Official Title of Study:

A Phase 1/2 Study of Relatlimab (anti-LAG-3 Monoclonal Antibody) Administered in Combination with Both Nivolumab (anti-PD-1 Monoclonal Antibody) and BMS-986205 (IDO1 inhibitor) or in Combination with Both Nivolumab and Ipilimumab (anti-CTLA-4 Monoclonal Antibody) in Advanced Malignant Tumors

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Revised Date: 04-Jan-2023

CLINICAL PROTOCOL CA224048

A Phase 1/2 Study of Relatlimab (anti-LAG-3 Monoclonal Antibody) Administered in Combination with Both Nivolumab (anti-PD-1 Monoclonal Antibody) and BMS-986205 (IDO1 inhibitor) or in Combination with Both Nivolumab and Ipilimumab (anti-CTLA-4 Monoclonal Antibody) in Advanced Malignant Tumors

Short Title: An Investigational Study of Immunotherapy Combinations in Participants With Solid Cancers That Are Advanced or Have Spread

Protocol Amendment Number: 07

Incorporates Administrative Letter 03

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DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Protocol Amendment 07	04-Jan-2023	The purpose of this protocol amendment is to: update ipilimumab vial size, [redacted] clarify the Response Follow-up period and Survival Follow-up period durations, [redacted] The study personnel contact information has been updated. Appendix 2 was updated.
Administrative Letter 03	17-Aug-2022	Updated study personnel.
Protocol Amendment 06	13-Dec-2021	Removed erroneous nivolumab myocarditis adverse event management algorithms. Updated study personnel information and incorporated Administrative Letter 02.
Administrative Letter 02	24-Sep-2021	Study personnel information updated and corrected a typographical error in [redacted]
Protocol Amendment 05	07-Sep-2021	[redacted]
Protocol Amendment 04	23-Jul-2021	The primary reasons for these changes are to align dose modification criteria and immuno-oncology (IO) agent management algorithms (Appendix 5) with the current Common Terminology Criteria for Adverse Event (CTCAE) version (v5); [redacted] vaccination and washout periods; and incorporate additional updates to improve alignment across protocol sections and/or clarify expectations for eligibility, assessments, tumor tissue collections and treatment administration. Study personnel information updated. Appendices 1, 2, 3, 4, and 5 were updated.
Administrative Letter 01	17-Oct-2019	Study personnel information updated.
Revised Protocol 03	18-Jan-2019	The primary reasons for these changes include: correction of inconsistencies in language for targetable mutations; replacement of Appendix 3 to align with latest BMS standards; correction of text concerning survival follow-up to ensure uniformity throughout the protocol; [redacted] update Appendix 5 Management Algorithms and add "Myocarditis Adverse Event Management Algorithm" table to Appendix 5; correction of other minor inconsistencies.
Revised Protocol 02	26-Jun-2018	To update the starting dose of BMS-986205 to 25 mg once daily in Part 1A of the dose-finding phase of the study, clarify details, scenarios, and timing for some assessments and follow-up, update contraceptive requirements for males, add information for adverse events of special interest, update the pharmacokinetics and immunogenicity sampling schedule, and update guidance on concomitant therapies.

Document	Date of Issue	Summary of Change
Revised Protocol 01	21-Feb-2018	To address [redacted] comments regarding safety, enrollment, inclusion criteria, exclusion criteria, dose modification criteria and assignment of participants to the study cohorts.
Original Protocol	05-Jan-2018	Not applicable

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 07:

[redacted]

[redacted]

Revisions apply to future participants enrolled in the study and, where applicable, to all participants currently enrolled.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 07		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	• Updated the name and contact information for the clinical scientist. • Updated the name and contact information for the clinical trial physician.	• Updated due to administrative changes and incorporation of Administrative Letter 03. • Updated due to administrative changes in study personnel.
Protocol Summary	• Updated the protocol summary to align with relevant protocol revisions.	• Updated to reflect changes in the protocol body as summarized below.
Table 2-2: On-treatment Procedural Outline Part 1A (Relatlimab + Nivolumab + BMS-986205) and Part 1B (Relatlimab + Nivolumab + Ipilimumab) Table 2-3: On-treatment Procedural Outline: Part 2A (Relatlimab + Nivolumab + BMS-986205) and Part 2B (Relatlimab + Nivolumab + Ipilimumab)	[redacted]	[redacted]
Table 2-4: Follow-Up Procedural Outline CA224048	• [redacted] Replaced with "Refer to Section 5: Study Design" statement and footnote c.	• Updated to ensure consistency with Section 5.1.5 and Section 5.1.6 changes.

[redacted]

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 07		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.1: Overall Design Section 5.1.2: Treatment Period Figure 5.1.6-1: Study Visit Schematic	• Clarified Response Follow-up and Survival Follow-up guidance.	• [redacted]
Section 5.1.5: Response Follow-up Period (Renamed) Section 5.1.6: Survival Follow-up Period	[redacted]	• Provided clarification to the Response Follow-up and Survival Follow-up guidance by specifying time in Follow-up for Part A and Part B participants. [redacted]
Table 7.1: Study treatments for CA224048	• [redacted]	• [redacted]
[redacted]	[redacted]	[redacted]
Table 7.1-2 Part 1A Table 7.1.-3 Part 1B	• Removed abbreviation D for dose.	• Revised for consistency and clarity.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 07		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 9.1.1: Imaging Efficacy Assessments	• [redacted] (refer to Section 5.1.5 and Section 5.1.6)."	• Updated to ensure consistency with Section 5.1.5 and Section 5.1.6 changes.
Table 9.4.4-1: Laboratory Assessments	[redacted]	• [redacted]
Section 10.3: Statistical Analyses	• [redacted]	• [redacted]

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 07		
Section Number & Title	**Description of Change**	**Brief Rationale**
Appendix 2: Study Governance Considerations	Added new subsections: • BMS Commitment to Diversity in Clinical Trials. • Data Protection, Data Privacy, and Data Security.	• To align with BMS' commitment to diversity and European Union Clinical Trials Regulation (EU CTR) requirement for data protection in clinical trials.
All	• Minor formatting and typographical corrections.	• Minor; therefore, they have not been summarized.

TABLE OF CONTENTS

1 PROTOCOL SUMMARY

Protocol Title: A Phase 1/2 Study of Relatlimab (anti-LAG-3 monoclonal antibody) Administered in Combination with Both Nivolumab (anti-PD-1 monoclonal antibody) and BMS-986205 (IDO1 inhibitor) or in Combination with Both Nivolumab and Ipilimumab (anti-CTLA-4 monoclonal antibody) in Advanced Malignant Tumors

Short Title: An Investigational Study of Immunotherapy Combinations in Participants With Solid Cancers That Are Advanced or Have Spread

Study Phase: 1/2

Rationale:

Individually targeting immune checkpoint receptors, such as programmed death-1 (PD 1), has demonstrated clinical activity across multiple tumor types; several studies to date have demonstrated activity of therapeutic compounds aimed at the PD-1 receptor and its ligand, programmed death-ligand 1 (PD-L1). This benefit is further extended by dual combination therapy of cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) and PD-1 inhibitors. Despite the demonstrated benefit of single or dual combinations of cancer immunotherapies on clinical outcome, a large proportion of patients with many tumor types do not respond, or will relapse after an initial response to these agents. Substantial efforts are needed to provide therapy to patients who do not respond to currently approved single or dual combination immunotherapeutic agents, as well as to provide treatment options for relapse patients to increase their survival.

Relatlimab is a human lymphocyte activation gene 3 (LAG-3)-specific antibody expressed as an IgG4 isotype antibody including a stabilizing hinge mutation (S228P) isolated after immunization of transgenic mice expressing human Ig genes. Relatlimab binds to LAG-3 with high affinity and inhibits the negative regulatory function of LAG-3 in vitro. Binding of relatlimab to LAG-3 prevents binding of this receptor to cells bearing its ligand, major histocompatibility complex (MHC) Class II, the peptide antigen presentation molecule recognized by CD4+ T cells. [redacted]

Linrodostat mesylate (BMS-986205) is an optimized indoleamine 2,3-dioxygenase 1 (IDO1) inhibitor, characterized by once-daily [redacted] dose administration and deeper inhibition of IDO1 activity, as measured by peripheral blood kynurenine suppression, than other inhibitors. [redacted]

The above data support the testing of triple combinations of relatlimab combined with nivolumab and BMS-986205 or with nivolumab and ipilimumab to simultaneously engage multiple

immuno-oncology (IO) targets. Triple combinations may have the potential to offer superior efficacy to single-agent anti PD-1 regimens in the immunotherapy-naive treatment setting as well as provide meaningful efficacy to patients that have progressed during anti-PD-1 therapy. In therapy naive patients, constitutive LAG-3 expression may limit the antitumor activity of PD-1 pathway blockade, preventing the maximum magnitude and/or durability of response that a patient might otherwise benefit from immunotherapy. Relatlimab triple combinations may increase the numbers of responders and/or deepen or increase the durability of responses. In patients previously exposed to PD-1 pathway blockade, adaptive upregulation of LAG-3 expression may lead to treatment resistance and tumor progression. Relatlimab triple combinations may help to restore T cell activation and tumor response.

The current study aims to demonstrate safety and preliminary activity with triple combinations of relatlimab in combination with nivolumab and BMS-986205, or in combination with nivolumab and ipilimumab in [redacted] across select tumor types of [redacted]

[redacted]

Study Population:

Males and Females, ages ≥ 18 years with select solid tumor histologies as listed below.

Part 1A and Part 1B: [redacted]

Part 2A and Part 2B: [redacted]

[redacted]

[redacted]

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

Objectives and Endpoints:

Information on objectives and endpoints is provided in Table 1, below.

Table 1: Objectives and Endpoints

Objectives	Endpoints
Primary	
• Part 1A and Part 1B: To determine the safety, tolerability, DLTs, and MTD of relatlimab administered in combination with nivolumab and BMS-986205 or nivolumab and ipilimumab in participants with advanced malignant tumors.	• Incidence of clinical laboratory test abnormalities, AEs, SAEs, AEs meeting protocol-defined DLT criteria, AEs leading to discontinuation, and deaths.
• Part 2A and Part 2B: To investigate safety and tolerability of relatlimab triple combinations in distinct cohorts of participants with advanced malignant tumors.	• Incidence of clinical laboratory test abnormalities, AEs, SAEs, AEs leading to discontinuation, and deaths.
• To investigate the antitumor activity of relatlimab triple combinations in participants with advanced malignant tumors.	• ORR, DCR, and mDOR in participants with advanced malignant tumors.
Secondary	
• To investigate the antitumor activity of relatlimab triple combinations in participants with advanced malignant tumors.	• mPFS and PFSR at 6 and 12 months in participants with advanced malignant tumors.

[redacted]

Table 1: Objectives and Endpoints

[redacted]

Abbreviations: AE = adverse event; DCR = disease control rate; DLT = dose-limiting toxicity; IgG = immunoglobulin G; [redacted]; mDOR = median duration of response; [redacted]; mPFS = median progression-free survival; MTD = maximum tolerated dose; [redacted]; PFSR = progression-free survival rate; [redacted]; SAE = serious adverse event; [redacted]

Overall Design:

This is a Phase 1/2, open-label study of relatlimab in combination with nivolumab and BMS-986205 or in combination with nivolumab and ipilimumab in participants with advanced solid tumors. Participants will complete up to 5 periods of the study: **Screening**, **Treatment**, **Clinical Safety Follow-up**, and **Response Follow-up,** and **Survival Follow-up (see below)**. Relatlimab, nivolumab, and ipilimumab will be administered intravenously in the clinical facility per the treatment schedule. BMS-986205 will be administered orally at home except for Day 1 of Cycle 1, where it will be administered in the clinic.

After establishment of a tolerable and safe dose administration regimen in both Part 1A and Part 1B, the Part 2A and Part 2B expansion cohorts will be initiated. The purpose of the cohort expansions is to gather preliminary efficacy information in specific patient populations regarding relatlimab in combination with nivolumab and BMS-986205, or in combination with nivolumab and ipilimumab. Expansion cohorts will only open after data is evaluated from Part 1A and Part 1B to guide doses selected for Part 2A and Part 2B respectively. Part 2A and Part 2B may be initiated independently from each other based on the timing of data evaluation in Part 1.

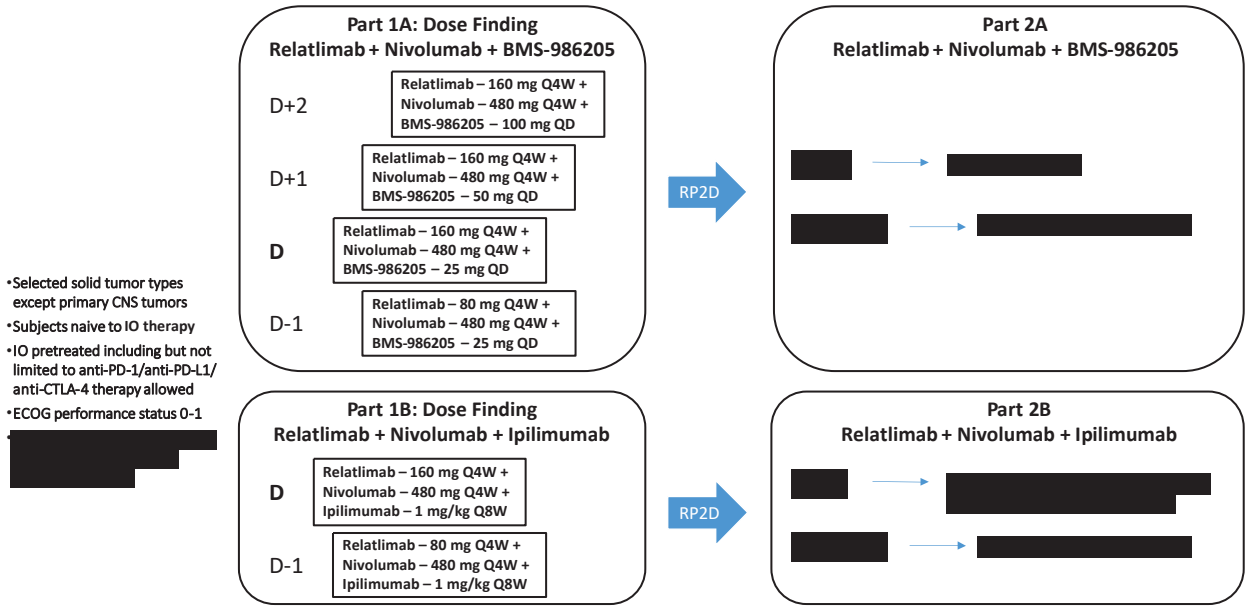
Part 1A and Part 1B consist of dose finding cohorts of 2 triplet combinations relatlimab, nivolumab and BMS-986205, or relatlimab, nivolumab and ipilimumab. [redacted]

[redacted] If the starting dose is not tolerable in the [redacted] dose-limiting toxicity (DLT) evaluation phase, the dose will be de-escalated to D-1 upon safety review from initial dose level D. In Part 1A, if the starting dose is tolerable in the [redacted] DLT evaluation phase, participants will be treated at the next dose levels. Part 1A and Part 1B will be initiated in parallel. The evaluation of combination doses of relatlimab with nivolumab and BMS-986205 (Part 1A) and relatlimab with nivolumab and ipilimumab (Part 1B) will be performed based on safety and tolerability.

Part 2A and Part 2B consist of tumor-specific expansion cohorts of respective triple combinations. The dose selected for Part 2A and Part 2B will not exceed the maximum administered dose in Part 1; [redacted] The goal of Part 2 is to estimate the antitumor activity of relatlimab in combination with nivolumab and BMS-986205 or relatlimab in combination with nivolumab and ipilimumab.

