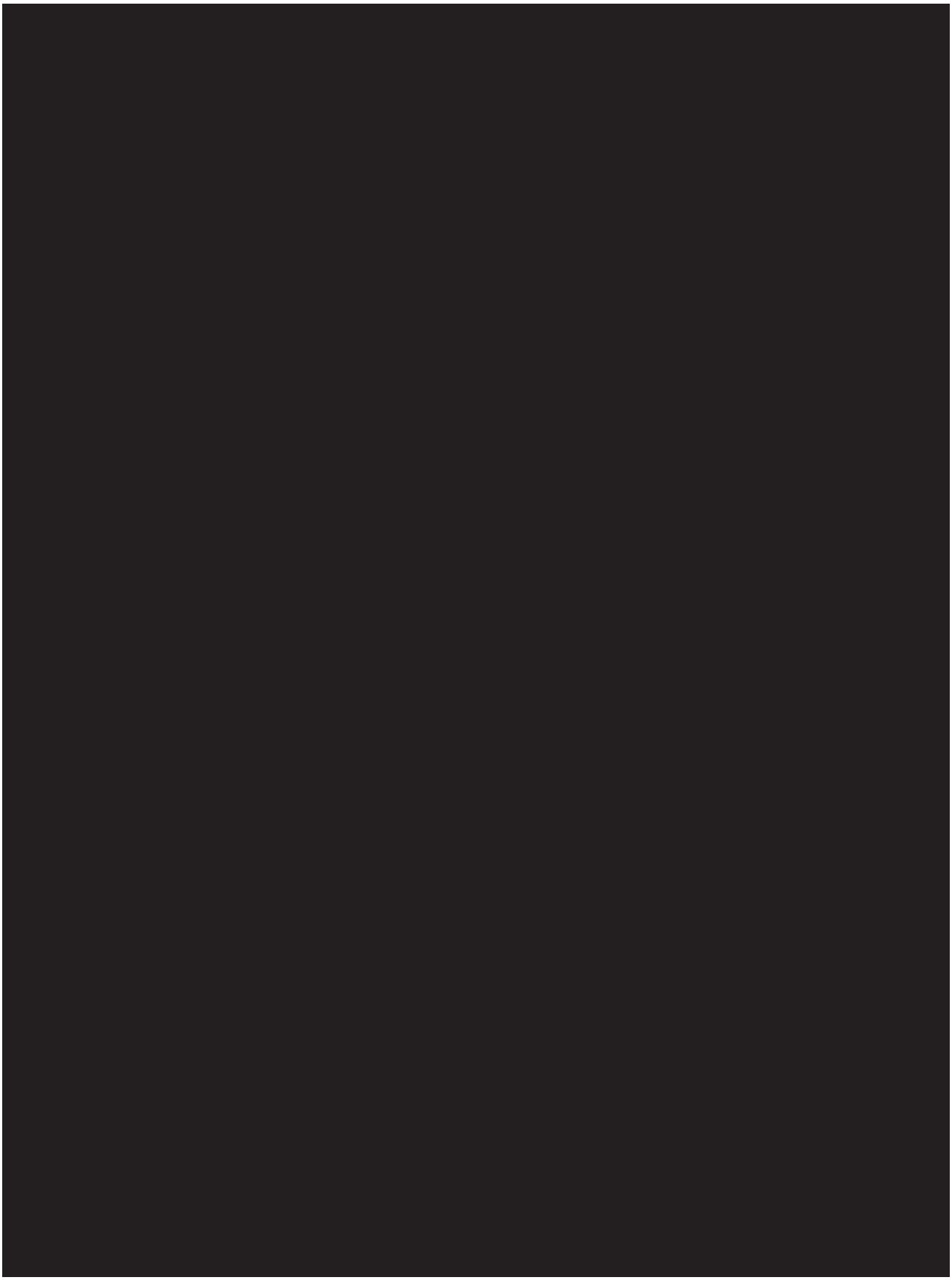
<u>BLRM Stopping Rules during Dose Escalation</u>

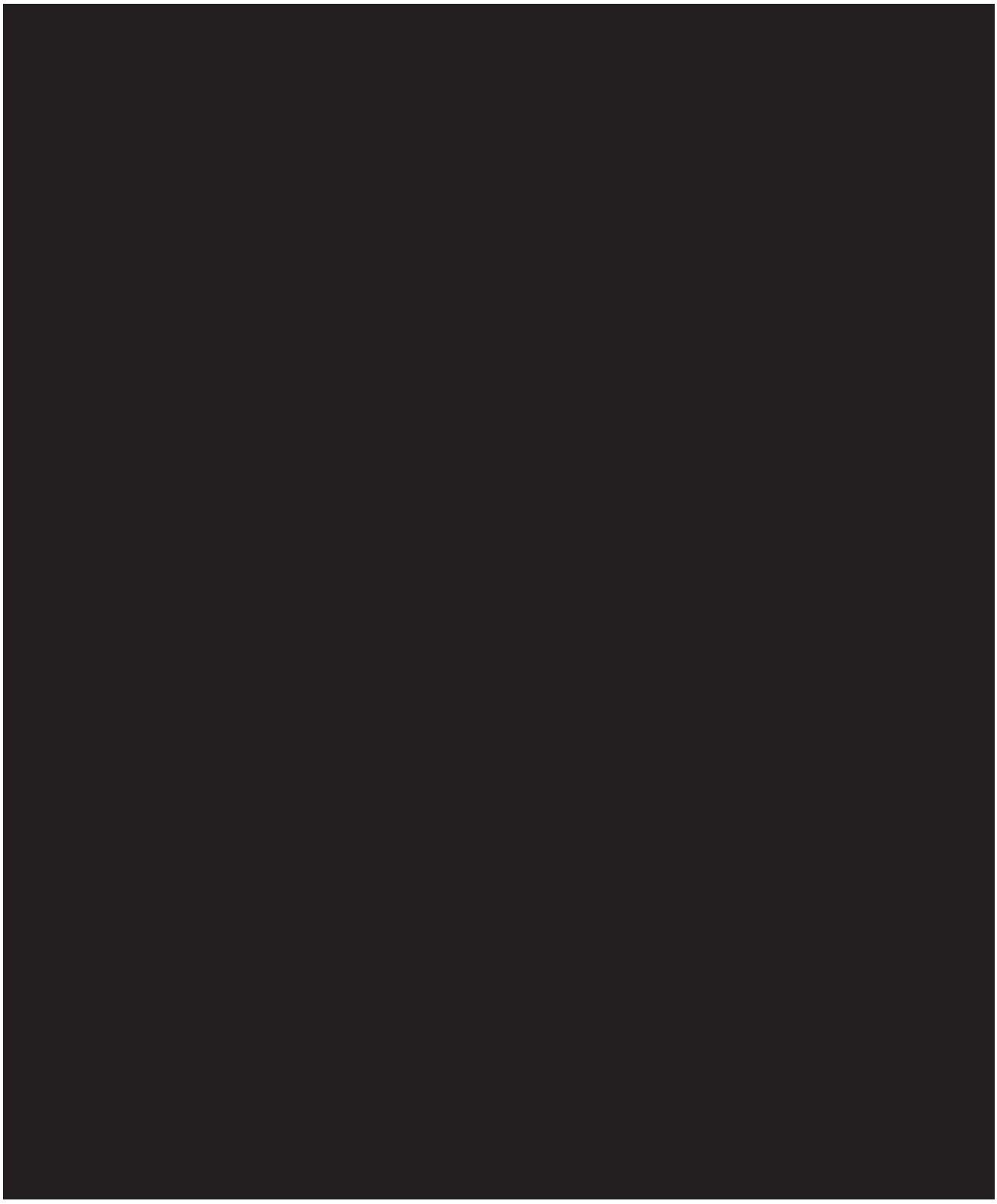
- If all of the current pre-specified doses are considered intolerable according to the pre-specified cutoff, then the model will recommend stopping the current dose level and a new dose level lower than the current lowest dose level will need to be identified (EWOC stopping).
- The maximum number of subjects in a dose level will be 12. This limit is set to avoid instances in which the model could recommend adding subjects indefinitely to a specific dose level due to uncertainty in the tolerability profile.
- If, for a specific dose level, 6 subjects have been treated and the chance of determining that dose level to be the "target" dose is > 50%, then the model will suggest to stop the arm and declare the current dose level to be MTD.