The study design schematic is presented in Figure 1, below.

Figure 1: Study Design Schematic



Abbreviations: CNS = central nervous system; CTLA-4 = cytotoxic T lymphocyte antigen-4; D = starting dose level; ECOG = Eastern Cooperative Oncology Group; [redacted]; IO = immuno-oncology; [redacted]; PD-1 = programmed death-1; PD-L1 = programmed death-ligand 1; Q4W = every 4 weeks; Q8W = every 8 weeks; QD = once daily; [redacted]

Screening: The screening period will be up to 28 days and begins by establishing the participant's initial eligibility and signing of the informed consent form. Informed consent will be obtained prior to any study-specific procedures. Participants will be evaluated based on the assessments as outlined in the Schedule of Activities and Inclusion and Exclusion criteria. If a participant exceeds the 28-day screening period due to a study-related procedure [redacted] the participant must be re consented but will not

require a new participant identification number. In this situation, the fewest number of procedures from the initial screening should be repeated to qualify the participant, while maintaining participant safety and eligibility.

[redacted]

Treatment Period

Dose Finding Part 1A (Relatlimab, Nivolumab, and BMS-986205)

The DLT evaluation period is [redacted] in participants with melanoma, NSCLC, SCCHN, RCC, and GC/GEJ. BMS-986205 will be administered orally once daily (QD) prior to relatlimab and nivolumab infusions. Relatlimab will be co-administered with nivolumab in the clinic as an intravenous (IV) infusion every 4 weeks (Q4W). [redacted]

Part 1A starting doses will be:

D = Relatlimab 160 mg Q4W + Nivolumab 480 mg Q4W + BMS-986205 25 mg QD.

If during the dose-finding phase, it appears the dose is associated with an acceptable frequency of toxicities, then the BMS-986205 dose will be increased as follows:

D+1 = Relatlimab 160 mg Q4W + Nivolumab 480 mg Q4W + BMS-986205 50 mg QD.

D+2 = Relatlimab 160 mg Q4W + Nivolumab 480 mg Q4W + BMS-986205 100 mg QD.

If during the dose-finding phase, it appears the starting dose is associated with an unacceptable frequency of toxicities, the relatlimab dose will be decreased as follows:

D-1 = Relatlimab 80 mg Q4W + Nivolumab 480 mg Q4W + BMS-986205 25 mg QD.

Dose Finding Part 1B (Relatlimab, Nivolumab, and Ipilimumab)

The DLT evaluation period is [redacted] in participants with melanoma, NSCLC, SCCHN, RCC, and GC/GEJ. Relatlimab will be co-administered with nivolumab in the clinic as an IV infusion Q4W. [redacted]

Part 1B starting doses will be:

D = Relatlimab 160 mg Q4W + Nivolumab 480 mg Q4W + Ipilimumab 1 mg/kg Q8W.

If during the dose-finding phase, it appears the dose is associated with an unacceptable frequency of toxicities, then the relatlimab dose will be decreased as follows:

D-1 = Relatlimab 80 mg Q4W + Nivolumab 480 mg Q4W + Ipilimumab 1 mg/kg Q8W.

Expansion: Part 2A (Relatlimab, Nivolumab, and BMS-986205) and Part 2B (Relatlimab, Nivolumab, and Ipilimumab)

Part 2 is the safety evaluation, tolerability, and cohort expansion of the triple combinations in distinct cohorts advanced malignant tumors to gather preliminary efficacy information. The doses to be administered are determined from Part 1A and Part 1B of the study. The recommended Phase 2 dose (RP2D) selected for Part 2 are as follows:

Part 2A: Relatlimab 160 mg Q4W, Nivolumab 480 mg Q4W, BMS-986205 100 mg QD

Part 2B: Relatlimab 160 mg Q4W, Nivolumab 480 mg Q4W, Ipilimumab 1 mg/kg Q8W

The tumor cohorts and regimens are:

- [redacted]

The dose-finding phase of the study (Part 1A and Part 1B) evaluates the safety and tolerability of relatlimab in combination with nivolumab and BMS-986205 (Part 1A) or nivolumab and ipilimumab (Part 1B) based on DLTs, using [redacted] and safety evaluation beyond the DLT phase. Any toxicities that occur beyond the DLT period will be accounted for in making dose level decisions and/or dose level modifications.

After the initial participants (approximately 3) are evaluated at the starting dose levels in Part 1A and Part 1B, additional increments of approximately 3 to 6 participants will be treated in the same cohort (or at the next dose level) [redacted] At least 6 DLT-evaluable participants will be treated and assessed in the selected combination dose level before starting the cohort-expansion phase at the same dose. [redacted]

[redacted]

Prior to declaring the maximum tolerated dose, and in consultation with Investigators, the Sponsor has the option to expand any dose level previously established to be tolerable, in order to obtain additional experience or to investigate dose levels intermediate to those defined in the protocol.

[redacted]

Physical examinations, vital sign measurements, 12-lead electrocardiograms (ECGs), and clinical laboratory evaluations will be performed at selected times throughout the dose administration interval. Participants will be closely monitored for adverse events (AEs) throughout the study.

[redacted]

Continuous safety evaluation and tumor assessment [redacted] will guide the decision to treat a participant with additional cycles of study therapy if the participant has confirmed clinical benefit.

[redacted]

Participants with unconfirmed progressive disease, stable disease (SD), or partial response (PR) at the end of a given cycle will continue to the next treatment cycle.

[redacted]

Continuous evaluation of toxicity events in the cohort expansions will be performed throughout enrollment for all expansion cohorts. [redacted] Depending on the nature and grade of the toxicity, and after assessing the benefit-risk ratio, a new dose for all cohorts may be initiated at a previously tested lower dose level or at a dose level intermediate to previously tested lower dose levels.

Clinical Safety Follow-up Period

Upon completion of study therapy, or once the decision is made to discontinue the participant from treatment (ie, at end of treatment [EOT]), all participants will enter a Clinical Safety Follow-up period.

For participants who complete all scheduled cycles of therapy, the [redacted] Accordingly, for these participants, this visit will be considered the start of the [redacted]

[redacted]

Response Follow-up Period

Participants with SD, PR, or CR at the time of the EOT visit or at the time of study treatment discontinuation will continue to have radiologic and clinical tumor assessments every [redacted] Subsequently, they will continue to receive tumor assessment scans per standard-of-care guidelines or [redacted] Participants who have disease progression after an initial course of study therapy will not be evaluated for response beyond the EOT visit and will be allowed to receive other tumor-directed therapy as required. [redacted]

Survival Follow-up Period

In parallel with the Clinical Safety and Response Follow-up periods (as applicable), Part B participants will start the Survival Follow-up period. Participants will be followed until death, loss to Follow-up, withdrawal of consent, or conclusion of the study, whichever comes first (see Figure 2). [redacted]

[redacted]

Treatment Groups and Duration

Information on treatment groups and duration is provided in Table 2, Table 3, and Table 4.

Table 2: Treatments Administered

Study Treatment	Dose Level	Frequency of Administration and Duration of Treatment	Route of Administration	Infusion Time, minutes
Relatlimab[a]	160 mg, 80 mg	Q4W Until progression, unacceptable toxicity, withdrawal of consent, or CR	IV	[redacted]
Nivolumab[a]	480 mg	Q4W Until progression, unacceptable toxicity, withdrawal of consent, or CR	IV	[redacted]

Table 2: Treatments Administered

Study Treatment	Dose Level	Frequency of Administration and Duration of Treatment	Route of Administration	Infusion Time, minutes
BMS-986205[c]	100 mg, 50 mg 25 mg	QD Until progression, unacceptable toxicity, withdrawal of consent, or CR	PO	[redacted]
Ipilimumab	1 mg/kg	Q8W Until progression, unacceptable toxicity, withdrawal of consent, or CR	IV	[redacted]

Abbreviations: [redacted] IV = intravenous; NA = not applicable; PO = by mouth; Q4W = every 4 weeks; Q8W = every 8 weeks; QD = once daily.

[a] Relatlimab and nivolumab are administered as either a co-administration (relatlimab 160 mg and nivolumab 480 mg) or a sequential administration (relatlimab 80 mg and nivolumab 480 mg).

[redacted]

Table 3: Part 1A

Dose	Treatment [redacted]
Starting Dose	
Dose	Relatlimab 160 mg Q4W, Nivolumab 480 mg Q4W, BMS-986205 25 mg QD
Dose Escalation	
Dose +1	Relatlimab 160 mg Q4W, Nivolumab 480 mg Q4W, BMS-986205 50 mg QD
Dose +2	Relatlimab 160 mg Q4W, Nivolumab 480 mg Q4W, BMS-986205 100 mg QD
Dose De-escalation	
Dose -1	Relatlimab 80 mg Q4W, Nivolumab 480 mg Q4W, BMS-986205 25 mg QD

Abbreviations: Q4W = every 4 weeks; QD = once daily.
Note: recommended Phase 2 dose from Part1A will be used in Part 2A.

Table 4: Part 1B

Dose	Treatment [redacted]
Starting Dose	
Dose	Relatlimab 160 mg Q4W, Nivolumab 480 mg Q4W, Ipilimumab 1 mg/kg Q8W
Dose De-escalation	
Dose -1	Relatlimab 80 mg Q4W, Nivolumab 480 mg Q4W, Ipilimumab 1 mg/kgQ8W

Abbreviations: Q4W = every 4 weeks; Q8W = every 8 weeks.
Note: recommended Phase 2 dose from Part 1B will be used in Part 2B.

The RP2D selected for Part 2 are as follows:

Part 2A: Relatlimab 160 mg Q4W, Nivolumab 480 mg Q4W, BMS-986205 100 mg QD

Part 2B: Relatlimab 160 mg Q4W, Nivolumab 480 mg Q4W, Ipilimumab 1 mg/kg Q8W

Dose Limiting Toxicities

For the purpose of guiding dose selection, DLTs will be defined based on the incidence, intensity, and duration of AEs that are possibly related to study treatment. The DLT period will be [redacted] in Part 1A and Part 1B. Any toxicities that occur beyond the DLT period will be accounted for in making final dose level decisions.

Number of Participants:

Part 1A (relatlimab, nivolumab, and BMS-986205): [redacted]

Part 1B (relatlimab, nivolumab, and ipilimumab): [redacted]

The sample size in each of the 2 groups in Part 1 (A and B) will depend on observed toxicity and posterior inference from the [redacted]

Part 2: [redacted]

A Simon 2-stage (optimal) design will be used as a guide for many of the tumor specific cohorts.

STUDY ASSESSMENTS AND ANALYSES:

Safety Analyses:

Safety assessments will be based on reported AEs and the measurement results of vital signs, ECGs, physical examinations, and clinical laboratory tests. AEs will be coded using the most current version of Medical Dictionary for Regulatory Activities and the incidence of observed AEs will be tabulated and reviewed for potential significance and clinical importance.

[redacted]

[redacted]

[redacted] Both AEs and laboratory tests will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events v5.0.

[redacted]

Efficacy Assessments:

Disease assessment with computed tomography and/or magnetic resonance imaging, as appropriate, will be performed at baseline, and the date of the first dose, and then periodically [redacted] Disease assessments at other time points may be performed as clinically indicated. [redacted] Sites will be trained prior to scanning the first study participant. Image acquisition guidelines and submission process will be outlined in the CA224048 Imaging Manual to be provided by [redacted] Changes in tumor measurements will be assessed by the Investigator and tumor responses will be determined using RECIST v1.1 criteria.

Data Monitoring Committee: No

2 SCHEDULE OF ACTIVITIES

Table 2-1: Screening Procedural Outline for All Study Parts (CA224048)

Procedure	Screening Visit -28 days	Day -14 to Day -1 Visit	Notes[a]
Eligibility Assessments			
Informed Consent	X		A participant is considered enrolled only when a protocol-specific informed consent is signed. Obtain participant's number from interactive response technology (IRT). For Protocol Amendment 05, all current participants will be re-consented. New participants will sign the updated informed consent for Protocol Amendment 05.
IRT Participant Assignment	X		After the participants meet all eligibility criteria, sites will use IRT for participant number assignment. Subsequent visits will be registered into the IRT system for drug supply (see Section 7.2). If the IRT system is not available, participants will be enrolled manually.
Inclusion/Exclusion Criteria	X		See Section 6.1 and Section 6.2.
Medical History	X		[redacted]
Performance Status	X		Eastern Cooperative Oncology Group (ECOG) Performance Status (see Appendix 6).
Prior Systemic Therapies	X		Includes prior cancer treatment regimens and medications administered within 4 weeks (28 days) of study dose administration.
[redacted]	X		[redacted]

Table 2-1: Screening Procedural Outline for All Study Parts (CA224048)

Procedure	Screening Visit -28 days	Day -14 to Day -1 Visit	Notes[a]
Concomitant Medications	X		Collected during the 4 weeks (28 days) prior to Cycle 1 Day 1.
Safety Assessments			
Physical Examination (PE)	X		If PE screening is performed within 24 hours prior to dose administration on Day 1, a single examination may count as both the screening and predose evaluation.
Physical Measurements	X		Includes height and weight.
Vital Signs		X	Includes body temperature, seated blood pressure, and heart rate. Blood pressure and heart rate should be measured after the participant has been seated quietly for at least 5 minutes.
Oxygen Saturation	X		Collected at rest via pulse oximetry to establish baseline. .
[redacted]			
Chest Radiograph	X		Posterior-anterior and lateral chest x-ray to establish baseline.
Laboratory Tests			
Laboratory Tests		X	[redacted]
[redacted]	X		[redacted]
[redacted]		X	[redacted]

Table 2-1: Screening Procedural Outline for All Study Parts (CA224048)

Procedure	Screening Visit -28 days	Day -14 to Day -1 Visit	Notes[a]
Urinalysis		X	See Section 9.4.4.
Thyroid Function Tests		X	See Section 9.4.4.
Genetic Mutation Status	X		[redacted]
Serology	X		See Section 9.4.4. Viral testing to be completed within 28 days prior to treatment assignment. For human immunodeficiency virus (HIV): testing at sites where locally mandated. [redacted]
Pregnancy Test (Women of Childbearing Potential [WOCBP] Only)	X		Women of childbearing potential (WOCBP) only. Sample tested **at screening and within 24 hours prior to dose administration.** The serum pregnancy test may be completed on the first day of treatment, provided the results are available before the start of study drug.
Follicle Stimulating Hormone (FSH)	X		Women only, as needed to document postmenopausal status. Females under the age of 55 years must have a serum FSH level > 40 mIU/mL to confirm menopause.

Table 2-1: Screening Procedural Outline for All Study Parts (CA224048)

Procedure	Screening Visit -28 days	Day -14 to Day -1 Visit	Notes[a]
Adverse Event Reporting			
Monitor for Serious Adverse Events (SAEs)	X		All SAEs must be collected from the date of participant's written consent until [redacted] after discontinuation of dose administration or participation in the study if the last scheduled visit occurs at a later time. [redacted] Electronic SAEs (eSAEs) should be approved in the BMS Electronic Data Capture (EDC) tool within 5 business days of entry.
Clinical Complaints		X	Collected during the 2 weeks prior to Cycle 1 Day 1.
Tumor Assessments/Baseline Efficacy Assessments			
Body Imaging	X		See Section 9.1; must be performed within 28 days prior to first dose.
Brain Imaging	X		Magnetic resonance imaging (MRI) of the brain without and with contrast is required for participants with known or suspected brain metastases who have not had brain imaging within [redacted] of anticipated first study drug administration. See imaging assessment details in Section 9.1.
Other Imaging: Bone Scan	X		See Section 9.1; as clinically indicated per local standards.

Abbreviations: AE = adverse events; [redacted]; CRF = case report form; [redacted] ECOG = Eastern Cooperative Oncology Group; EDC = electronic data capture; [redacted]; eSAEs = electronic serios adverse events; FSH = follicle stimulating hormone; G6PD = glucose-6-phosphate dehydrogenase; HIV = human immunodeficiency virus; IgG = immunoglobulin; IRT = interactive response technology; [redacted]; MRI = magnetic resonance imaging; [redacted] PE = physical examination; [redacted]; SAE = serious adverse events; [redacted]; WOCBP = women of childbearing potential.

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

Table 2-2: On-treatment Procedural Outline Part 1A (Relatlimab + Nivolumab + BMS-986205) and Part 1B (Relatlimab + Nivolumab + Ipilimumab)

Procedure	Cycle 1 [redacted]					Cycle 2+ [redacted]						Notes[e,f]
	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted]	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted]	End of Treatment (EOT)[a,b,c]	
Safety Assessments												
Physical Examination (PE)	X					X					X	Predose.
Symptom-directed PE		X	X	X				X				Predose. [redacted]
Performance Status	X	X	X	X		X		X			X	Eastern Cooperative Oncology Group (ECOG) Performance Status for all participants (see Appendix 6). [redacted]

Table 2-2: On-treatment Procedural Outline Part 1A (Relatlimab + Nivolumab + BMS-986205) and Part 1B (Relatlimab + Nivolumab + Ipilimumab)

Procedure	Cycle 1 [redacted]					Cycle 2+ [redacted]						Notes[e,f]
	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted]	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted]	End of Treatment (EOT)[a,b,c]	
Vital Signs	X See notes.	X	X	X		X		X			X	Includes temperature, seated blood pressure (BP), and heart rate (HR). BP and HR should be measured after the participant has been seated quietly for at least 5 minutes. **On Cycle 1 Day 1**, vital signs will be obtained prior to the infusion [redacted] Vital signs on subsequent treatment visits will be collected prior to the first infusion [redacted] If any vital sign is abnormal (based upon clinician assessment) at the final check, the participants must be observed further for a period of time, as clinically indicated. [redacted]
Oxygen Saturation	X	X	X	X		X		X			X	Collected at rest via pulse oximetry. Oxygen levels will be used in combination with clinical signs and symptoms and radiographic images to evaluate pulmonary/respiratory status. Changes in O_2 levels will not be used in isolation to document or diagnose pulmonary toxicity. [redacted]

Table 2-2: On-treatment Procedural Outline Part 1A (Relatlimab + Nivolumab + BMS-986205) and Part 1B (Relatlimab + Nivolumab + Ipilimumab)

Procedure	Cycle 1 [redacted]					Cycle 2+ [redacted]						Notes[e,f]
	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted]	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted]	End of Treatment (EOT)[a,b,c]	
[redacted]	X	X	X	X		X					X	[redacted]
Chest Radiograph	See notes.											As clinically indicated.
Laboratory Tests[d]	X	X	X	X		X		X			X	On-study laboratory tests (including hematology, serum chemistry, endocrine panel, troponin, [redacted] urinalysis, and pregnancy testing) to be done on site/locally. Laboratory tests may be collected within 3 days prior to dose administration. [redacted]

Table 2-2: On-treatment Procedural Outline Part 1A (Relatlimab + Nivolumab + BMS-986205) and Part 1B (Relatlimab + Nivolumab + Ipilimumab)

Procedure	Cycle 1 [redacted]					Cycle 2+ [redacted]						Notes[e,f]
	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted]	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted]	End of Treatment (EOT)[a,b,c]	
[redacted]	See Notes											[redacted] For C1D1, value taken at screening (pre-treatment assignment) may be used and need not be repeated. See Section 9.4.4 for laboratory test requirements.
Clinical Observation[d]	See Notes											All participants should be evaluated for any immune-mediated adverse events. Evaluations should occur every week (± 1 day) up to and including Week 8. Participants with any clinical symptoms should immediately be evaluated. For non-dosing visits, assessments may be performed remotely by the Investigator/delegate.
Part 1A Only (BMS-986205 treated) Methemoglobin	X	X	X	X		X		X			X	Predose, [redacted], and additional assessments as clinically indicated (see Section 9.4.4). [redacted]

Table 2-2: On-treatment Procedural Outline Part 1A (Relatlimab + Nivolumab + BMS-986205) and Part 1B (Relatlimab + Nivolumab + Ipilimumab)

Procedure	Cycle 1 [redacted]					Cycle 2+ [redacted]						Notes[e,f]
	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted]	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted]	End of Treatment (EOT)[a,b,c]	
Pregnancy Test (Women of Childbearing Potential [WOCBP])	X		X			X		X			X	A pregnancy test must be performed within 24 hours prior to administration of intravenous study drug. Serum or urine pregnancy test may be performed (for urine pregnancy test, minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [hCG] is required). If results are positive, hold all study drug and perform confirmatory testing. If pregnancy is confirmed, permanently discontinue all study drug and immediately notify Sponsor per Section 9.2.6.
Assess Adequate Contraceptive Use	X		X			X		X				For WOCBP and male participants who are sexually active with WOCBP, assess for continued use of acceptable methods of contraception (see Appendix 4).
Adverse Event Reporting and Concomitant Medication Assessments												
Concomitant Medication Assessments	Continuously											Review prior to dose administration.
Monitor for Non-serious Adverse Events (AEs)	X											Non-serious AEs will be collected starting with the first dose of study drug and through [redacted] after discontinuation of treatment. See Section 9.2: Adverse Events.

Table 2-2: On-treatment Procedural Outline Part 1A (Relatlimab + Nivolumab + BMS-986205) and Part 1B (Relatlimab + Nivolumab + Ipilimumab)

Procedure	Cycle 1 [redacted]					Cycle 2+ [redacted]						Notes[e,f]
	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted]	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted]	End of Treatment (EOT)[a,b,c]	
Monitor for Serious Adverse Events (SAEs)	X											All SAEs must be collected from the date of participant's written consent until [redacted] post discontinuation of treatment or participation in the study if the last scheduled visit occurs at a later time. eSAEs should be approved in the BMS Electronic Data Capture (EDC) tool within 5 business days of entry. See Section 9.2: Adverse Events.
Sample Collection												
[redacted]						X						[redacted]
[redacted]						X						[redacted]
[redacted]						X						[redacted]
[redacted]						X						[redacted]

Table 2-2: On-treatment Procedural Outline Part 1A (Relatlimab + Nivolumab + BMS-986205) and Part 1B (Relatlimab + Nivolumab + Ipilimumab)

Procedure	Cycle 1 [redacted]					Cycle 2+ [redacted]						Notes[e,f]
	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted]	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted]	End of Treatment (EOT)[a,b,c]	
Additional Research Sampling	X											Residual samples will be used for additional research. See Section 9.8.3.
[redacted]												
Efficacy Assessments												
Body Imaging	See Notes											See Section 9.1; tumor assessments will occur [redacted].
Brain Imaging	See Notes											See Section 9.1; only for participants with a history of brain metastasis. Surveillance magnetic resonance imaging (MRI) approximately [redacted] or sooner if clinically indicated.

Table 2-2: On-treatment Procedural Outline Part 1A (Relatlimab + Nivolumab + BMS-986205) and Part 1B (Relatlimab + Nivolumab + Ipilimumab)

Procedure	Cycle 1 [redacted]					Cycle 2+ [redacted]						Notes[e,f]
	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted]	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted]	End of Treatment (EOT)[a,b,c]	
Other Imaging: (Bone Scan)	See Notes											See Section 9.1; as clinically indicated per local standards.
Response Assessment					X					X		Assessed by Response Evaluation Criteria in Solid Tumors v1.1 (see Appendix 11). Assessment must be performed prior to initiating the next cycle of treatment and continue on a [redacted]
Study Treatment												
IRT Drug Assignment and Study Drug Dispensation	X											Participant must receive the first dose of study medication within 3 calendar days from vial allocation. Thereafter, a ± 2-day window is permissible.
Study Drug Administration Part 1A (Relatlimab + Nivolumab + BMS-986205)												Details regarding preparation and administration of study drugs are provided in the site/pharmacy training materials.
BMS-986205	Oral Daily Administration											For the first administration of BMS-986205 on Day 1 of Cycle 1, BMS-986205 will be administered in the clinic. [redacted]

Table 2-2: On-treatment Procedural Outline Part 1A (Relatlimab + Nivolumab + BMS-986205) and Part 1B (Relatlimab + Nivolumab + Ipilimumab)

Procedure	Cycle 1 [redacted]					Cycle 2+ [redacted]						Notes[e,f]
	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted]	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted]	End of Treatment (EOT)[a,b,c]	
Nivolumab and Relatlimab Administration	X		X			X		X				[redacted]
BMS-986205 Pill Diary	X	X	X	X	X	X	X	X	X	X	X	Review pill diary during each visit for compliance of daily administration of BMS-986205. Collect pill diary at completion of each cycle, or earlier, and at EOT. [redacted]
Study Drug Administration Part 1B (Relatlimab + Nivolumab + Ipilimumab)												Details regarding preparation and administration of study drugs are provided in the site/pharmacy training materials.
Nivolumab and Relatlimab administration	X		X			X		X				[redacted]

Table 2-2: On-treatment Procedural Outline Part 1A (Relatlimab + Nivolumab + BMS-986205) and Part 1B (Relatlimab + Nivolumab + Ipilimumab)

Procedure	Cycle 1 [redacted]					Cycle 2+ [redacted]						Notes[e,f]
	[redacted] (± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	[redacted]	(± 2 days)	(± 2 days)	(± 2 days)	(± 2 days)	[redacted]	End of Treatment (EOT)[a,b,c]	
Ipilimumab Administration	X					X						[redacted].

Abbreviations: AE = adverse event; BP = blood pressure; C= cycle; [redacted] D = day; [redacted]; ECOG = Eastern Cooperative Oncology Group; EDC = electronic data capture; EOT = end of treatment; eSAE = electronic serious adverse event; HCG = of human chorionic gonadotropin; HR = heart rate; IRT = interactive response technology; MRI = magnetic resonance imaging; O2 = oxygen; PE = physical examination; [redacted]; SAE = serious adverse event; [redacted]; [redacted]; WOCBP = women of childbearing potential.

[a] EOT is defined as the visit when a participant discontinues study therapy.

[b] For participants who complete all scheduled cycles of therapy, the EOT visit will be the same as the last scheduled and completed dosing or non-dosing on-treatment visit.

[c] For participants who do not complete all scheduled cycles of therapy, the EOT visit will be the most recent dosing or non-dosing on-treatment visit (with all available safety and response data) when treatment is discontinued, does not need to be repeated, and will be considered the start of the Week 1 Clinical/Safety Follow-up visit.

[redacted]

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

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

Table 2-3: On-treatment Procedural Outline: Part 2A (Relatlimab + Nivolumab + BMS-986205) and Part 2B (Relatlimab + Nivolumab + Ipilimumab)

Procedure	Cycle 1 onwards [redacted]					End of Treatment (EOT)[a,b,c]	Notes[e,f]
	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted]		
Safety Assessments							
Physical Examination (PE)	X					X	Predose.
Symptom-directed PE		X	X	X			Predose. [redacted]
Performance Status	X	X	X	X		X	Eastern Cooperative Oncology Group (ECOG) Performance Status for all participants (see Appendix 6). [redacted]
Vital Signs	X See notes.	X	X	X		X	Includes temperature, seated blood pressure (BP) and heart rate (HR). BP and HR should be measured after the participant has been seated quietly for at least 5 minutes. **On Cycle 1 Day 1**, vital signs will be obtained prior to the [redacted] Vital signs on subsequent treatment visits will be collected prior to the first infusion [redacted]

Table 2-3: On-treatment Procedural Outline: Part 2A (Relatlimab + Nivolumab + BMS-986205) and Part 2B (Relatlimab + Nivolumab + Ipilimumab)

Procedure	Cycle 1 onwards [redacted]					End of Treatment (EOT)[a,b,c]	Notes[e,f]
	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted]		
							If any vital sign is abnormal (based upon clinician assessment) at the final check, the participants must be observed further for a period of time, as clinically indicated. [redacted]
Oxygen Saturation	X	X	X	X		X	Collected at rest via pulse oximetry. Oxygen levels will be used in combination with clinical signs and symptoms and radiographic images to evaluate pulmonary/respiratory status. Changes in O_2 levels will not be used in isolation to document or diagnose pulmonary toxicity. [redacted]
12-lead [redacted]	X	X See notes.	X See notes.	X See notes.		X	[redacted]
Chest Radiograph	See notes.						As clinically indicated.
Laboratory Tests[d]	X	X	X	X		X	On-study laboratory tests (including hematology, serum chemistry,

Table 2-3: On-treatment Procedural Outline: Part 2A (Relatlimab + Nivolumab + BMS-986205) and Part 2B (Relatlimab + Nivolumab + Ipilimumab)

Procedure	Cycle 1 onwards [redacted]					End of Treatment (EOT)[a,b,c]	Notes[e,f]
	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted]		endocrine panel, troponin, [redacted], urinalysis, and pregnancy testing) to be done on site/locally. Laboratory tests are performed locally and may be collected within 3 days prior to dose administration. See Section 9.4.4 for laboratory test requirements. [redacted]
[redacted]	See Notes						[redacted]

Table 2-3: On-treatment Procedural Outline: Part 2A (Relatlimab + Nivolumab + BMS-986205) and Part 2B (Relatlimab + Nivolumab + Ipilimumab)

Procedure	Cycle 1 onwards [redacted]					End of Treatment (EOT)[a,b,c]	Notes[e,f]
	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted]		
Clinical Observation[d]	See Notes						All participants should be evaluated for any immune-mediated adverse events. Evaluations should occur every week (± 1 day) up to and including [redacted] Participants with any clinical symptoms should immediately be evaluated. For non-dosing visits, assessments may be performed remotely by the Investigator/delegate.
Part 2A only (BMS-986205 treated) [redacted]	X	X	X	X		X	Predose, every 2 weeks for Cycle 1, then every [redacted]
Pregnancy Test (Women of Childbearing Potential [WOCBP])	X		X			X	See notes in Table 2-2: Pregnancy Testing.
Assess Adequate Contraceptive Use	X		X				For WOCBP and male participants who are sexually active with WOCBP, assess for continued use of acceptable methods of contraception (see Appendix 4).