[redacted]



[redacted]





[redacted]

4 INTERIM MONITORING CASE STUDY TO ILLUSTRATE BLRM (-COPULA) PROVISION OF RECOMMENDATIONS DURING DOSE ESCALATION

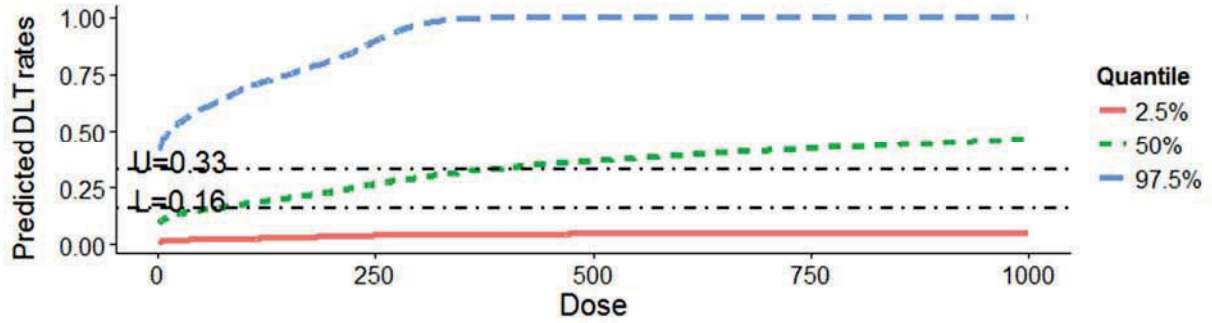
In order to provide a comprehensive view of the dynamics of the models, different hypothetical scenarios exploring all possibilities are examined. For the simplicity of illustration purposes, a static cohort size of 3 subjects is applied for dose levels 10 mg, 30 mg, 100 mg and 240 mg in the BMS-986156 monotherapy and for the dose level 30 mg in the combination setting. This cohort size could vary during the actual clinical trial, and the BLRM (-Copula) models are designed to fit various different cohort sizes, adaptively. In general, there are 4 possible scenarios for a specific dose level, which are 0 DLT observed in 3 total subjects in that cohort (denoted as 0/3), 1 DLT observed in 3 subjects (1/3), 2 DLTs observed in 3 subjects (2/3), and 3 DLTs observed in 3 subjects (3/3).

During interim monitoring, posterior probabilities will be updated when there is new DLT information available. The following three visualization plots will be produced to reflect the real time dose-DLT relationship, to quantify benefit (in the form of target dosing) and risk (in the form

of overdosing and underdosing) during model's recommendation process, and to facilitate clinical team's interpretation of the model recommendations for the final decision making:

- Dose-DLT profile for the doses ranging between 0 mg and 1000 mg (Figure 1).
- Stacking histograms displaying predictive probabilities on DLT rates classified into 3 different categories (Underdosing, Target dosing and Overdosing) (Figure 2).
- Box plots summarizing the Markov Chain Monte Carlo (MCMC) samples of predicted DLT rates for the 5 pre-specified dose levels (Figure 3).

Figure 1: **Updated dose-DLT profile after incorporating prior information and all previous DLT information up to 30 mg (including all monotherapy DLT data for BMS-986156 up to 100 mg)**



Interpretation and usage of Figure 1:

Figure 1 is a snapshot of an updated dose-DLT profile with DLT information available at dose level 30 mg for combination studies. The dose-DLT profile is captured with a continuous dose spectrum ranging from 0 mg to 1000 mg, which is a slice of the dose-DLT surface of the combination of two drugs with Nivolumab fixed at 240mg. For each dose within the range, there is a corresponding distribution of the predicted DLT rates calculated from the posterior samples of the model parameters. This figure will be updated each time new DLT information becomes available from the combination studies. Similar graphs will also be produced for the BMS-986156 monotherapy.

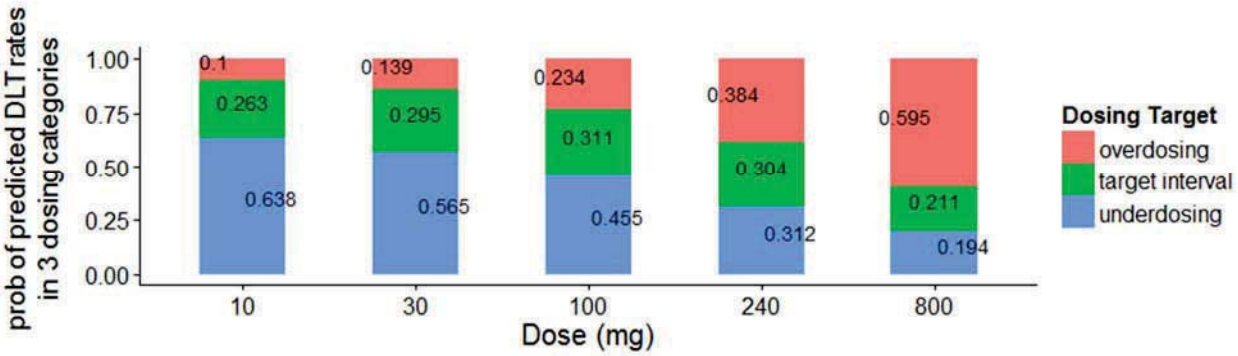
In Figure 1, there are 3 different quantiles (2.5%, 50%, and 97.5%) plotted to characterize the current trend of the toxicity profile (as shown by the 50% quantile), as well as the variation of the dose-DLT profile (as shown by the 2.5% percentile and the 97.5% percentile), according to the accumulation of DLT data from all previous and current dose levels. The toxicity boundaries (0.16 and 0.33) are illustrated in two dotted horizontal lines to benchmark the way in which the dose-DLT profile is trending.

Intermediate dose levels can be identified using different boundary cutoffs. For example, using the 50% percentile curve (green highlight), which represents the nearly average DLT distribution for each dose level, the 50 mg could be a potential intermediate dose level corresponding to the lower

pre-specified DLT rate boundary of 0.16, and the 375 mg could be a fitted MTD dose level associated with the upper boundary of 0.33.

Moreover, if all of the current pre-specified doses are considered intolerable (overdosing probabilities > 0.35 for combination therapy, a case not shown on the current Figure 1), the model will recommend to stop the current dose level, and the clinical team can leverage the current updated dose-DLT curve to pinpoint a new dose, which is lower than pre-specified lowest dose (10 mg) by using the DLT rate boundaries.

Figure 2: **Updated stacking histogram after incorporating prior information and all previous DLT information up to 30 mg (including all monotherapy DLT data up to 100 mg for BMS-986156) to classify predicted DLT rates into 3 categories (Underdosing, Target Dosing and Overdosing)**



Interpretation and usage of Figure 2:

Figure 2 is a snapshot of stacking histogram with DLT information available at dose level 30 mg for the combination studies. This figure will be updated each time new DLT information becomes available in the combination setting. Similar graphs will also be produced for the BMS-986156 monotherapy.