Table 2-3: On-treatment Procedural Outline: Part 2A (Relatlimab + Nivolumab + BMS-986205) and Part 2B (Relatlimab + Nivolumab + Ipilimumab)

Procedure	Cycle 1 onwards [redacted]					End of Treatment (EOT)[a,b,c]	Notes[e,f]
	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted]		
Adverse Event Reporting and Concomitant Medication Assessments							
Concomitant Medication Assessments	X	X	X	X	X	X	Review prior to dose administration.
Monitor for Non-serious Adverse Events (AEs)	X						Non-serious AEs will be collected starting with the first dose of study drug and through [redacted] after discontinuation of study treatment. See Section 9.2: Adverse Events.
Monitor for Serious Adverse Events (SAEs)	X						All SAEs must be collected from the date of participant's written consent until [redacted] post discontinuation of treatment or participation in the study if the last scheduled visit occurs at a later time. eSAEs should be approved in the BMS Electronic Data Capture (EDC) tool within 5 business days of entry. See Section 9.2: Adverse Events.
Sample Collection							
[redacted]							

Table 2-3: On-treatment Procedural Outline: Part 2A (Relatlimab + Nivolumab + BMS-986205) and Part 2B (Relatlimab + Nivolumab + Ipilimumab)

Procedure	Cycle 1 onwards [redacted]					End of Treatment (EOT)[a,b,c]	Notes[e,f]
	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted]		
							[redacted]
Additional Research Sampling	X						Residual samples will be used for additional research (see Section 9.8.3).
[redacted]							

Table 2-3: On-treatment Procedural Outline: Part 2A (Relatlimab + Nivolumab + BMS-986205) and Part 2B (Relatlimab + Nivolumab + Ipilimumab)

Procedure	Cycle 1 onwards [redacted]					End of Treatment (EOT)[a,b,c]	Notes[e,f]
	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted]		
Efficacy Assessments							
Body Imaging					X		Contrast enhanced computed tomography (CT) of the chest, CT/magnetic resonance imaging (MRI) of the abdomen, pelvis, and all other known and/or suspected sites of disease should occur [redacted]
Brain Imaging	X						See Section 9.1; only for participants with a history of brain metastasis. Surveillance magnetic resonance imaging (MRI) approximately every [redacted] or sooner if clinically indicated.
Other Imaging: Bone Scan	X						See Section 9.1; as clinically indicated per local standards.
Response Assessment					X		Assessed by Response Evaluation Criteria in Solid Tumors v1.1 (see Appendix 11). Assessment must be performed prior to initiating the next cycle of treatment and continue on a [redacted] schedule relative to the

Table 2-3: On-treatment Procedural Outline: Part 2A (Relatlimab + Nivolumab + BMS-986205) and Part 2B (Relatlimab + Nivolumab + Ipilimumab)

Procedure	Cycle 1 onwards [redacted]					End of Treatment (EOT)[a,b,c]	Notes[e,f]
	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted]		
							participant's first dose, regardless of any treatment delay incurred.
Study Drug Administration Part 2A							Details regarding preparation and administration of study drugs are provided in the site/pharmacy training materials.
BMS-986205 Administration	Oral daily administration.						For the first administration of BMS-986205 on Day 1 of Cycle 1, BMS-986205 will be administered in the clinic. [redacted]
Nivolumab and Relatlimab Administration	X		X				[redacted]

Table 2-3: On-treatment Procedural Outline: Part 2A (Relatlimab + Nivolumab + BMS-986205) and Part 2B (Relatlimab + Nivolumab + Ipilimumab)

Procedure	Cycle 1 onwards [redacted]					End of Treatment (EOT)[a,b,c]	Notes[e,f]
	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted] (± 2 days)	[redacted]		
Pill Diary for BMS-986205	X	X	X	X	X	X	Review pill diary during each visit for compliance of daily administration of BMS-986205. Collect pill diary at the completion of each cycle and EOT. [redacted]
Study Drug Administration Part 2B							Details regarding preparation and administration of study drugs are provided in the site/pharmacy training materials.
Nivolumab and Relatlimab Administration	X		X				[redacted]
Ipilimumab Administration	X						[redacted]

Abbreviations: AE = adverse event; BP = blood pressure; C= cycle; [redacted] CT = computed tomography; D = day; [redacted]; ECOG = Eastern Cooperative Oncology Group; EDC = electronic data capture; EOT = end of treatment; eSAE = electronic serios adverse event; HCG = of human chorionic gonadotropin; HR = heart rate; PE = physical examination; MRI = magnetic resonance imaging; O2 = oxygen;

[redacted]; SAE = serious adverse event; [redacted] WOCBP = women of childbearing potential.

[a] EOT is defined as the visit when a participant discontinues study therapy.

[b] For participants who complete all scheduled cycles of therapy, [redacted]

[c] For participants who do not complete all scheduled cycles of therapy, [redacted]

[redacted]

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

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

Table 2-4: Follow-Up Procedural Outline CA224048

Procedure	Clinical Follow-up (FU)			Response Follow-up[a,c] Only for Participants with CR, PR, or SD at End of Treatment	Survival/Long-term Follow-up All Participants[c]	Notes
	FU 1 [redacted] (± 10 days)	FU 2 [redacted] (± 10 days)	FU 3 [redacted] (± 10 days)	Refer to Section 5: Study Design	Refer to Section 5: Study Design	
Safety Assessments						
Physical Examination	X	X	X			
Vital Signs, and Performance Status	X	X	X			Includes body temperature, seated blood pressure, and heart rate. Blood pressure and heart rate should be measured after the participant has been seated quietly for at least 5 minutes.
Electrocardiograms	X	X	X			See note in screening procedures.
Pregnancy Test (Women of Childbearing Potential [WOCBP])	X	X	X			See notes in Table 2-2 (Pregnancy Testing)
Assess Adequate Contraceptive Use	X	X	X			See notes in Table 2-2 (contraceptive use)
Laboratory Tests						
Laboratory Tests	X	X	X			See Section 9.4.4.

Table 2-4: Follow-Up Procedural Outline CA224048

Procedure	Clinical Follow-up (FU)			Response Follow-up[a,c] Only for Participants with CR, PR, or SD at End of Treatment	Survival/Long-term Follow-up All Participants[c]	Notes
	FU 1 [redacted] (± 10 days)	FU 2 [redacted] (± 10 days)	FU 3 [redacted] (± 10 days)	Refer to Section 5: Study Design	Refer to Section 5: Study Design	
[redacted]						
Adverse Event Reporting and Concomitant Medication Assessments						
Adverse Events (AEs) Assessment	X	X	X		X	See note in screening procedures. All serious adverse events (SAEs) and non-serious AEs should be collected continuously during the treatment period and for a minimum of [redacted] following discontinuation of study treatment. [redacted]

Table 2-4: Follow-Up Procedural Outline CA224048

Procedure	Clinical Follow-up (FU)			Response Follow-up[a,c] Only for Participants with CR, PR, or SD at End of Treatment Refer to Section 5: Study Design	Survival/Long-term Follow-up All Participants[c] Refer to Section 5: Study Design	Notes
	FU 1 [redacted] (± 10 days)	FU 2 [redacted] (± 10 days)	FU 3 [redacted] (± 10 days)			
Concomitant Medication Assessments	X	X	X			
Sample Collection						
[redacted]						
Efficacy Assessments						
Body Imaging	X					Tumor assessments should occur [redacted] for the first year after discontinuation of study treatment/end-of-treatment visit. Subsequent tumor assessments should occur every [redacted] For further details, see Section 5.1.5.
Brain Imaging	X					See Section 9.1; only for participants with a history of brain metastasis. Surveillance magnetic resonance imaging (MRI) approximately every [redacted], or sooner if clinically indicated.

Table 2-4: Follow-Up Procedural Outline CA224048

Procedure	Clinical Follow-up (FU)			Response Follow-up[a,c] Only for Participants with CR, PR, or SD at End of Treatment	Survival/Long-term Follow-up All Participants[c]	Notes
	FU 1 [redacted] (± 10 days)	FU 2 [redacted] (± 10 days)	FU 3 [redacted] (± 10 days)	Refer to Section 5: Study Design	Refer to Section 5: Study Design	
Other Imaging: Bone Scan	X					See Section 9.1; as clinically indicated per local standards.
Assessment of Participant Survival Status					X	Participants will be assessed by either a clinic visit or telephone contact.
New Subsequent Anticancer Therapies	X	X	X		X	

Abbreviations: AE = adverse even; CR = complete response; FU = Follow-up; IgG = immunoglobulin; MRI = magnetic resonance imaging; O2 = oxygen; SAE = serious adverse event; [redacted]; SD = stable disease; WOCBP = women of childbearing potential.

[a] Only for participants with complete response (CR), partial response (PR), or stable disease (SD) at end of treatment.

[redacted]

In the event that multiple procedures are required at a single time point, electrocardiograms (ECGs) may be obtained up to 15 minutes earlier, vital signs may be obtained up to 10 minutes earlier or later, and clinical laboratory samples may be obtained up to 5 minutes earlier than the nominal time point to [redacted]

3 INTRODUCTION

CA224048 is a Phase 1/2, open-label, dose-finding and cohort-expansion study of relatlimab (BMS-986016) in combination with nivolumab and linrodostat mesylate (BMS-986205) or with nivolumab and ipilimumab in participants with advanced solid tumors. Relatlimab is a fully human lymphocyte activation gene 3 (LAG-3)-specific antibody that was isolated following immunization of transgenic mice expressing human immunoglobulin (Ig) genes. Relatlimab binds to LAG-3 expressed on T-cells with high affinity and prevents binding of this checkpoint receptor to cells bearing its ligand, major histocompatibility complex (MHC) Class II, the peptide antigen presentation molecule recognized by CD4+ T cells. Relatlimab binding inhibits the negative regulatory function of LAG-3 in vitro. By blocking the normal down-regulatory pathway, relatlimab enhances the antitumor immune response and, thus, has the potential to inhibit the growth of multiple malignancies when administered in combination with other therapeutic immuno-oncology (IO) agents.

This study will be conducted in 2 parts. Part 1, subdivided into Part 1A and Part 1B, consists of dose-finding cohorts of triple combinations of relatlimab, nivolumab, and BMS-986205, or relatlimab, nivolumab, and ipilimumab, respectively. Part 1A will and Part 1B will enroll participants with [redacted]. Part 1A and Part 1B will evaluate the safety profile, tolerability, [redacted] of relatlimab in combination with nivolumab and BMS-986205 or nivolumab and ipilimumab, respectively, in order to identify the maximum tolerated dose (MTD)/maximum administered dose (MAD) to be used in Part 2. Part 2, subdivided into Part 2A and Part 2B, contains dose-expansion cohorts of participants with [redacted]. Part 2A and Part 2B will assess the preliminary efficacy of relatlimab in combination with nivolumab and BMS-986205 or nivolumab and ipilimumab, respectively, in specific malignant disease populations.

3.1 Study Rationale

Individually targeting immune checkpoint receptors, such as programmed death-1 (PD-1), has demonstrated clinical activity across multiple tumor types; several studies to date have demonstrated activity of therapeutic compounds aimed at the PD-1 receptor and its ligand, programmed death-ligand 1 (PD-L1). This benefit is further extended by dual combination therapy of cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) and PD-1 inhibitors. Despite the demonstrated benefit of single or dual combinations of cancer immunotherapies on clinical outcome, a large proportion of patients with many tumor types do not respond or will relapse after an initial response to these agents. Substantial efforts are needed to provide therapy to patients who do not respond to currently approved single or dual combination immunotherapeutic agents, as well as to provide treatment options for relapse patients to increase their survival.

Relatlimab is a human LAG-3-specific antibody expressed as an IgG4 isotype antibody including a stabilizing hinge mutation (S228P) isolated after immunization of transgenic mice expressing human Ig genes. Relatlimab binds to LAG-3 with high affinity and inhibits the negative regulatory function of LAG-3 in vitro. Binding of relatlimab to LAG-3 prevents binding of this receptor to

cells bearing its ligand, MHC Class II, the peptide antigen presentation molecule recognized by CD4+ T cells. [redacted].

BMS-986205 is an optimized indoleamine 2,3-dioxygenase 1 (IDO1) inhibitor, characterized by once-daily (QD) dose administration and deeper inhibition of IDO1 activity, as measured by peripheral blood kynurenine suppression, than other inhibitors. [redacted]

The above data support the testing of triple combinations of relatlimab combined with nivolumab and BMS-986205 or with nivolumab and ipilimumab to simultaneously engage multiple IO targets. Triple combinations may have the potential to offer superior efficacy to single-agent anti-PD-1 regimens in the immunotherapy-naive treatment setting as well as provide meaningful efficacy to patients that have progressed during anti-PD-1 therapy. In therapy-naive patients, constitutive LAG-3 expression may limit the antitumor activity of PD-1 pathway blockade, preventing the maximum magnitude and/or durability of response that a patient might otherwise benefit from immunotherapy. Relatlimab triple combinations may increase the numbers of responders and/or deepen or increase the durability of responses. In patients previously exposed to PD-1 pathway blockade, adaptive upregulation of LAG-3 expression may lead to treatment resistance and tumor progression. Relatlimab triple combinations may help to restore T-cell activation and tumor response.

The current study aims to demonstrate safety and preliminary activity with triple combinations of relatlimab in combination with nivolumab and BMS-986205, or in combination with nivolumab and ipilimumab in [redacted] across select tumor types of [redacted]

3.1.1 Research Hypothesis

Part 1A and Part 1B: It is anticipated that relatlimab, administered in combination with nivolumab and BMS-986205 or with nivolumab and ipilimumab will demonstrate adequate safety and

tolerability, as well as a favorable benefit-risk profile, to support further clinical testing. No prospective hypotheses are being formally evaluated.

Part 2A and Part 2B: Treatment with relatlimab in combination with nivolumab and BMS-986205 or with nivolumab and ipilimumab will lead to clinical benefit, as demonstrated by a clinically meaningful overall response rate (ORR), including durable responses with substantial magnitude of tumor burden reduction in participants who are immunotherapy treatment-naive (IO naive), or progressed on IO therapies (including but not limited to PD-1/PD-L1 inhibitors, CTLA-4 inhibitors, or combinations) in select metastatic solid tumors.

3.2 Background

Cancer immunotherapy rests on the premise that tumors can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. An effective immune response in this setting is thought to rely on immune surveillance of tumor antigens expressed on cancer cells that ultimately results in an adaptive immune response and cancer cell death. Meanwhile, tumor progression may depend upon acquisition of traits that allow cancer cells to evade immuno-surveillance and escape effective innate and adaptive immune responses.[2,3,4] Current immunotherapy efforts attempt to break the apparent tolerance of the immune system to tumor cells and antigens by either introducing cancer antigens by therapeutic vaccination or by modulating regulatory checkpoints of the immune system. T-cell stimulation is a complex process involving the integration of numerous positive as well as negative co-stimulatory signals in addition to antigen recognition by the T-cell receptor.[5] Collectively, these signals govern the balance between T-cell activation and tolerance.

Information for nivolumab (OPDIVO, BMS-936558, anti-PD-1 antibody), relatlimab (BMS-986016, anti-LAG-3 antibody), BMS-986205 (optimized IDO1 inhibitor), and ipilimumab (Yervoy, BMS-734016, anti-CTLA-4 antibody) is provided in the sections below; additional details are provided in the respective Investigator Brochures (IBs)/package inserts.[6,7,8,9]

3.2.1 Relatlimab Mechanism of Action

Relatlimab is a fully human antibody specific for human LAG-3 that was isolated from immunized transgenic mice expressing human Ig genes. It is expressed as an IgG4 isotype antibody that includes a stabilizing hinge mutation (S228P) for attenuated Fc receptor binding in order to reduce or eliminate the possibility of antibody- or complement-mediated target cell killing. Relatlimab binds to a defined epitope on LAG-3 with high affinity [redacted] and specificity and potently blocks the interaction of LAG-3 with its ligand, MHC Class II [redacted] The antibody exhibits potent in vitro functional activity in reversing LAG-3-mediated inhibition of an antigen-specific murine T-cell hybridoma overexpressing human LAG-3 [redacted]

Also refer to Section 4.1 (nonclinical pharmacology studies with relatlimab) and Section 4.2 (nonclinical pharmacokinetics with relatlimab) of the relatlimab IB.[7]

3.2.2 Nivolumab Mechanism of Action

Nivolumab is a fully human, IgG4 (kappa) isotype, monoclonal antibody that binds PD-1. Blockade of the PD-1 pathway by nivolumab was studied using the mixed lymphocyte reaction (MLR) method. PD-1 blockade resulted in a reproducible enhancement of both proliferation and IFN-γ release in the MLR.[10] The effect of nivolumab on antigen-specific recall response was investigated using a cytomegalovirus (CMV) restimulation assay with human peripheral blood mononuclear cells (PBMCs), and was evaluated by enzyme-linked immunosorbent assay (ELISA).

In vitro, nivolumab (BMS-936558) binds to PD-1 with high affinity (half-maximal effective concentration [EC50], 0.39 to 2.62 nM), and inhibits the binding of PD-1 to its ligands PD-L1 and programmed death-ligand 2 (PD-L2; IC50, ± 1 nM). Nivolumab binds specifically to PD-1 and not to related members of the CD28 family, such as CD28, ICOS, CTLA-4, and BTLA. Blockade of the PD-1 pathway by nivolumab results in a reproducible enhancement of both proliferation and IFN-γ release in the MLR. Using a CMV restimulation assay with human PBMCs, the effect of nivolumab on antigen-specific recall response indicates that nivolumab augments IFN-γ secretion from CMV-specific memory T cells in a dose-dependent manner vs isotype-matched controls. In vivo blockade of PD-1 by a murine analog of nivolumab enhances the antitumor immune response and results in tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/N, and PAN02).[11]

3.2.3 BMS-986205 Mechanism of Action

BMS-986205 is a small molecule inhibitor of IDO1 with [redacted]

The enzyme IDO1 catalyzes the degradation of tryptophan along the kynurenine pathway, and is frequently expressed in human malignancies. In healthy humans, high IDO1 expression is found in the placenta, the mucosa of the female genital tract, the lungs, and the lymphoid organs.[12] The activity of IDO1 induces an immunosuppressive microenvironment in tissues by inhibiting T-cell function through local depletion of the essential amino acid tryptophan and through generation of active kynurenine pathway metabolites.[13] High IDO1 expression in cancers is correlated with more aggressive tumor progression and shorter patient survival time in most cancer types.[14] Tumor IDO1 transcript is elevated in patients with metastatic melanoma and RCC after treatment with the anti-PD-1 antibody nivolumab.[15,16] In the mouse tumor model, IDO1 is a critical resistance mechanism in antitumor T-cell immunotherapy targeting CTLA-4 with a neutralizing antibody.[17] Another IDO1 inhibitor in Phase 2 and Phase 3 clinical studies (epacadostat, Incyte corporation) has been shown to have a favorable safety profile as monotherapy (ie, well tolerated across all dose levels),[18] suggesting no intrinsic risk of severe toxicity with IDO1 blockade. These observations suggest that IDO1 is a mechanism that contributes to tumor escape from host immune surveillance. Therefore, inhibition of IDO1 using pharmaceutical agents may diminish the immunosuppressive tumor microenvironment and achieve more durable responses and greater patient survival benefits, particularly when used in combination with other cancer immunotherapy agents, such as nivolumab and ipilimumab.

3.2.4 Ipilimumab Mechanism of Action

Ipilimumab is a fully human IgG1 (kappa) monoclonal antibody that has specificity and a high affinity for human CTLA-4. The calculated dissociation constant value from an average of several studies was 5.25 nM. Binding of ipilimumab to purified, recombinant human CTLA-4 antigen was also demonstrated by ELISA with half-maximal binding at 15 ng/mL, whereas saturation was observed at approximately 0.1 μg/mL. No cross-reactivity was observed against human CD28. Ipilimumab completely blocked binding of B7.1 and B7.2 to human CTLA-4 at concentrations higher than 6 and 1 μg/mL, respectively.

3.2.5 Nivolumab Combined with Ipilimumab Clinical Activity

Multiple clinical studies have evaluated nivolumab combined with ipilimumab at different doses and schedules.

Nivolumab 1 mg/kg, in combination with ipilimumab 3 mg/kg for 4 three-week cycles, followed by nivolumab 3 mg/kg maintenance every 2 weeks (Q2W) is indicated for the treatment of patients with unresectable or metastatic melanoma (BRAF-mutant and BRAF wild-type) based on CA209067 (CheckMate 067) in previously untreated participants with advanced melanoma. In the United States (US), accelerated approval was granted based on a progression-free survival (PFS) advantage compared to either control group. An update of the study had demonstrated 3-year overall survival (OS) advantage compared to ipilimumab alone with median survival not yet reached in the combination group.[19]

Subsequent studies have suggested that enhanced anticancer effects may be achieved with the combination of nivolumab (N) and ipilimumab (I) compared to either agent alone in historic or parallel datasets in other cancers, and that administration of N 3 mg/kg (N3) with I 1 mg/kg (I1) is better tolerated than N 1 mg/kg (N1) with I 3 mg/kg (I3) without obvious difference in anticancer activity.

In CA209032 (CheckMate 032), a Phase 1/2, open-label study of nivolumab monotherapy or nivolumab combined with ipilimumab in participants with advanced or metastatic solid tumors, the safety and anticancer efficacy of N3 Q2W, N+I at N1I1, N1I3, and I3N1 every 3 weeks (Q3W) ×4 followed by N3 Q2W were evaluated in 216 participants with small-cell lung cancer who had received at least 1 prior platinum-containing regimen. Responses were achieved in 10 (10%) of 98 participants treated with N3, 1 (33%) of 3 treated with N1I1, 14 (23%) of 61 who received N1I3, and 10 (19%) of 54 who received N3I1. Grade 3 or 4 treatment-related adverse events (AEs) occurred in 13 (13%) participants in N3 group, 18 (30%) in the N1I3 cohort, and 10 (19%) in the N3I1 cohort; none of the 3 participants treated with N1I1 experienced treatment-related Grade 3 or higher AEs.[20]

CA209016 (CheckMate 016) was a Phase 1 study of nivolumab plus sunitinib, pazopanib, or ipilimumab in participants with metastatic RCC. Three different N+I regimens were assessed: N3I3, N1I3, and N3I1 Q3W for 4 cycles followed by N3 Q2W. The N3I3 group was closed due to poor tolerance. The N3I1 and N1I3 groups accrued 47 participants each, and Grade 3 to 4 treatment-related AEs were reported in 38.3% and 61.7% of the patients in the N3I1 and N1I3

groups, respectively. At a median follow-up of 22.3 months, the confirmed ORR was 40.4% in both groups, with ongoing responses in 42.1% and 36.8% of patients in the N3I1 and N1I3 arms, respectively. The 2-year OS was 67.3% and 69.6% in the N3I1 and N1I3 groups, respectively.[21]

Based on the CA209016 (CheckMate 016) study, a randomized study (CA209214; CheckMate 214) of nivolumab combined with ipilimumab (N3I1 Q3W ×4 followed by N3 Q2W) vs sunitinib monotherapy was conducted in participants with previously untreated advanced, or metastatic RCC. After a minimum follow-up of 17.5 months, improved ORRs (41.6% vs 26.5%, $p < 0.0001$) and median PFS (11.6 vs 8.4 months, $p = 0.0331$) were seen in intermediate and high-risk RCC participants treated with nivolumab and ipilimumab (n = 425) compared to sunitinib (n = 422), respectively. Drug-related AEs in the entire study population (including low-risk RCC participants) were observed in 509 of 547 participants (93% any Grade, 46% Grade 3 to 4) with nivolumab + ipilimumab vs 521 of 535 (97% any Grade, 63% Grade 3 to 5) with sunitinib. Death occurred in 159 N+I participants (7 [1%] drug-related) and 202 sunitinib participants (4 [1%] drug-related).[22]

CA209012 (CheckMate 012) was a Phase 1, multiple-cohort study of nivolumab as monotherapy, in combination with ipilimumab, or in combination with chemotherapy or targeted therapy, in chemotherapy-naive adult (≥ 18 years) participants with Stage IIIB/IV NSCLC or recurrent disease that assessed the safety, tolerability, ORR, and progression-free survival (PFS) rate at 24 weeks based on Independent Radiologic Review Committee assessment. Cohort P included 38 participants who received nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg every 12 weeks (Q12W), while Cohort Q included 39 participants who received nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg every 6 weeks (Q6W). Confirmed objective responses were achieved in 18 (47% [95% CI: 31, 64]) participants in the ipilimumab Q12W cohort and 15 (38% [95% CI: 23, 55]) participants in the ipilimumab Q6W cohort. Median duration of response was not reached in either cohort, with median follow-up times of 12.8 months (interquartile range [IQR]: 9.3, 15.5) in the ipilimumab Q12W cohort and 11.8 months (IQR: 6.7, 15.9) in the ipilimumab Q6W cohort. The safety profiles in Cohorts P and Q were similar; no new types of AEs were observed, and AEs were manageable with established algorithms. There were no deaths due to study drug toxicity. The rate of treatment-related AEs in the Q12W (82%) and Q6W (72%) groups were comparable to monotherapy (69%). In the study, the frequency of Grade 3 to 4 treatment-related AEs was 37%, 33%, and 19% for the Q12W, Q6W, and nivolumab monotherapy groups, respectively. Treatment-related serious adverse events (SAEs) occurred in 32% and 28% of participants in the Q12W and Q6W cohorts, respectively, compared to 19% with nivolumab monotherapy.[23,24]

Randomized data on the use of nivolumab in combination with ipilimumab in advanced non-small cell lung cancer (NSCLC) as first-line therapy is available from one Phase 3 study, CheckMate 227 (NCT02477826), an open-label, randomized Phase 3 trial evaluating the use of the following regimens versus histology-based chemotherapy (chemo) in biomarker-selected populations with chemotherapy-naïve Stage IV or recurrent NSCLC: nivolumab 3 mg/kg every 2 weeks (Q2W) + ipilimumab 1 mg/kg every 6 weeks (Q6W; nivolumab [NIVO] + ipilimumab [IPI]); nivolumab

360 mg every 3 weeks (Q3W) plus platinum doublet chemotherapy (NIVO + chemo; in participants with tumor PD-L1 < 1%); and nivolumab 3 mg/kg Q2W (NIVO; in participants with tumor PD-L1 expression ≥ 1%).[25] The study showed that NIVO + IPI provided clinically meaningful and durable improvement in efficacy (OS, PFS, ORR, duration of response [DoR]) compared with chemotherapy for participants with first-line (1L) advanced NSCLC, in PD-L1 ≥ 1% and < 1% (exploratory) populations and regardless of histology. The reported 3-year OS rates were 33% vs 22% in the PD-L1 ≥ 1% cohort; and 34% vs 15% PD-L1 < 1% cohort.[26] With 3 years' minimum follow-up, the safety of NIVO + IPI was consistent with previous reports; there were no new safety signals were identified with the extended follow-up as participants were off treatment for at least 12 months.

Based on Phase 3 data showing improved survival over standard of care therapies, nivolumab combined with ipilimumab has been approved in multiple countries for the treatment of participants with unresectable or metastatic melanoma, intermediate or poor risk, previously untreated advanced RCC, and microsatellite instability-high or mismatch repair deficient colorectal cancer (CRC). Details of the clinical activity in these various malignancies are provided in the United States Prescribing Information and Summary of Product Characteristics.

3.2.6 Relatlimab Combined with Nivolumab Clinical Activity

[redacted]

More recently, CA224047, a global, double-blind, randomized, Phase 2/3 study comparing relatlimab plus nivolumab in a fixed-dose combination (FDC) formulation (relatlimab [RELA] 160 mg + nivolumab 480 mg Q4W [RELA + NIVO FDC]) to nivolumab 480 mg Q4W in participants with previously untreated advanced melanoma, demonstrated a statistically significant and clinically meaningful benefit by dual inhibition of the LAG-3 and PD-1 pathways. The study achieved its primary endpoint, demonstrating statistically significant improvement in PFS by blinded independent clinical review (BICR) with RELA + NIVO FDC compared to nivolumab monotherapy in all randomized subjects (N = 714) (PFS hazard ratio = 0.75 [95% CI: 0.62, 0.92], P-value = 0.0055). With a median follow-up of 13.2 months, the median PFS in the RELA + NIVO FDC group was 10.1 months (95% CI, 6.4–15.7) compared to 4.6 months (95% CI, 3.4–5.6) in the nivolumab monotherapy arm. PFS rates at 12 months were 47.7% (95% CI, 41.8-53.2) and 36.0% (95% CI, 30.5–41.6) for RELA + NIVO FDC and NIVO, respectively. The PFS benefit of RELA + NIVO FDC were consistent across key prespecified subgroups. Follow up for the secondary endpoints of OS and ORR is ongoing.[28]

3.2.7 Nivolumab Combined with BMS-986205 Clinical Activity

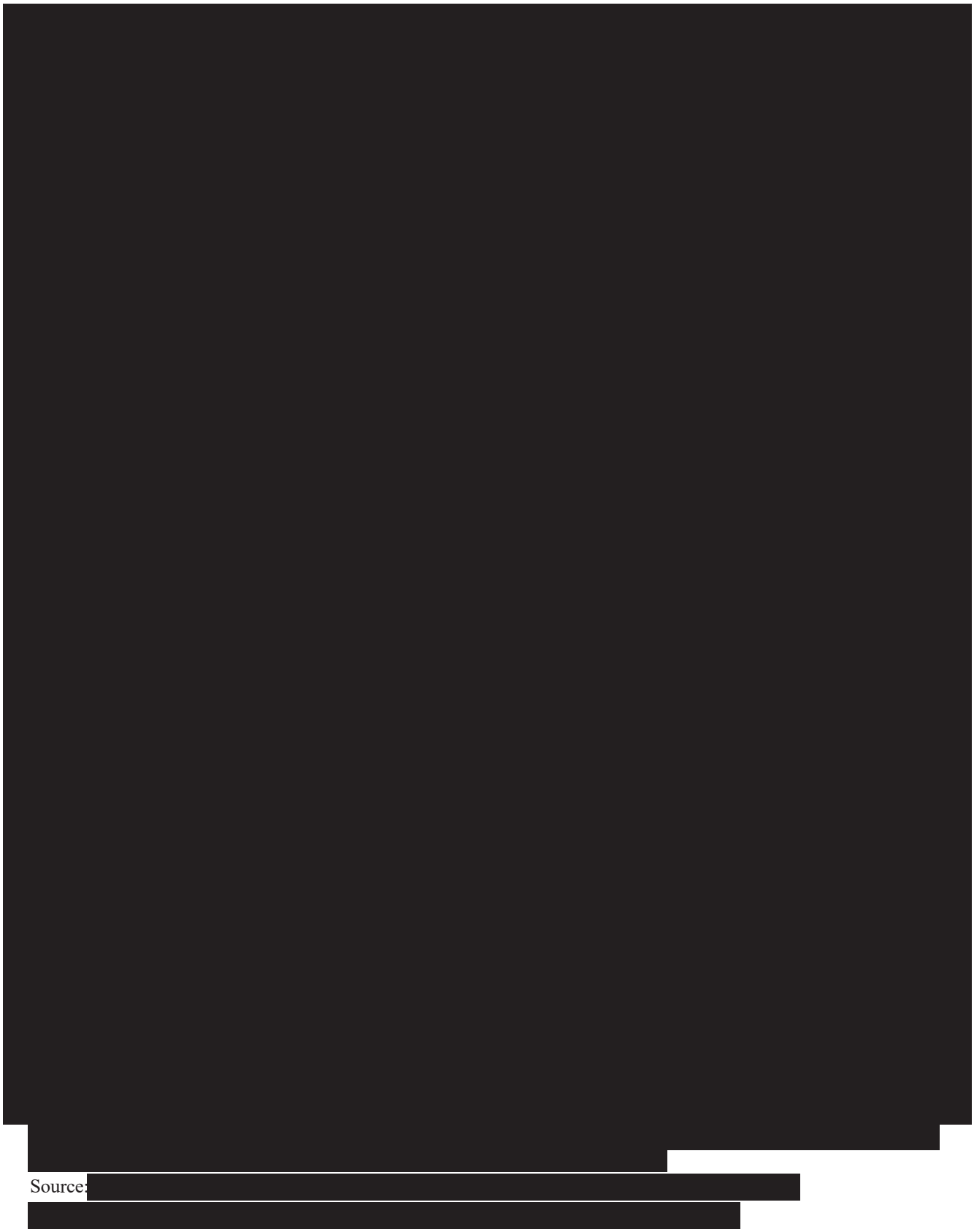
[redacted]

[redacted] The preliminary activity seen with BMS-986205 combined with nivolumab indicates that BMS-986205 itself has potential benefit when combined with nivolumab and potentially with other IO agents, and further efficacy evaluation is appropriate.