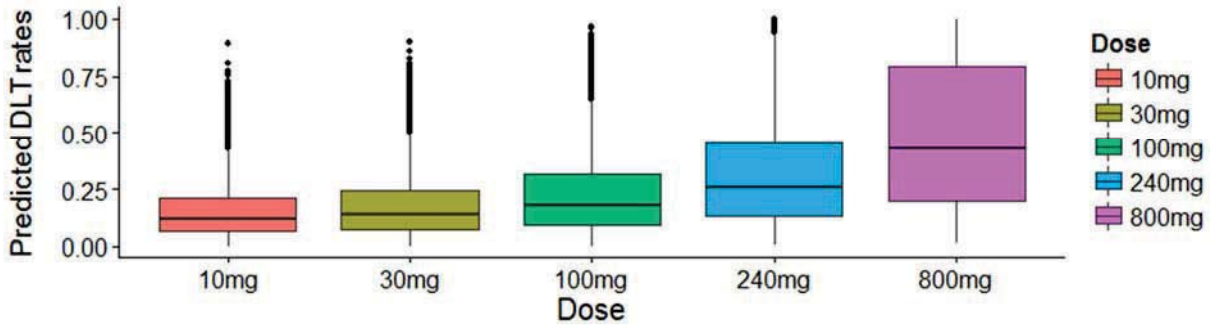
When recommending the next dose level, the model will first exclude doses that are intolerable (with overdosing probabilities > 35%, the rate that has been specified for BMS-986156 in combination with nivolumab). Among those qualified candidate doses that are considered "tolerable", the model will select the dose that maximizes the probability of being within the target toxicity range (DLT rate of 16% up to 33%).

As illustrated in Figure 2, when there is 1 DLT observed out of 3 subjects for the dose level 30 mg, the distribution of predicted DLT rates will be characterized into possibilities falling into 3 different categories. First, dose levels of 240 mg and 800 mg for BMS-986156 are excluded according to the higher-than-cutoff (0.35 for combination therapy) overdosing probabilities (0.384 for 240mg and 0.595 for 800mg). Among the remainder of tolerable dose levels (10 mg, 30 mg, and 100 mg), the BLRM-Copula model recommends the dose that maximizes the probability of being within the target dosing interval. Therefore, the model's recommendation would be to

escalate to 100 mg, which is associated with the highest target dosing probability of 0.311 compared with that of 30 mg (0.295) and 10 mg (0.263).

Similarly (although not shown on Figure 2), according to the rules specified above, the model could possibly recommend to de-escalate to a lower dose level than current treated dose level, extend the current dose level, or even recommend to stop and identify a new dose level lower than 10mg, the lowest pre-specified dose level. Please refer to description of Figure 1 for details on how to specify the new dose levels.

Figure 3: Updated box plot after incorporating prior information and all previous DLT information up to 30 mg in combination setting (including all monotherapy DLT data up to 100 mg for BMS-986156) for pre-specified dose levels



Interpretation and usage of Figure 3:
Figure 3 is a snapshot with DLT information available at dose level 30 mg for the combination setting. The dose-DLT distributions calculated from the posterior samples of the model parameters are characterized in the format of boxplots for the pre-specified dose levels. This figure will be updated each time there is new DLT information available. Similar graphs will also be produced for the BMS-986156 monotherapy.

This plot supplements the information provided in Figure 1. It allows for a more in-depth and focused visualization of general trend of dose-DLT relationship, as well as the magnitude and variability in the DLT rates for each pre-specified dose level.

4.1 Illustration for BMS-986156 Monotherapy Dose Escalation under Different Scenarios using the BLRM Model

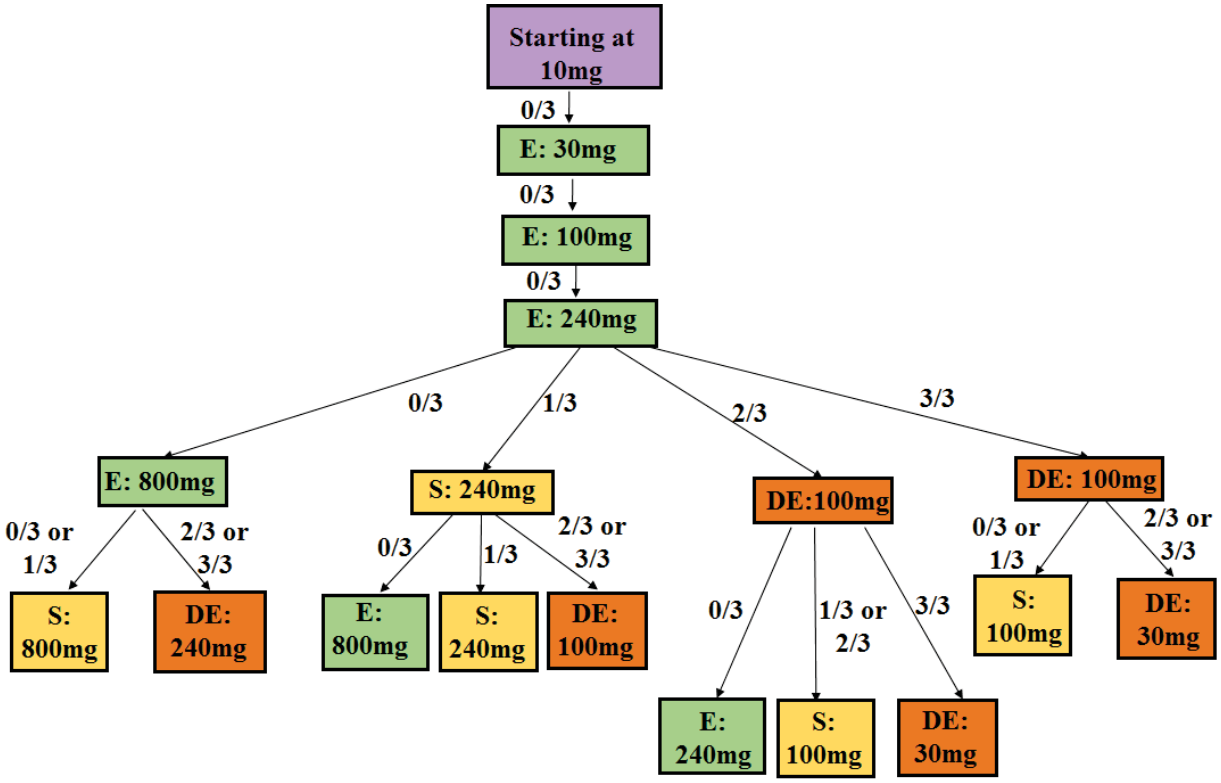
According to safety consideration and clinical judgement, the dose level 10 mg is recommended as the starting dose for BMS-986156 monotherapy. With the current BMS-986156 prior specified in the Section 1.2.1 (Table 2) and all available DLT information up to 100 mg, a corresponding decision tree illustrating various models' recommendations under all possible scenarios (for dose levels of 240 mg and 800 mg) is provided in Figure 4.

Tracing a branch of the decision tree in Figure 4 illustrates the decision making process. Taking the left-most branch of the tree as an example, starting at 10 mg, there was 0 DLT observed at

10 mg in the real clinical trial, the model recommended to escalate to 30 mg, one level above the current treated dose level according escalation rules per protocol (as detailed in Protocol Section 5.1). Additionally, there was 0 DLT observed at 30 mg in real data, the model recommended to escalate further one dose level to 100 mg. A further 0 DLT observation at 100 mg enabled the model to make a recommendation to escalate to 240 mg, currently 240 mg is within DLT observation period to collect DLT information.

As illustrated in Figure 4, there are 10 potential decision paths for dose levels 240 mg and moving onwards up to 800 mg, as real time clinical data has been taken into consideration of this decision tree. During the actual clinical study, the tree would be narrowed or deepened based on actual DLT. The clinical team will be able to leverage this decision tree to preview decisions at each interim monitoring step and to plan proactively.