3.2.8 Relatlimab Combined with Nivolumab Clinical Safety

[redacted] Refer to the IB Table 5.5.1-1 for details of the dose levels and DLTs for participants treated in the Part B (combination therapy escalation).[7] [redacted]

[redacted]



Source:

More information can be found in the relatlimab IB.[7]

The safety profile of the combination of RELA + NIVO FDC (N = 355) was confirmed in the pivotal Phase 2/3 global, multicenter study, CA224047, in previously untreated advanced melanoma participants. The study findings demonstrated a well-tolerated regimen with a manageable safety profile and without unexpected safety signals. The incidence of Grade 3-4 drug-related AEs was 18.9% in the RELA + NIVO FDC group versus 9.7% in the nivolumab monotherapy group. There were 3 treatment-related deaths with RELA + NIVO FDC and 2 with nivolumab-treated participants. Drug-related AEs (any grade) led to treatment discontinuation in 14.6% and 6.7% of participants in the RELA + NIVO FDC and nivolumab monotherapy groups, respectively.[28]

3.3 Benefit/Risk Assessment

All agents to be used in the triple combinations in this study have shown well-defined toxicity profiles based on a safety database comprised of participants treated with either monotherapy or double combinations across multiple tumor types.

Extensive details on the safety profile of nivolumab are available in the Investigator Brochure and will not be repeated herein.

Overall, the safety profile of nivolumab monotherapy as well as in combination with ipilimumab is manageable and generally consistent across completed and ongoing clinical trials with no MTD reached [redacted] There was no pattern in the incidence, severity, or causality of AEs with respect to nivolumab dose level.

As described in Section 3.2.6, clinical activity was seen in multiple indications in the CA224020 study with the combination of RELA + NIVO.[7] Preliminary clinical efficacy has been demonstrated in CA224020, where combination dosing of [redacted]

[redacted] The clinical efficacy of the combination was further confirmed in the CA224047 study, a global, double-blind Phase 2/3 randomized controlled trial, which demonstrated a statistically significant and clinically relevant PFS benefit of RELA + NIVO FDC Q4W compared to nivolumab 480 mg Q4W.[28]

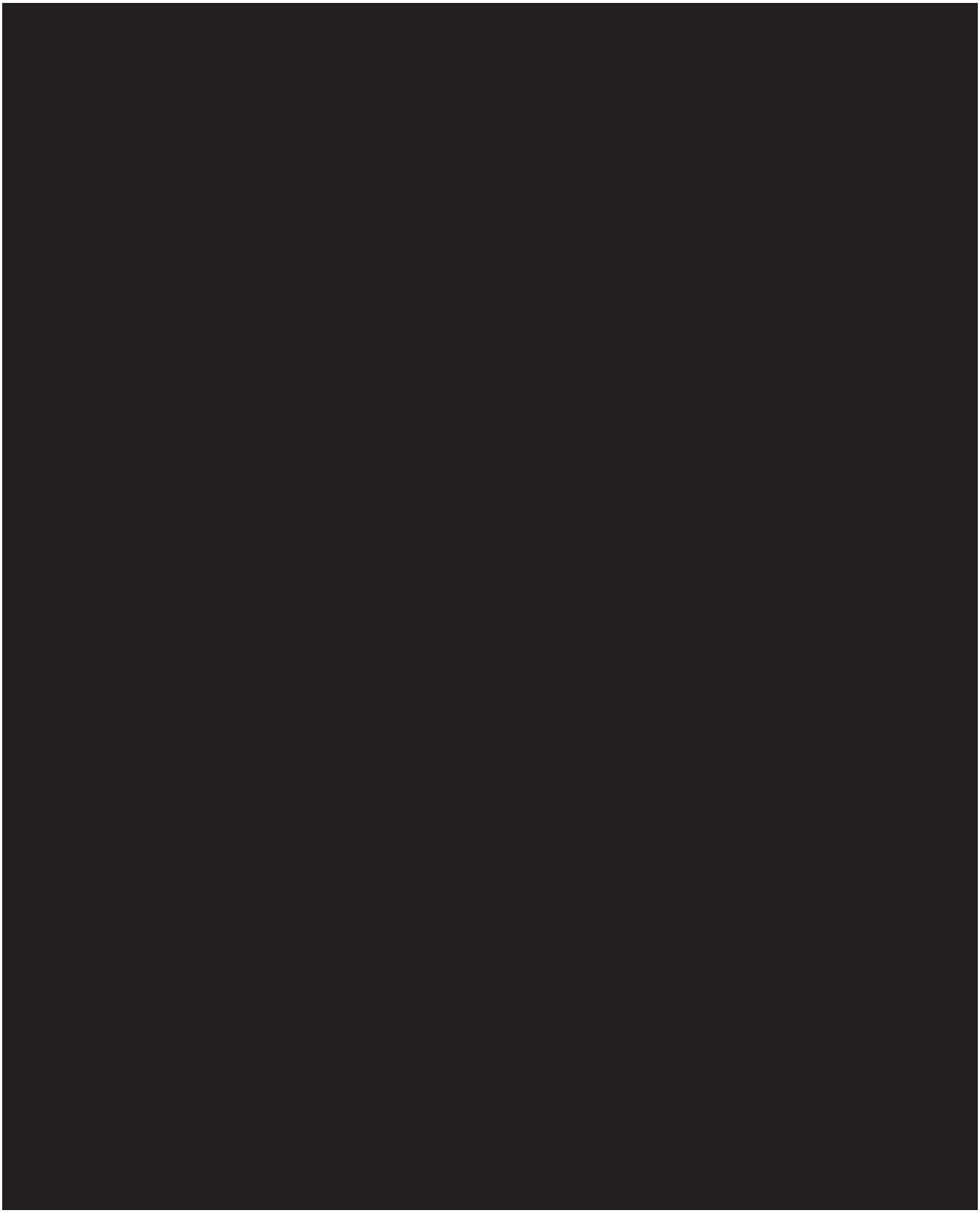
Both relatlimab and nivolumab have shown well-defined toxicity profiles based on a safety database comprised of participants treated with either monotherapy or combination therapies across multiple tumor types. [redacted] Safety evaluation of the combination dose is ongoing. The safety of relatlimab in combination with nivolumab and either ipilimumab or IDO-1 inhibitor (BMS-986205) is manageable and evaluation remains ongoing.[7]

[redacted]

Furthermore, the RELA + NIVO FDC (relatlimab doses of 160 mg + nivolumab 480 mg in a fixed-dose combination, administered Q4W) was confirmed to be well tolerated with a manageable safety profile in 355 participants treated in the CA224047 study. There were no unexpected safety signals from this combination.[28]

Given the safety profile of relatlimab as monotherapy and combination therapy observed to-date and the positive benefit-risk of the pivotal Phase 2/3 study of RELA + NIVO FDC (CA224047) demonstrated in participants with previously untreated metastatic or unresectable advanced melanoma[28] and the significant unmet medical need in the studied populations, the continuing

evaluation of the combination of relatlimab plus nivolumab is justified for the patient population in this protocol.



The triple combination of relatlimab, nivolumab, and BMS-986205 has not been previously evaluated; however, based on well-tolerated safety profiles of respective double combinations, this triple combination is expected to be safe and pharmacodynamically active.

Nivolumab and ipilimumab combinations have a well-defined toxicity profile based on a safety database of patients treated with the combination across multiple tumor types. Multiple dose administration regimens have been evaluated.

[redacted]

Investigators and the Sponsor will utilize continuous safety assessments to determine whether additional safety measures or termination from the study is required at any time. In addition, AEs and SAEs will be reviewed on an ongoing basis by the Sponsor's Medical Monitor, Clinical Scientist and Worldwide Patient Safety (WWPS) representatives to monitor for any safety signals or trends. As relatlimab and BMS-986205 are experimental agents and administered in new combinations in this protocol, it is possible that unforeseen, unknown, or unanticipated reactions may occur; however, data shows that the combination of relatlimab plus nivolumab and BMS-986205 plus nivolumab are safe and tolerable at the doses evaluated in this study and at higher doses in other studies.

A pattern of immune-related AEs has been defined, for which management algorithms have been developed; these are provided in Appendix 5. [redacted]

Additional details on the safety profiles of relatlimab, nivolumab, BMS-986205, and ipilimumab, including results from other clinical studies, are also available in IBs.

For dose-finding in Part 1A and Part 1B, the study will utilize a [redacted] that will allow evaluation of safety events. This period will be sufficient to cover unanticipated acute toxicities associated with all 3 drugs in combination; however, to offset the limited period, safety events after subsequent doses will be evaluated very closely throughout the study, focusing on close monitoring of drug component specific toxicities. At any time, if the triple combination is not considered safe for long-term evaluation, the lower dose will be studied and proposed for expansion cohorts. In addition, the study will monitor immune-mediated adverse events (IMAEs) and drug-specific toxicities [redacted]

Individually targeting immune checkpoint receptors such as PD-1 and CTLA-4 has proven clinical efficacy and is indicated across multiple tumor types. This benefit is further extended by dual combination therapy of CTLA-4 and PD-1 inhibitors. Despite the demonstrated benefit of single or dual combinations of cancer immunotherapies on clinical outcome, a large proportion of patients with many tumor types do not respond or will relapse after an initial response to these agents. Substantial efforts are needed to provide therapy to patients who do not respond to currently approved single or dual combination immunotherapeutic agents, as well as to provide treatment options for relapse patients to increase the survival.

Triple combinations of relatlimab combined with nivolumab and BMS-986205 or with nivolumab and ipilimumab to simultaneously engage distinct IO targets may have potential to offer superior efficacy to anti-PD-1 monotherapy and in combination with anti-CTLA-4 in the immunotherapy-naive treatment setting, as well as provide meaningful efficacy to patients that have progressed during anti-PD-1 therapy. In therapy-naive patients, constitutive LAG-3 expression may limit the antitumor activity of PD-1 pathway blockade, preventing the maximum

magnitude and/or durability of response that a patient might otherwise benefit from immunotherapy. Relatlimab triple combinations may increase the numbers of responders and/or deepen or increase the durability of responses. In patients previously exposed to PD-1 pathway blockade, adaptive upregulation of LAG-3 expression may lead to treatment resistance and tumor progression.

4 OBJECTIVES AND ENDPOINTS

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

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Primary	
• Part 1A and Part 1B: To determine the safety, tolerability, DLTs, and MTD of relatlimab administered in combination with nivolumab and BMS-986205 or nivolumab and ipilimumab in participants with advanced malignant tumors.	• Incidence of clinical laboratory test abnormalities, AEs, SAEs, AEs meeting protocol-defined DLT criteria, AEs leading to discontinuation, and deaths.
• Part 2A and Part 2B: To investigate safety and tolerability of relatlimab triple combinations in distinct cohorts of participants with advanced malignant tumors.	• Incidence of clinical laboratory test abnormalities, AEs, SAEs, AEs leading to discontinuation, and deaths.
• To investigate the antitumor activity of relatlimab triple combinations in participants with advanced malignant tumors.	• ORR, DCR, and mDOR in participants with advanced malignant tumors.
Secondary	
• To investigate the antitumor activity of relatlimab triple combinations in participants with advanced malignant tumors.	• mPFS and PFSR at 6 and 12 months in participants with advanced malignant tumors.
Exploratory	
[redacted]	

Abbreviations: AE = adverse event; DCR = disease control rate; DLT = dose-limiting toxicity; IgG = immunoglobulin G; [redacted]; mDOR = median duration of response; [redacted] mPFS = median progression-free survival; MTD = maximum tolerated dose; ORR = overall response rate; [redacted]; PFSR = progression-free survival rate; [redacted]; SAE = serious adverse event; [redacted]

5 STUDY DESIGN

5.1 Overall Design

This is a Phase 1/2, open-label study of relatlimab in combination with nivolumab and BMS-986205 or in combination with nivolumab and ipilimumab in participants with advanced solid tumors. Participants will complete up to 5 periods of the study: [redacted]

Relatlimab, nivolumab, and ipilimumab will be administered intravenously in the clinical facility per the treatment schedule. BMS-986205 will be administered orally at home except for Day 1 of Cycle 1, where it will be administered in the clinic. For further details of dose administration, see Section 7.1.1.

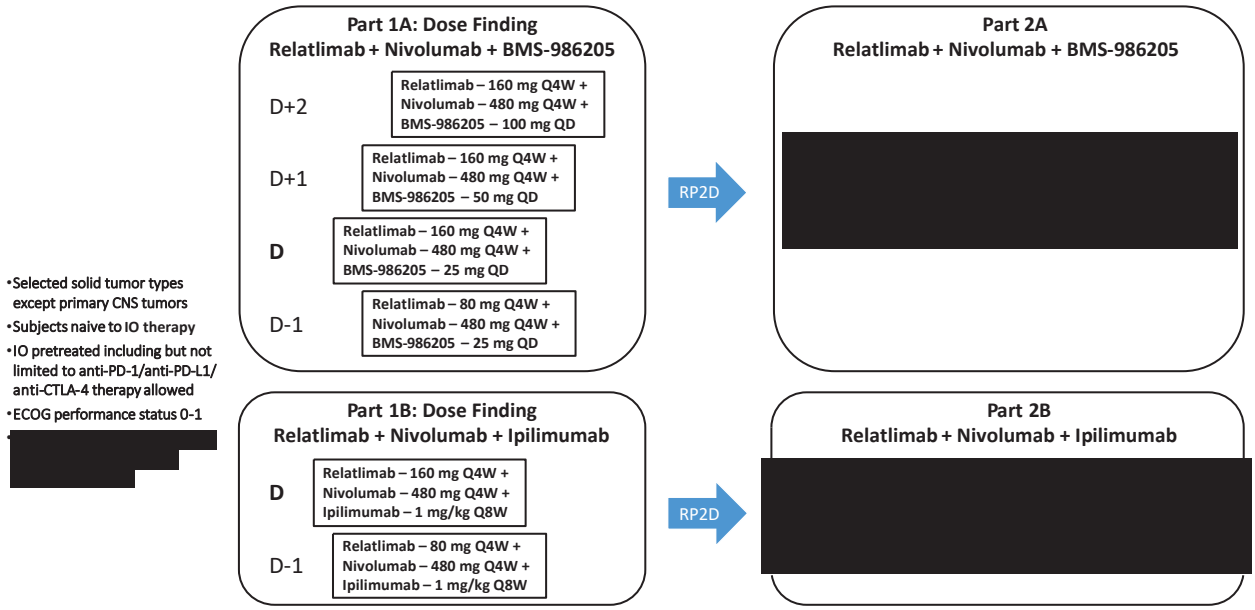
After establishment of a tolerable and safe dose administration regimen in both Part 1A and Part 1B, Part 2A and Part 2B expansion cohorts will be initiated. The purpose of the cohort expansions is to gather preliminary efficacy information in specific patient populations regarding relatlimab in combination with nivolumab and BMS-986205, or in combination with nivolumab and ipilimumab. Expansion cohorts will only open after data is evaluated from Part 1A and Part 1B to guide doses selected for Part 2A and Part 2B, respectively. Part 2A and Part 2B may be initiated independently from each other based on the timing of data evaluation in Part 1.

Part 1A and Part 1B consist of dose-finding cohorts of 2 triplet combinations: relatlimab, nivolumab, and BMS-986205, or relatlimab, nivolumab, and ipilimumab. [redacted]. If the starting dose is not tolerable in the [redacted] DLT evaluation phase, the dose will be de-escalated to D-1 upon safety review from initial dose level D. In Part 1A, if the starting dose is tolerable in the [redacted] DLT evaluation phase, participants will be treated at the next dose levels. Part 1A and Part 1B will be initiated in parallel. The evaluation of combination doses of relatlimab with nivolumab and BMS-986205 (Part 1A) and relatlimab with nivolumab and ipilimumab (Part 1B) will be performed based on safety and tolerability.

Part 2A and Part 2B consist of tumor-specific expansion cohorts of respective triple combinations. The dose selected for Part 2A and Part 2B will not exceed the MAD in Part 1; however, dose selection will be determined based on assessment of other data including toxicities, [redacted] The goal of Part 2 is to estimate the antitumor activity of relatlimab in combination with nivolumab and BMS-986205 or relatlimab in combination with nivolumab and ipilimumab.

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

Figure 5.1-1: Study Design Schematic



Abbreviations: CNS = central nervous system; CTLA-4 = cytotoxic T lymphocyte antigen-4; D = starting dose level; ECOG =-Eastern Cooperative Oncology Group; [redacted] IO = immuno-oncology; [redacted] PD-1 = programmed death-1; PD-L1 = programmed death-ligand 1; Q4W = every 4 weeks; Q8W = every 8 weeks; QD = once daily; [redacted]

5.1.1 Screening Period

The screening period will be up to 28 days and begins by establishing the participant's initial eligibility and signing of the informed consent form (ICF). Informed consent will be obtained prior to any study-specific procedures. Participants will be evaluated based on the assessments as outlined in Table 2-1 and the Inclusion and Exclusion criteria (see Section 6). If a participant exceeds the 28-day screening period due to a study-related procedure [redacted], the participant must be reconsented but will not require a new participant identification (PID) number. In this situation, the fewest number of procedures from the initial screening should be repeated to qualify the participant, while maintaining participant safety and eligibility.

[redacted]

[redacted]

[redacted]

5.1.2 Treatment Period

Dose Finding Part 1A (Relatlimab, Nivolumab, and BMS-986205)

The DLT evaluation period is [redacted] in participants with melanoma, NSCLC, SCCHN, RCC, and GC/GEJ. BMS986205 will be administered orally QD prior to relatlimab and nivolumab infusions. Relatlimab will be co-administered with nivolumab in the clinic as an intravenous (IV) infusion Q4W. [redacted]

Part 1A starting dose will be:

D = Relatlimab 160 mg Q4W + Nivolumab 480 mg Q4W + BMS-986205 25 mg QD.

If during the dose-finding phase, it appears the dose is associated with an acceptable frequency of toxicities, then the BMS-986205 dose will be increased as follows:

D+1 = Relatlimab 160 mg Q4W + Nivolumab 480 mg Q4W + BMS-986205 50 mg QD.

D+2 = Relatlimab 160 mg Q4W + Nivolumab 480 mg Q4W + BMS-986205 100 mg QD.

If during the dose-finding phase, it appears the starting dose is associated with an unacceptable frequency of toxicities, then the relatlimab dose will be decreased as follows:

D-1 = Relatlimab 80 mg Q4W + Nivolumab 480 mg Q4W + BMS-986205 25 mg QD.

Dose Finding Part 1B (Relatlimab, Nivolumab, and Ipilimumab)

The DLT evaluation period is [redacted] in participants with melanoma, NSCLC, SCCHN, RCC, and GC/GEJ. Relatlimab will be coadministered with nivolumab in the clinic as an IV infusion Q4W. [redacted]

Part 1B starting dose will be:

D = Relatlimab 160 mg Q4W + Nivolumab 480 mg Q4W + Ipilimumab 1 mg/kg Q8W.

If during the dose-finding phase, it appears the dose is associated with an unacceptable frequency of toxicities, then the relatlimab dose will be decreased as follows:

D-1 = Relatlimab 80 mg Q4W + Nivolumab 480 mg Q4W + Ipilimumab 1 mg/kg Q8W.

Expansion: Part 2A (Relatlimab, Nivolumab, and BMS-986205) and Part 2B (Relatlimab, Nivolumab, and Ipilimumab)

Part 2 is the safety evaluation, tolerability, and cohort expansion of the triple combinations in distinct cohorts of advanced malignant tumors to gather preliminary efficacy information. The doses to be administered will be determined from Part 1A and Part 1B of the study. The recommended Phase 2 dose (RP2D) selected for Part 2 are as follows:

Part 2A: Relatlimab 160 mg Q4W, Nivolumab 480 mg Q4W, BMS-986205 100 mg QD.

Part 2B: Relatlimab 160 mg Q4W, Nivolumab 480 mg Q4W, Ipilimumab 1 mg/kg Q8W.

The tumor cohorts and regimens are:

[redacted]

The dose-finding phase of the study (Part 1A and Part 1B) will evaluate the safety and tolerability of relatlimab in combination with nivolumab and BMS-986205 (Part 1A), or nivolumab and ipilimumab (Part 1B), based on DLTs, using [redacted] Any toxicities that occur beyond the DLT period will be accounted for in making dose level decisions and/or dose level modifications. See Section 7.4.6 for additional information on DLTs.

After the initial participants (approximately 3) are evaluated at the starting dose levels in Part 1A and Part 1B, additional increments of approximately 3 to 6 participants will be treated in the same cohort (or at the next dose level) [redacted] At least [redacted] DLT-evaluable participants will be treated and assessed in the selected combination dose level before starting the cohort-expansion phase at the same dose. In Part 1A, approximately [redacted] are expected to be treated.

Planned dose levels may be modified, or additional dose levels added, based upon the [redacted] for combination and clinical evaluation of all available safety and [redacted] data. Once the tolerability (during DLT evaluation) of a dose level has been established, additional participants may be added at that dose level to better characterize the safety, [redacted]

Prior to declaring the MTD, and in consultation with Investigators, the Sponsor has the option to expand any dose level previously established to be tolerable, in order to obtain additional experience or to investigate dose levels intermediate to those defined in the protocol.

As previously mentioned, [redacted] are being explored in the dose-expansion phase, Part 2A and Part 2B. Sample size details for Part 2A and Part 2B are provided in Section 10.1.2.

Physical examinations, vital sign measurements, 12-lead ECGs, and clinical laboratory evaluations will be performed at selected times throughout the dose administration interval. Participants will be closely monitored for AEs throughout the study. Samples will be collected after study drug administration for [redacted]. [redacted]

Continuous safety evaluation and tumor assessment [redacted] will guide the decision to treat a participant with additional cycles of study therapy if the participant has confirmed clinical benefit.

Tumor assessments should continue until disease progression or treatment discontinuation, whichever occurs later, participant withdrawal of consent, start of subsequent treatment, or death, or until completion of the Follow-up periods (see below).

Participants with unconfirmed progressive disease, SD, or PR at the end of a given cycle will continue to the next treatment cycle.

[redacted]

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

[redacted]

[redacted]

5.1.4 Clinical Safety Follow-up Period

Upon completion of study therapy or once the decision is made to discontinue the participant from treatment, that is, at end of treatment (EOT), all participants will enter a Safety Follow-up period.

For participants who complete all scheduled cycles of therapy, the [redacted] Accordingly, for these participants, this visit will be considered the start of the Safety Follow-up period.

After the EOT visit, all participants will be evaluated for any new AEs for [redacted] after the last dose of study treatment. Follow-up visits should occur at [redacted] after the last dose or at the date of discontinuation (± 10 days; see Figure 5.1.6-1). All participants should complete the [redacted] Clinical Safety Follow-up visits regardless of whether new anticancer therapy is started, except those participants who withdraw consent for study participation.

5.1.5 Response Follow-up Period

Participants with SD, PR, or CR at the time of the EOT visit or at the time of study treatment discontinuation will continue to have radiologic and clinical tumor assessments [redacted]

5.1.6 Survival Follow-up Period

In parallel with the Clinical Safety and Response Follow-up periods (as applicable), Part B participants will start the Survival Follow-up period. Participants will be followed until death, loss to Follow-up, withdrawal of consent, or conclusion of the study, whichever comes first (see Figure 5.1.6-1). [redacted]

[redacted]

[redacted]

Abbreviations: C = cycle; D = day; DLT = dose-limiting toxicity; EOT = end of treatment; FUP = Follow-up; IRT = interactive response technology; [redacted]

[redacted]

[redacted]

5.2 Number of Participants

[redacted]

See Section 10.1 for details on sample size estimation.

5.3 End of Study Definition

The start of the trial is defined as the date the first participant signs a study-specific ICF. A participant is considered enrolled when the study-specific informed consent is signed. End of trial is defined as the last visit or scheduled procedure shown in the Schedule of Activities

(Section 2) for the last participant. Study completion is defined as the final date on which data for the primary endpoint was or is expected to be collected, if this is not the same.

5.4 Scientific Rationale for Study Design

Despite innovations in cancer treatment, alternative therapies are needed for participants with advanced cancer. The emerging role of combination immune-modulating therapies in producing deep and durable responses in a variety of tumor types, as well as early clinical data from trials studying relatlimab in combination with nivolumab, the combination of an IDO1 inhibitor with pembrolizumab, and the combination of nivolumab and ipilimumab, suggest that there may be a potential benefit with a triple combination that targets multiple mechanisms in action.

Overall, the safety profile of relatlimab in combination with nivolumab has been manageable, and there were no additional toxicities with relatlimab in combination with nivolumab. Similarly, the safety profile of BMS-986205 has been manageable both as monotherapy and in combination with nivolumab. Therefore, it is expected that the addition of relatlimab to nivolumab and BMS-986205 (in doses already shown to be safe in combination with nivolumab) or to nivolumab and ipilimumab backbone regimens (with known tolerability in specific tumor types) will be safe. The incidence of IMAEs will continue to be monitored across both triple combinations as participants are treated in the study in order to assess the impact of relatlimab on the known toxicity of nivolumab monotherapy and nivolumab combination regimens. The benefit-risk ratio supports evaluation of these triple combinations in participants with advanced cancer.

5.5 Justification for Dose

5.5.1 Justification for Relatlimab Dose

The relatlimab dose of 160 mg Q4W was selected in this study. [redacted]

[redacted]

5.5.2 Justification for Nivolumab Dose

The nivolumab dose of 480 mg Q4W was selected for this study based on clinical data and modeling and simulation approaches using population [redacted] with body weight-normalized dose administration (mg/kg). A flat dose is expected to reduce the potential for medication preparation and administration errors, shorten pharmacy preparation time, and improve ease of administration. [redacted]

[redacted]

[redacted]

5.5.3 Justification for BMS-986205 Dose

In this study, BMS-986205 25 mg by mouth (PO) QD, as a starting dose, will be administered in combination with relatlimab 160 mg Q4W and nivolumab 480 mg Q4W. The selection of the dose and schedule for BMS-986205 is primarily based on available data from the ongoing Phase 1/2, first-in-human CA017003 study.

[redacted]

[redacted]

5.5.4 Justification for Ipilimumab Dose

In this study, ipilimumab 1 mg/kg Q8W will be administered in combination with relatlimab 160 mg Q4W and nivolumab 480 mg Q4W. Ipilimumab 3 mg/kg Q3W for a total of 4 doses is approved as monotherapy and in combination with nivolumab in unresectable and metastatic melanoma. In the adjuvant melanoma setting, ipilimumab monotherapy at a dose of 10 mg/kg Q3W is approved for total of 4 doses, followed by 10 mg/kg Q12W for 3 years. [redacted]

[redacted]

5.5.5 Justification for Relatlimab, Nivolumab, and BMS-986205 Combination Dose (Part 1A and Part 2A)

In this study, relatlimab 160 mg Q4W IV will be administered in combination with nivolumab 480 mg Q4W IV and BMS-986205 25 mg PO QD as a starting dose level. Nivolumab, relatlimab, and BMS-986205 administered as monotherapy were found to be tolerable up to the doses of [redacted] respectively. Additionally, clinical activity was demonstrated with relatlimab [redacted] and nivolumab [redacted] combination therapy and also with BMS-986205 [redacted] and nivolumab [redacted] combination therapy. There is no evidence of clinically relevant drug-drug interactions between monoclonal antibodies, and hence it is not expected that either nivolumab or relatlimab exposures would be altered. BMS-986205 is a small molecule and has a distinct pathway of metabolism and elimination and therefore [redacted]

5.5.6 Justification for Relatlimab, Nivolumab, and Ipilimumab Combination Dose (Part 1B and Part 2B)

In this study, ipilimumab 1 mg/kg Q8W will be administered in combination with relatlimab 160 mg Q4W and nivolumab 480 mg Q4W as a starting dose level. Nivolumab, relatlimab, and ipilimumab administered as monotherapy were found to be tolerable up to the doses of [redacted] respectively. [redacted]

[redacted]

6 STUDY POPULATION

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

6.1 Inclusion Criteria

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

[redacted]

2) Type of Participant and Target Disease Characteristics

a) Histologic or cytologic confirmation of an incurable solid malignancy that is advanced (metastatic and/or unresectable), with measurable disease per RECIST v1.1.

i) [redacted]

b) Presence of at least 1 lesion with measurable disease as defined by RECIST v1.1 criteria for response assessment. Participants with lesions in a previously irradiated field as the sole site of measurable disease will be permitted to enroll provided that the lesion(s) have demonstrated clear progression prior to the time of informed consent and can be measured accurately.

c) Documentation of IO-containing therapy should include start, stop, and progression dates of prior IO therapy.

d) Eastern Cooperative Oncology Group Performance Status (ECOG) status of 0 or 1 (see Appendix 6).

e) Life expectancy ≥ 12 weeks at the time of informed consent per Investigator assessment.

f) [redacted]

g) Ability to comply with scheduled visits, treatment schedule, laboratory testing, and other requirements of the study (for example, PK, and PD sample collection and required study follow-up).

h) Participants receiving BMS-986205: Availability of a suitable formulation and mode of administration for the participant's needs, as detailed in the IB and Pharmacy Manual at the time of enrollment ***Note:*** *at the time of original protocol finalization, BMS-986205 is available in a tablet formulation only and participants should be able to swallow intact tablets to enroll on the study. Ongoing clinical pharmacology studies have expanded the options available. Full details can be found in the IB and Pharmacy Manual, which will be updated throughout the study. Please contact the Medical Monitor with any queries*.

i) [redacted]

Participants who refuse potentially curative salvage surgery for recurrent disease are ineligible. Participants must have tumor progression or recurrence after prior platinum-containing systemic therapy for recurrent or metastatic disease. In addition, participants who have progressed within 6 months of platinum-based therapy used as part of concurrent chemoradiation (definitive or adjuvant therapy) are also eligible. Clinical progression is defined as progression of a lesion at least 10 mm in size that is amenable to caliper measurement (eg, superficial skin lesion per RECIST v1.1) or a lesion that has been visualized and photographically recorded with measurements and shown to have progressed.