Figure 4: **The BLRM model hypothetical decision tree for BMS-986156 monotherapy during dose escalation (up to 800 mg; E: escalation; S: stay; DE: de-escalation)**



[redacted]

[redacted]

References:

1 Babb J, Rogatko A, Zacks S. Cancer Phase I clinical trials: efficient dose escalation with overdose control. Stat Med 1998;17:1103-20.

2 Neuenschwander B, Branson M, Gsponer T. Critical aspects of the Bayesian approach to Phase I cancer trials. Stat Med 2008;27:2420-39.

3 Neuenschwander B, Capkun-Niggli G, Branson M, et al. Summarizing historical information on controls in clinical trials. Clin Trials 2010;7:5-18.

4 Yin G, Yuan Y. Bayesian dose finding in oncology for drug combinations by copula regression. J R Stat Soc Ser C Appl Stat 2009;58(2):211-24.

APPENDIX 2 ECOG PERFORMANCE STATUS

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

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

APPENDIX 3 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.

Central assessments may be planned for this study. Copies of all scans should be kept at the site as part of the subject study file. At the Sponsor's discretion, scans may be collected centrally for further analysis.

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

1.1 Measurable lesions

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

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

1.2 Non-measurable lesions

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

1.3 Special considerations regarding lesion measurability

1.3.1 Bone lesions

- Bone scan, PET scan or plain films are ***not*** considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

- Lytic bone lesions or mixed lytic-blastic lesions, with *identifiable soft tissue components*, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the *soft tissue component* meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

1.3.2 Cystic lesions

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

1.3.3 Lesions with prior local treatment

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

1.4 Specifications by methods of measurements

1.4.1 Measurement of lesions

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

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 lesion*s** 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 (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

3 TUMOR RESPONSE EVALUATION

3.1 Evaluation of target lesions

Complete Response (CR): **Disappearance of all target lesions.** Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a **30% decrease in the sum of diameters of target lesions,** taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a **20% increase in the sum of diameters of target lesions, taking as reference the *smallest sum on study*** (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an **absolute increase of at least 5 mm**. (*Note:* the appearance of 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 (eg, 2 mm). If the radiologist is able to provide an actual measurement, that should be recorded, even if it is below 5 mm.

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

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.

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

3.1.1.3 Target lesions that split or coalesce on treatment

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

3.2 Evaluation of non-target lesions

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

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

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

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

3.2.1 Special notes on assessment of non-target lesions

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

3.2.1.1 When the subject also has measurable disease

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

3.2.1.2 When the subject has only non-measurable disease

- To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening such that the overall tumor burden has increased sufficiently to merit discontinuation of therapy.
- A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.
- Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are non-measurable) a useful test that can be applied when assessing subjects for

unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'.

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

3.2.1.3 Tumor markers

Tumor markers *alone* cannot be used to assess objective tumor responses. If markers are initially above the upper normal limit, however, they must normalize in order for a subject to be considered as having attained a complete response.

3.3 New lesions

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

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

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

3.3.1 FDG-PET evaluation

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

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up:

- If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
- If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial positive FDG-PET scan).
- If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

4 RESPONSE CRITERIA

4.1 Time point response

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

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

Table 4.1-1: Time point response: subjects with target (+/– non-target) disease

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

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE =not evaluable.

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.

4.1.1 Confirmation Scans

- **Verification of Response:** *Confirmation of PR and CR is required at least 4 weeks later to ensure responses identified are not the result of measurement error.*

4.2 Best overall response: All timepoints

The *best overall response* is determined once all the data for the subject is known. It is the best response recorded from the start of the study treatment until the date of objectively documented progression based on RECIST v1.1, taking into account any requirement for confirmation, or the date of subsequent anti-cancer therapy, whichever occurs first in the study. The subject's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

Best response is defined as the best response across all time points with subsequent confirmation. Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later).

In this circumstance, the best overall response can be interpreted as specified in Table 4.2-1. When SD is believed to be best response, it must meet the protocol specified minimum time from baseline. Measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6–8 weeks) that is defined in the study protocol.

Table 4.2-1: Best overall response when confirmation of CR and PR IS required

Overall response	Overall response	BEST overall response
First time point	**Subsequent time point**	
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR

Table 4.2-1: Best overall response when confirmation of CR and PR IS required		
Overall response	**Overall response**	**BEST overall response**
First time point	**Subsequent time point**	
PR	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. 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).

CR (Complete Remission)

The designation of CR requires the following:

1. Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms, if present before therapy.
   a) Typically [^{18}F] fluorodeoxyglucose (FDG)-avid lymphoma: in patients with no pretreatment positron emission tomography (PET) scan or when the PET scan was

positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative.

b) Variably FDG-avid lymphomas/FDG avidity unknown: in patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, all lymph nodes and nodal masses must have regressed on computed tomography (CT) scan to normal size (≤ 1.5 cm in their greatest transverse diameter for nodes > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their long axis and > 1.0 cm in their short axis before treatment must have decreased to ≤ 1.0 cm in their short axis after treatment.

2. The spleen and/or liver, if considered enlarged before therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies, and nodules related to lymphoma should disappear. However, determination of splenic involvement is not always reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma.
3. If the bone marrow was involved by lymphoma before treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (with a goal of > 20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry but demonstrates a small population of clonal lymphocytes by flow cytometry will be considered a CR until data become available demonstrating a clear difference in patient outcome.

PR (Partial Remission)

The designation of PR requires all of the following:

1. At least a 50% decrease in the sum of the product of the diameters (SPD) of up to 6 of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to all of the following: they should be clearly measurable in at least 2 perpendicular dimensions; if possible they should be from disparate regions of the body; and they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
2. No increase should be observed in the size of other nodes, liver, or spleen.
3. Splenic and hepatic nodules must regress by ≥ 50% in their SPD or, for single nodules, in the greatest transverse diameter.
4. With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present.
5. Bone marrow assessment is irrelevant for determination of a PR, if the sample was positive before treatment. However, if positive, the cell type should be specified (eg, large-cell lymphoma or small neoplastic B cells). Patients who achieve a CR by the above criteria but have persistent morphologic bone marrow involvement will be considered partial responders. When the bone marrow was involved before therapy and a clinical CR was achieved but with no bone marrow assessment after treatment, patients should be considered partial responders.
6. No new sites of disease should be observed.

7. FDG:
   a) Typically FDG-avid lymphoma: for patients with no pretreatment PET scan or if the PET scan was positive before therapy, the post-treatment PET should be positive in at least 1 previously involved site.
   b) Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, CT criteria should be used. In patients with follicular lymphoma or mantle-cell lymphoma, a PET scan is only indicated with 1 or at most 2 residual masses that have regressed by > 50% on CT; those with more than 2 residual lesions are unlikely to be PET negative and should be considered partial responders.

SD (Stable Disease)

SD is defined as the following:

1. A patient is considered to have SD when he or she fails to attain the criteria needed for a CR or PR but does not fulfill those for progressive disease (see Relapsed Disease [after CR]/Progressive Disease [after PR, SD]).
2. Typically FGD-avid lymphomas: the PET should be positive at prior sites of disease with no new areas of involvement on the post-treatment CT or PET scan.
3. Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pretreatment PET scan or if the pretreatment PET was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.

PD: Relapsed Disease (after CR)/Progressive Disease (after PR, SD)

Lymph nodes should be considered abnormal if the long axis is > 1.5 cm regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if its short axis is > 1.0. Lymph nodes ≤ 1.0 x ≤ 1.0 cm will not be considered abnormal for relapse or progressive disease.

1. Appearance of any new lesion > 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or PD after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.
2. At least a 50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (eg, splenic or hepatic nodules). To be considered PD, a lymph node with a diameter of the short axis of < 1.0 cm must increase by ≥ 50% and to a size of 1.5 x 1.5 cm or > 1.5 cm in the long axis.
3. At least a 50% increase in the longest diameter of any single previously identified node > 1 cm in its short axis.

4. Lesions should be PET positive if observed in a typical FDG-avid lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems (< 1.5 cm in its long axis by CT).

Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease. Disease that is only assessable (eg, pleural effusions, bone lesions) will be recorded as present or absent only, unless, while an abnormality is still noted by imaging studies or physical examination, it is found to be histologically negative.

In clinical trials where PET is unavailable to the vast majority of participants, or where PET is not deemed necessary or appropriate for use (eg, a trial in patients with MALT lymphoma), response should be assessed as above, but only using CT scans. However, residual masses should not be assigned CRu status, but should be considered partial responses.

Reference: Cheson BD, Pfisner B, Juweid ME, et al. Revised Response Criteria for Malignant Lymphoma. Journal of Clinical Oncology 2007;25:579-586.

APPENDIX 4 MANAGEMENT ALGORITHMS FOR IMMUNO-ONCOLOGY AGENTS

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

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

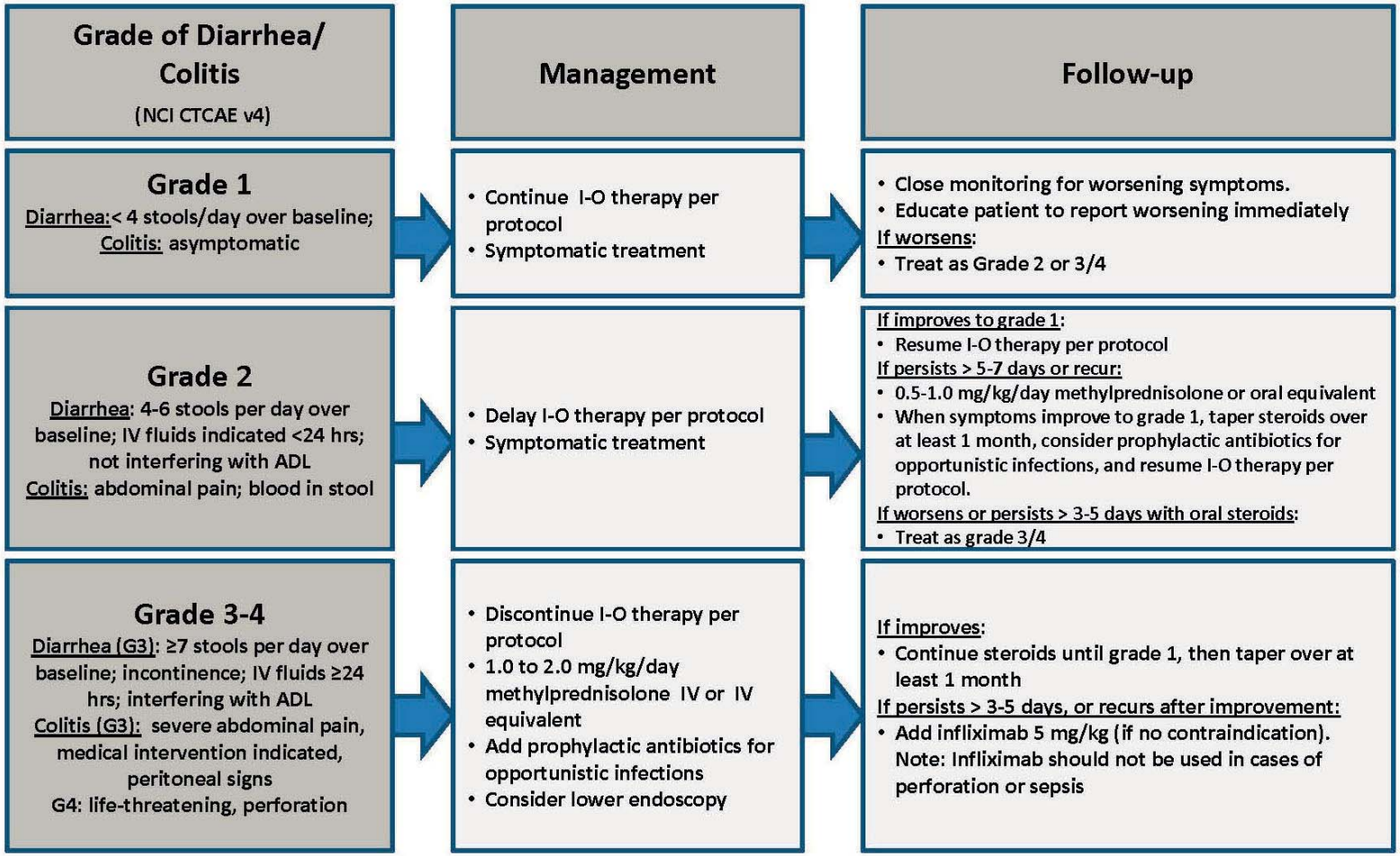
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the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

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

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

GI Adverse Event Management Algorithm

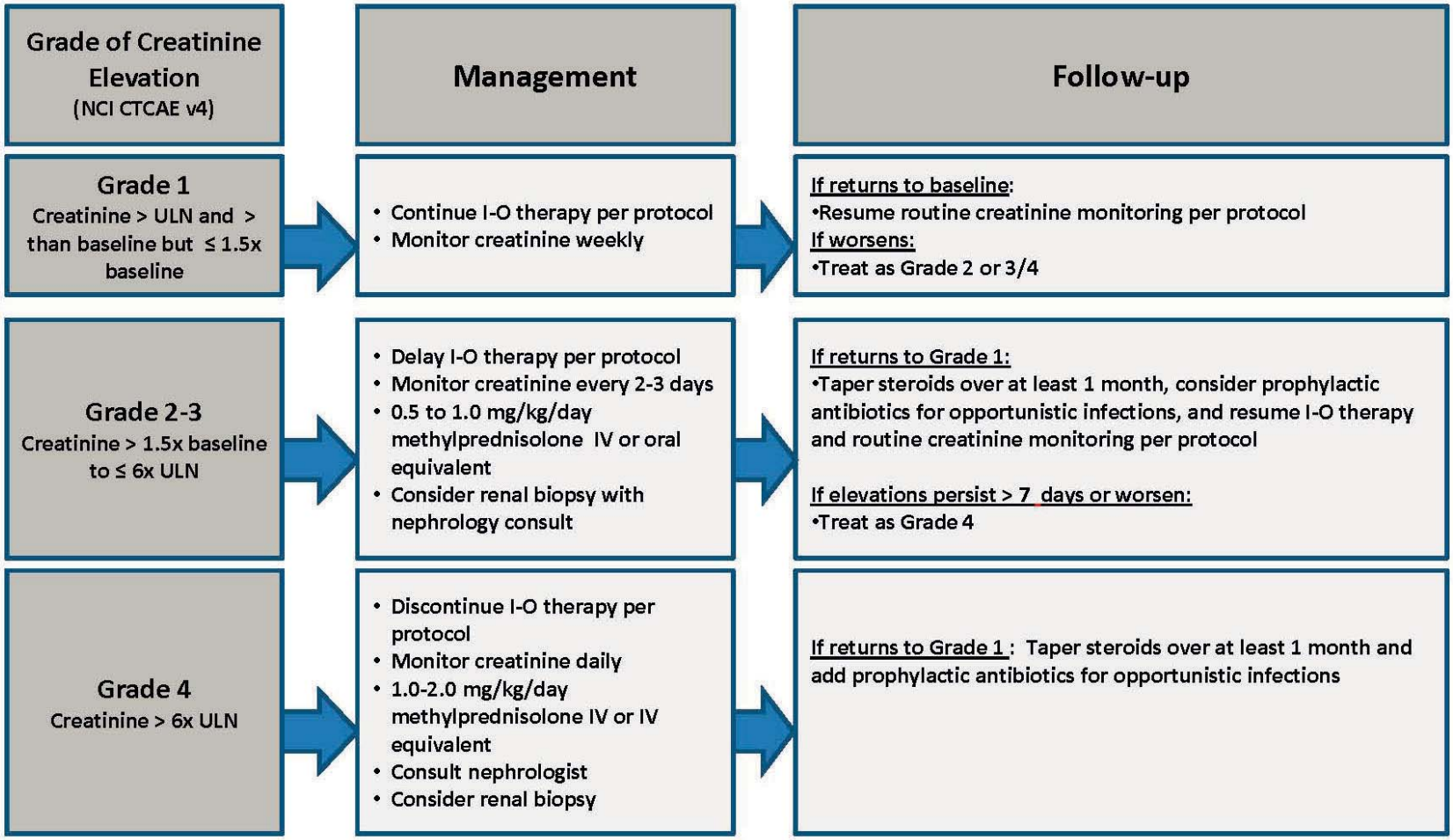
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



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

Renal Adverse Event Management Algorithm

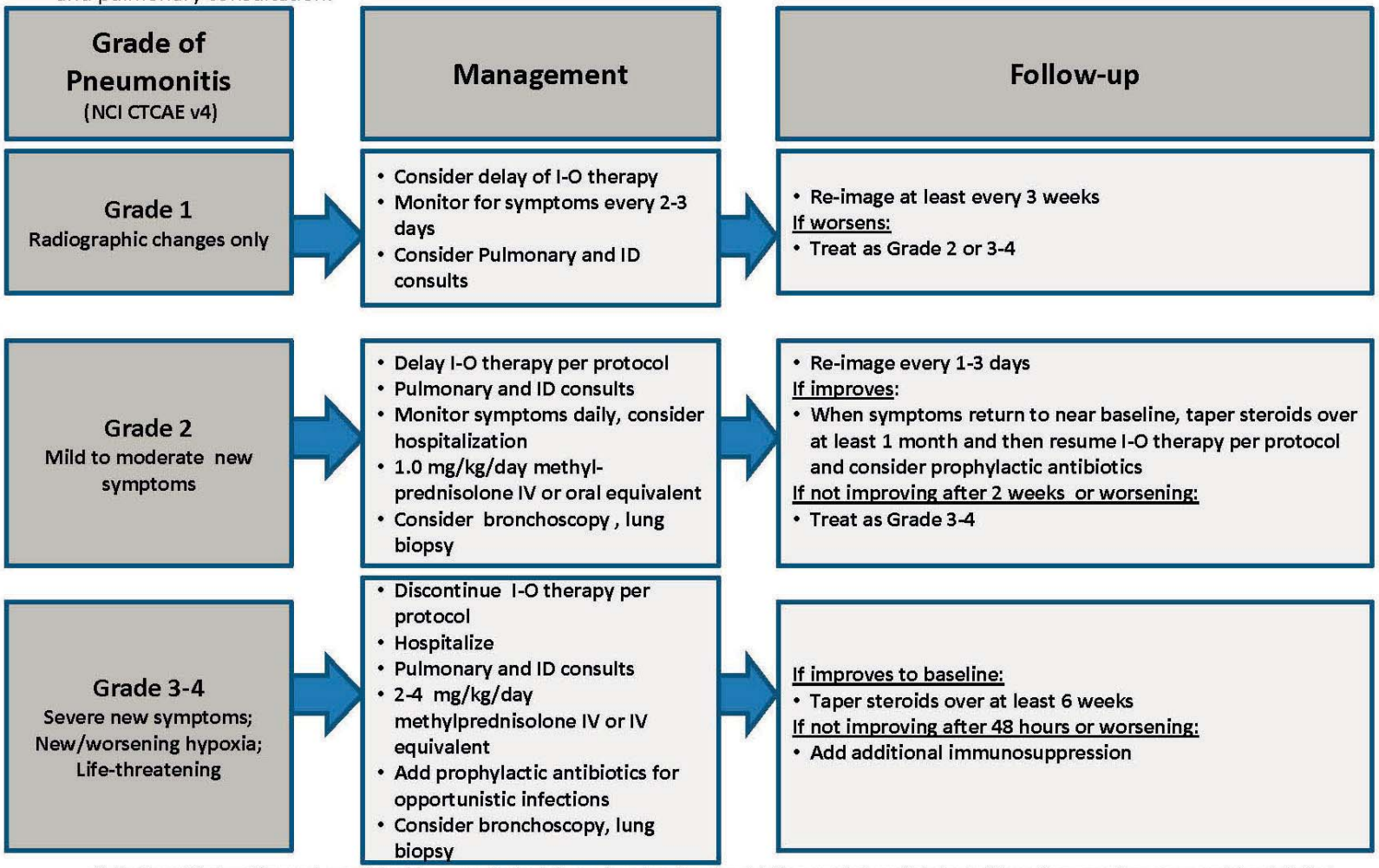
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy



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

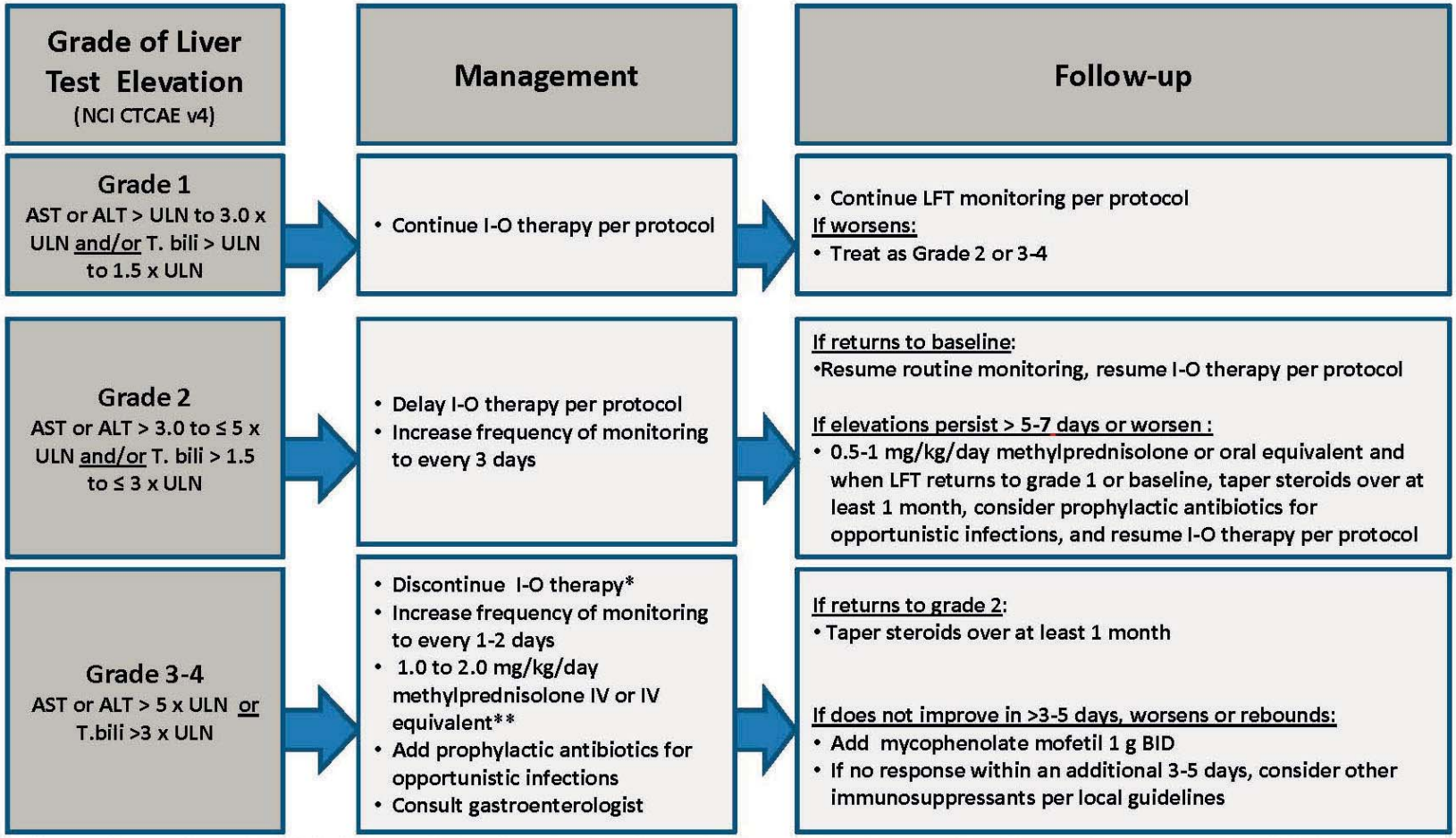
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



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.



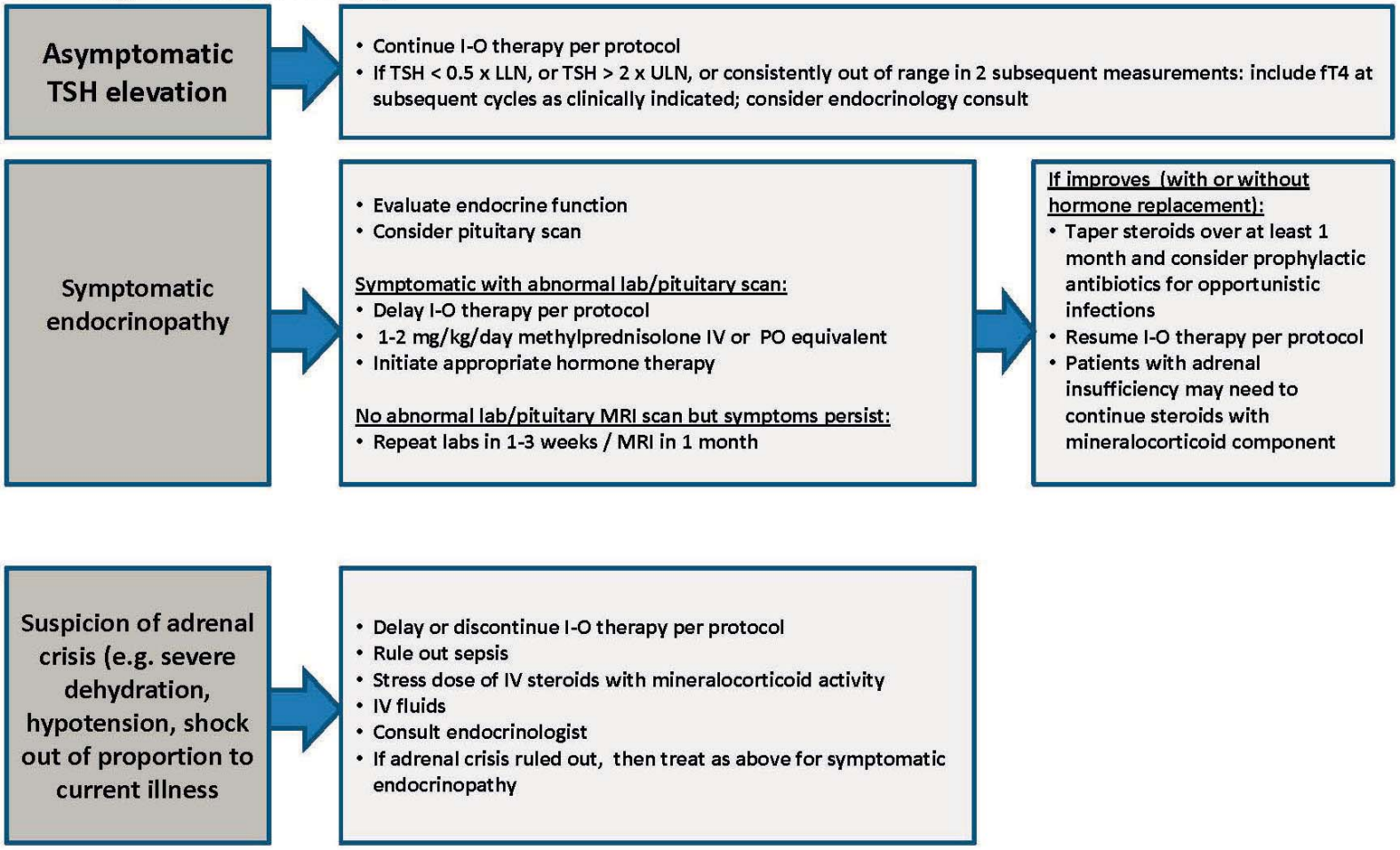
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

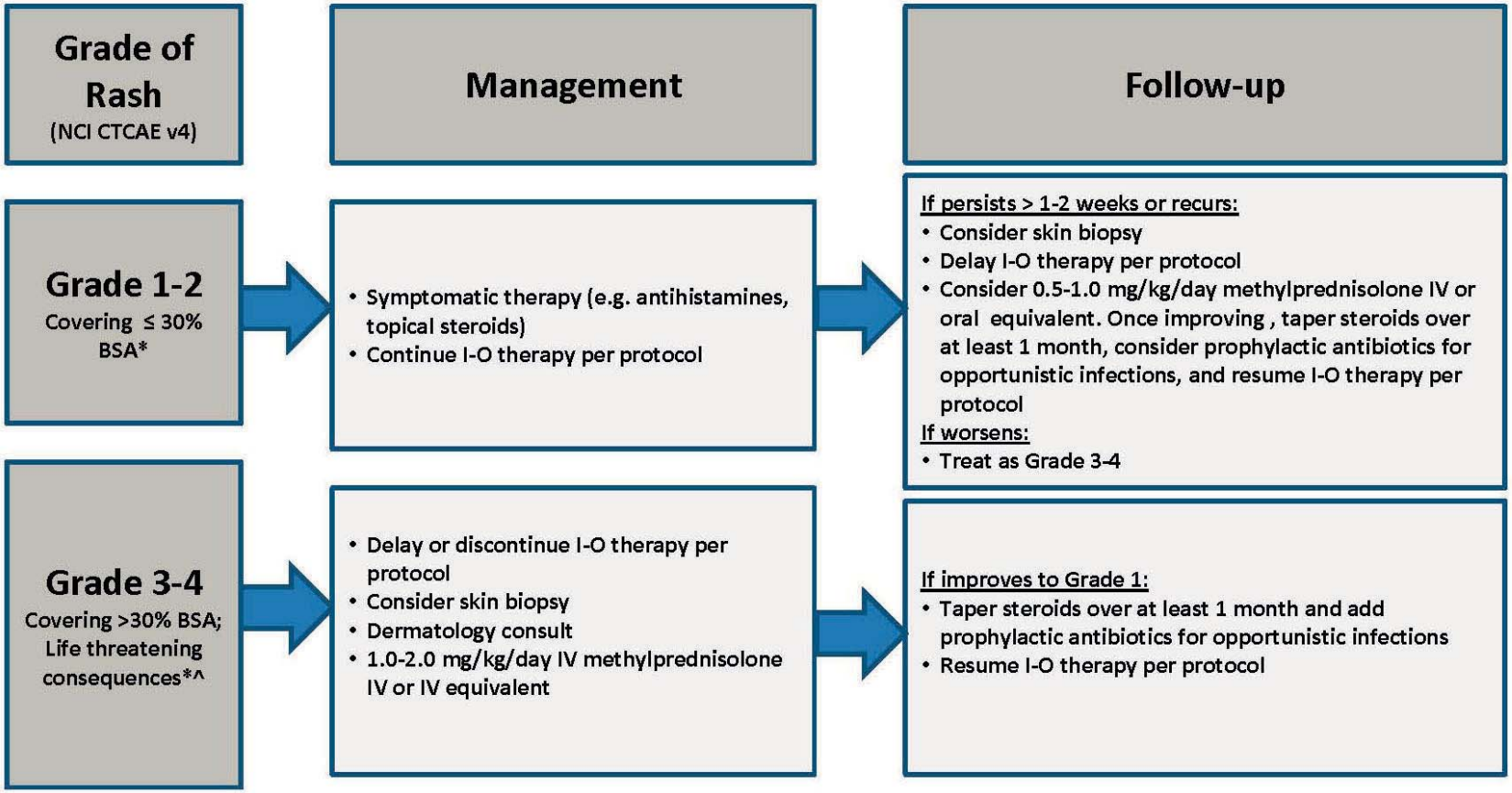
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



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

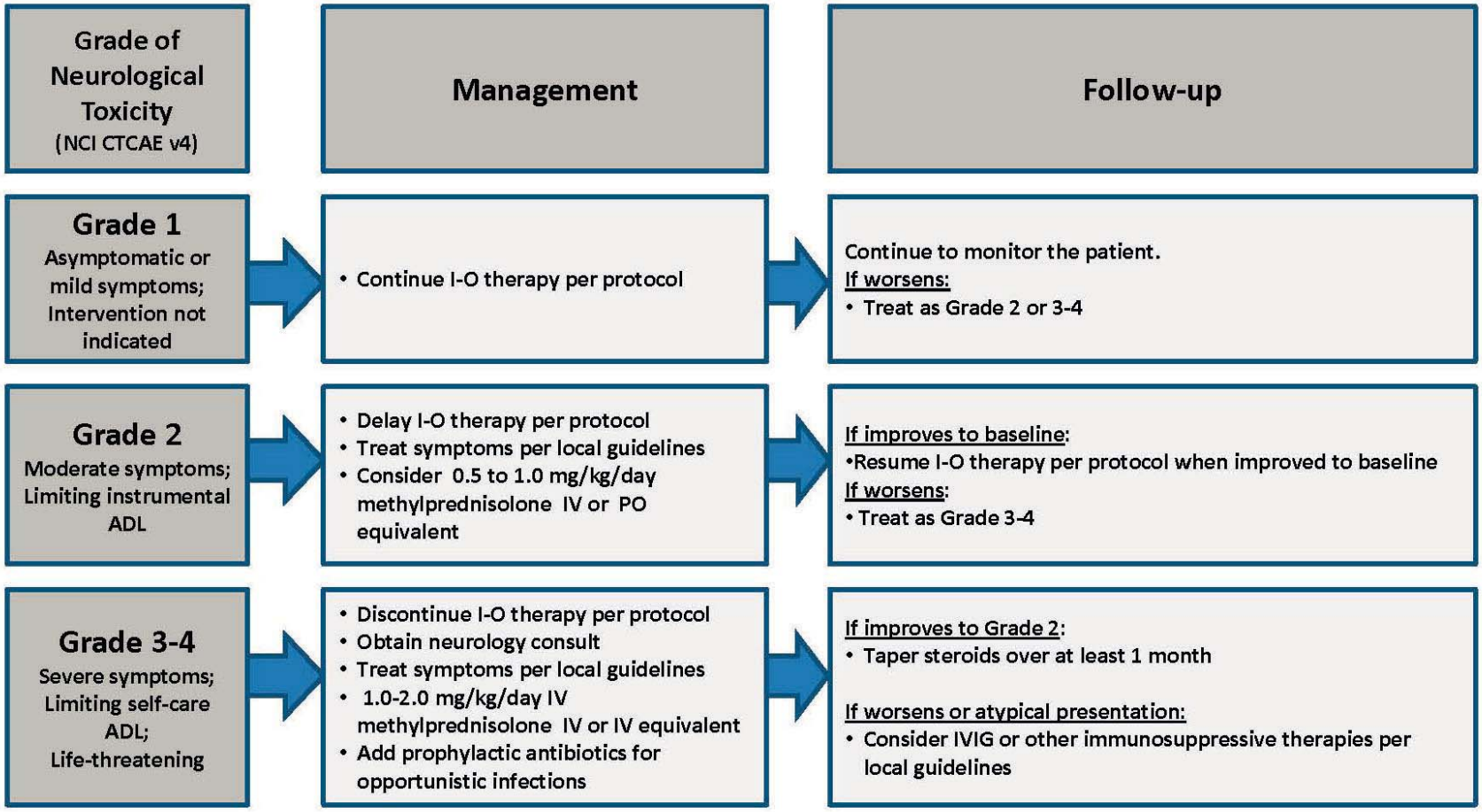
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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.

APPENDIX 5 CHILD-PUGH SCORE

Scoring

The score employs five clinical measures of liver disease. Each measure is scored 1-3, with 3 indicating most severe derangement.

	Points Assigned		
Parameter	**1**	**2**	**3**
Ascites	Absent	Slight	Moderate
Bilirubin (mg/dL)	≤ 2	2 to 3	> 3
Albumin (g/dL)	> 3.5	2.8 to 3.5	< 2.8
Prothrombin Time (seconds over control)	1-3	4 to 6	> 6
INR	< 1.7	1.8 to 2.3	> 2.3
Encephalopathy	None	Grade 1 to 2	Grade 3 to 4

Interpretation

Chronic liver disease is classified into Child-Pugh class A to C, employing the summation of score from above. These scores correlate with one and two year survival:

Points	Class	One year survival	Two year survival
5-6	A (well compensated disease)	100%	65%
7-9	B (significant functional compromise)	80%	60%
10-15	C (decompensated disease)	45%	35%

APPENDIX 6 REVISED PROTOCOL SUMMARY OF CHANGE HISTORY

Overall Rationale for the Revised Protocol 04, 22-Nov-2017

The significant change in revised protocol 04 is the extension of treatment with BMS 986156 and nivolumab for up to 2 years. Data suggest that 2 years of PD-1 checkpoint inhibitor treatment may be sufficient for long-term benefit.

Revisions apply to all participants enrolled as applicable.

Summary of key changes of Revised Protocol 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 3.1 Study Design and Duration Treatment Phase	Increased the number of maximum treatment cycles from 6 to 13.	This increases the number of cycles to support 2 year duration
Section 3.2 Treatment with additional cycles Beyond 24 weeks	After completion of 3 cycles (24 weeks), qualifying subjects may receive 3 additional cycles. Subjects completing 6 cycles (48 weeks) in CR, PR or SD may be eligible for an additional 7 cycles.	This increases the number of cycles to support 2 year duration of treatment
Figure 3.4.1	Updated Overall Schematic	This includes the number of possible additional cycles
Table 5.1-2 On treatment procedural Outline	Monitoring of vital signs can be decreased for patients from cycle 4-13 as long as the patient hasn't experienced an IRR	Safety data supports the decrease in monitoring for patients without IRR
[redacted]		
Table 5.5.1-1 and Table 5.5 1-2	Addition of PK and ADA samples being obtained for the additional cycles	PK/immunogenicity data will support identification of anti-drug antibodies during retreatment
6.1.1 Serious Adverse Event Collection and Reporting	Updated section for collection and reporting SAE	Adjusted guidance for reporting of SAE data in cases where patients have initiated new anti-neoplastic therapy
6.2.1 Non-serious Adverse Event Collection and Reporting	Updated section for collection and reporting AE	Adjusted guidance for reporting of AE data in cases where patients have initiated new anti-neoplastic therapy
[redacted]		

Summary of key changes of Revised Protocol 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
8.4.3 Efficacy Analyses	Added analyses of PFSR at month 12 in the treatment of BMS-986156 and nivolumab	To assess whether the subjects remain progression free and survival during treatment extension period
All	Minor formatting and typographical corrections	Minor, therefore have not been summarized