(3) Participants cannot have had prior exposure to IO therapies such as, but not limited to, anti-CTLA-4, anti-PD-1, anti-PD-L1, anti-PD-L2, anti-KIR, anti-CD137, anti-LAG-3, or anti-OX40 antibodies.

3) Age and Reproductive Status

a) Males and females, ages ≥ 18 years.

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

c) Women must not be breastfeeding.

d) WOCBP must agree to follow instructions for method(s) of contraception (see Appendix 4) for the duration of treatment with relatlimab, nivolumab, and ipilimumab plus 5 half-lives of study treatment for a total of 5 months post-treatment completion and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction for the same time period.

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception (see Appendix 4) for the duration of treatment with study treatments plus 1 month (approximately 4 weeks) after the last dose of BMS-986205. This criterion applies to azoospermic males as well. In addition, male participants must be willing to refrain from sperm donation during this time.

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

Investigators shall counsel WOCBP, and male participants who are sexually active with WOCBP, on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise on the use of highly effective methods of contraception (see Appendix 4), which have a failure rate of < 1% when used consistently and correctly. Hormonal contraceptives are not highly effective methods of contraception for participants in this study treated with BMS-986205 who are WOCBP.

6.2 Exclusion Criteria

1) Medical Conditions

a) Participants with known or suspected central nervous system (CNS) metastases or with the CNS as the only site of active disease are excluded with the following exceptions:

i) Participants with controlled brain metastases will be allowed to enroll. Controlled brain metastases are defined as those with no radiographic progression for at least 4 weeks after radiation and/or surgical treatment at the time of consent. Participants must have been off of steroids for at least 2 weeks prior to informed consent, and have no new or progressive neurological signs and symptoms.

ii) Participants with signs or symptoms of brain metastases are not eligible unless brain metastases are ruled out by computed tomography (CT) or magnetic resonance imaging (MRI).

b) Participants with a history of interstitial lung disease/pneumonitis.

c) For participants to be treated with BMS-986205: [redacted]

d) For participants to be treated with BMS-986205: [redacted]

e) For participants to be treated with BMS-986205: [redacted]

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

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

h) Requirement for daily supplemental oxygen.

i) Uncontrolled or significant cardiovascular disease including, but not limited to, any of the following:
   i) Myocardial infarction (MI) or stroke/transient ischemic attack within the 6 months prior to consent.
   ii) Uncontrolled angina within the 3 months prior to consent.
   iii) Any history of clinically significant arrhythmias (eg, ventricular tachycardia, poorly controlled atrial fibrillation ventricular fibrillation, torsades de pointes).
   iv) QTc prolongation > 480 ms.
   v) History of other clinically significant cardiovascular disease (ie, cardiomyopathy, congestive heart failure with New York Heart Association functional classification III-IV, pericarditis, significant pericardial effusion, significant coronary stent occlusion, poorly controlled venous thrombosis).
   vi) Cardiovascular disease-related requirement for daily supplemental oxygen.
   vii) History of 2 or more MIs OR 2 or more coronary revascularization procedures.
   viii) Participants with a history of myocarditis, regardless of etiology.

j) Participants a with history of life-threatening toxicity related to prior immune therapy (eg, anti-CTLA-4 or anti-PD-1/PD-L1 treatment, any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways) except those that are unlikely to re-occur with standard countermeasures (eg, hormone replacement after endocrinopathy).

k) A confirmed history of encephalitis, meningitis, or uncontrolled seizures in the year prior to informed consent.

l) Women who are pregnant or breast feeding.

m) Any significant acute or chronic medical illness. In the case of prior [redacted] infection, acute symptoms must have resolved and based on investigator assessment in consultation with the Medical Monitor, and there are no sequelae that would place the participant at a higher risk of receiving investigational treatment.

n) For participants to be treated with BMS-986205: current or recent (within 3 months of study drug administration) gastrointestinal disease that could impact upon the absorption of study drug.

o) For participants to be treated with BMS-986205: any gastrointestinal surgery that could impact upon the absorption of study drug for BMS-986205.

p) Blood transfusion within 4 weeks of study drug administration.

q) For participants to be treated with BMS-986205: inability to tolerate oral medication. See the Pharmacy Manual for updates to this criteria.

r) Inability to be venipunctured and/or tolerate venous access.

s) Any other sound medical, psychiatric, and/or social reason as determined by the Investigator.

t) [redacted]

2) Prior/Concomitant Therapy

a) Any of the following procedures or medications within 2 weeks prior to time of study drug administration:

i) Systemic or topical corticosteroids at immunosuppressive doses (>10 mg/day of prednisone or equivalent) are NOT permitted. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, **are** permitted in the absence of active autoimmune disease.

ii) Palliative radiation or gamma knife radiosurgery. Participants must have recovered (ie, Grade ≤ 1 or at baseline) from radiation-related toxicities prior to first study treatment.

iii) Treatment with complementary medications (eg, herbal supplements or traditional Chinese medicines) to treat the disease under study within 2 weeks prior to first study treatment. Such medications are permitted if they are used as supportive care. Refer to Section 7.7.1 for prohibited/restricted therapies. Note: Prior traditional Chinese medicines with anticancer claims are not considered as a prior line of therapy.

b) Any of the following procedures or medications within 4 weeks prior to study drug administration:

i) Any investigational cytotoxic drug. Exposure to any non-cytotoxic drug within 4 weeks or 5 half-lives (whichever is shorter) is prohibited. If 5 half-lives are shorter than 4 weeks, agreement with Sponsor/Medical Monitor is mandatory.

ii) Growth factors (eg, granulocyte-colony stimulating factor, granulocyte macrophage-colony stimulating factor, erythropoietin).

iii) Major surgery.

c) Any of the following procedures or medications within 4 weeks prior to study drug administration:
   i) Treatment with any live/attenuated vaccine within [redacted] of first study treatment, during treatment, and up to [redacted] post last dose.
   ii) Allergen hyposensitization therapy.

d) Inability to comply with restrictions and prohibited treatments as listed in Section 7.7 Concomitant Therapy.

e) Participation in any prior clinical study with nivolumab and/or ipilimumab, including participants in comparator arms, in which OS is listed as the primary or coprimary endpoint and which has not completed analysis based on the primary endpoint.

f) Prior treatment with LAG-3 or IDO targeted agents.

g) Participants currently in other interventional trials, including those for COVID-19, may not participate in BMS clinical trials until the protocol specific washout period is achieved. If a study participant has received an investigational COVID-19 vaccine or other investigational product designed to treat or prevent COVID-19 prior to screening, enrollment must be delayed until the biologic impact of the vaccine or investigational product is stabilized, as determined by discussion between the investigator and the Medical Monitor/designee.

3) Physical and Laboratory Test Findings

a) WBC < 2000/μL.

b) Neutrophils < 1500/μL.

c) Platelets < 100K/μL.

d) Hemoglobin < 9.0 g/dL.

e) Serum creatinine > 1.5 × ULN or calculated creatinine clearance (CrCl) < 40 mL/min (using the Cockcroft-Gault formula):

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

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

f) AST/ALT > 3.0 × ULN.

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

h) For participants to be treated with BMS-986205: blood methemoglobin > ULN, assessed in an arterial or venous blood sample.

i) Troponin T (TnT) or I (TnI) > 2 × institutional ULN. Participants with TnT or TnI levels between > 1 to 2 × ULN will be permitted if repeat levels within 24 hours are ≤ 1 × ULN. If TnT or TnI levels are between > 1 to 2 × ULN within 24 hours, the participant may undergo a cardiac evaluation and be considered for treatment, based on a favorable benefit-risk assessment by the Investigator. When repeat levels within 24 hours are not available, a repeat test should be conducted as soon as possible. If TnT or TnI repeat levels beyond 24 hours are < 2 × ULN, the participant may undergo a cardiac evaluation and be

considered for treatment, following favorable benefit-risk assessment by the Investigator. Notification of the decision to enroll the participant following cardiologist recommendation has to be made to the BMS Medical Monitor or designee.

j) Any positive test result for hepatitis B virus or hepatitis C virus (HCV) indicating presence of active viral replication (eg, hepatitis B surface antigen [HBsAg, Australia antigen] positive, detectable HCV-ribonucleic acid [RNA], hepatitis C antibody [anti-HCV] positive). NOTE: Participants with positive HCV antibody and an undetectable HCV-RNA are eligible to enroll.

k) Known history of positive test for human immunodeficiency virus (HIV) or active infection or known acquired immunodeficiency syndrome (AIDS). Note: Testing for HIV must be performed at sites where mandated locally or if status is unknown.

l) Evidence of organ dysfunction or any clinically significant deviation from normal in physical examination, vital signs, ECGs, or clinical laboratory determinations beyond what is consistent with the target population.

m) Any of the following on 12-lead ECGs prior to study drug administration, confirmed by repeat:

   i) PR ≥ 210 ms, except right bundle branch block.

   ii) QTcF ≥ 480 ms, except right bundle branch block.

n) For participants to be treated with BMS-986205: Quantitative or qualitative [redacted] assay results suggesting [redacted]

4) Allergies and Adverse Drug Reaction

a) History of allergy to monoclonal antibodies or related compounds.

b) History of any significant drug allergy (such as anaphylaxis or hepatotoxicity).

c) History of allergy or hypersensitivity to study drug components.

5) Other Exclusion Criteria

a) Prisoners or participants who are involuntarily incarcerated. (Note: under certain specific circumstances a person who has been imprisoned may be included or permitted to continue as a participant. Strict conditions apply and Bristol-Myers Squibb approval is required).

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

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

6.3 Lifestyle Restrictions

Not applicable. No restrictions are required.

6.3.1 Meals and Dietary Restrictions

See Section 7.7.1.1 for restrictions.

6.3.2 Caffeine, Alcohol, and Tobacco

No specific restrictions.

6.4 Screen Failures

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

6.4.1 Retesting During Screening or Lead-In Period

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

[redacted]

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

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

Laboratory parameters and/or assessments that are included in Table 9.4.4-1 may be repeated in an effort to find all possible well-qualified participants. Consultation with the Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

7 TREATMENT

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

Study treatment includes both investigational product (IP) and non-investigational product (Non-IP) and can consist of the following:

An IP, also known as an 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.

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, IPs are the following:

- Relatlimab
- Nivolumab
- BMS-986205 (linrodostat mesylate)
- Ipilimumab

All 4 drugs used in this open-label study qualify as IPs per previous text, and their descriptions and storage information are described in Table 7-1.

Table 7-1: Study treatments for CA224048

Product Description/ Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open-label	Packaging/Appearance	Storage Conditions (per label)
Relatlimab[a] Injection [redacted]	[redacted]	IP	[redacted]	Colorless to pale yellow liquid, clear to opalescent, light (few) particulates (consistent in appearance to protein particulates) may be present.	Refer to the label on container and/or Pharmacy Manual.
Nivolumab[a] Injection [redacted]	[redacted]	IP	[redacted]	Clear to opalescent, colorless to pale yellow liquid. Light (few) particulates may be present.	Refer to the label on container and/or Pharmacy Manual.
Ipilimumab Injection [redacted]	[redacted]	IP	[redacted]	Clear to slightly opalescent, colorless to pale yellow liquid. Light (few) particulates may be present.	Refer to the label on container and/or Pharmacy Manual.
BMS-986205-04 [redacted] Tablet	[redacted]	IP	[redacted]	A beige, oval shaped, plain faced, film-coated tablet.	Refer to the label on container and/or Pharmacy Manual.
BMS-986205-04 [redacted] Tablet	[redacted]	IP	[redacted]	A round, concave shaped film-coated tablet.	Refer to the label on container and/or Pharmacy Manual.
BMS-986205-04 [redacted] Tablet	[redacted]	IP	[redacted]	A light pink to pink, oval shaped, plain faced, film-coated tablet.	Refer to the label on container and/or Pharmacy Manual.

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

[a] Relatlimab is sometimes referred to as BMS-986016; Nivolumab is sometimes referred to as BMS-936558.

7.1 Treatments Administered

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

The dose administration schedule for each IP is detailed below in Table 7.1-1. Refer to the Pharmacy Manual for updated information.

Table 7.1-1: Treatments Administered

Study Treatment	Dose Level	Frequency of Administration and Duration of Treatment	Route of Administration	Infusion Time, minutes
Relatlimab[a]	160 mg, 80 mg	Q4W Until progression, unacceptable toxicity, withdrawal of consent, or CR	IV	[redacted]
Nivolumab[a]	480 mg	Q4W Until progression, unacceptable toxicity, withdrawal of consent, or CR	IV	[redacted]
BMS-986205[c]	100 mg, 50 mg, 25 mg	QD Until progression, unacceptable toxicity, withdrawal of consent, or CR	PO	[redacted]
Ipilimumab	1 mg/kg	Q8W Until progression, unacceptable toxicity, withdrawal of consent, or CR	IV	[redacted]

Abbreviations: CR = complete response; IV = intravenous; NA = not applicable; PO = by mouth; Q4W = every 4 weeks; Q8W = every 8 weeks; QD = once daily.

[a] Relatlimab and nivolumab are administered as either a co-administration (relatlimab 160 mg and nivolumab 480 mg) or a sequential administration (relatlimab 80 mg and nivolumab 480 mg) See Section 7.1.1.

[redacted]

Treatment information for Dose Finding (Part 1) is provided in Table 7.1-2 and Table 7.1-3.

Table 7.1-2: Part 1A

Dose	Treatment [redacted]
Starting Dose	
Dose	Relatlimab 160 mg Q4W, Nivolumab 480 mg Q4W, BMS-986205 25 mg QD
Dose Escalation	
Dose +1	Relatlimab 160 mg Q4W, Nivolumab 480 mg Q4W, BMS-986205 50 mg QD
Dose +2	Relatlimab 160 mg Q4W, Nivolumab 480 mg Q4W, BMS-986205 100 mg QD
Dose De-escalation	
Dose-1	Relatlimab 80 mg Q4W, Nivolumab 480 mg Q4W, BMS-986205 25 mg QD

Abbreviations: Q4W = every 4 weeks; QD: once daily.
Note: recommended Phase 2 dose from Part 1A will be used in Part 2A.

Table 7.1-3: Part 1B

Dose	Treatment [redacted]
Starting Dose	
Dose	Relatlimab 160 mg Q4W, Nivolumab 480 mg Q4W, Ipilimumab 1 mg/kg Q8W
Dose De-escalation	
Dose-1	Relatlimab 80 mg Q4W, Nivolumab 480 mg Q4W, Ipilimumab 1 mg/kgQ8W

Abbreviations: Q4W = every 4 weeks; Q8W = every 8 weeks.
Note: recommended Phase 2 dose from Part 1B will be used in Part 2B.

The RP2D selected for Part 2 are as follows:

Part 2A: Relatlimab 160 mg Q4W, Nivolumab 480 mg Q4W, BMS-986205 100 mg QD

Part 2B: Relatlimab 160 mg Q4W, Nivolumab 480 mg Q4W, Ipilimumab 1 mg/kg Q8W

7.1.1 Relatlimab Combined with Nivolumab Administration

Both study drugs will be coadministered at the 160 mg relatlimab and 480 mg nivolumab doses. [redacted]

After the dose-finding period, intra-participant dose escalation or de-escalation of immunotherapy (with the exception of BMS-986205) are not permitted.

[redacted]

Further details regarding preparation and administration of relatlimab and nivolumab will be provided separately in site/pharmacy training materials.

[redacted]

Premedications are not reommended for the first dose of immunotherapy. Participants should be carefully monitored for infusion reactions during administration. If an acute infusion reaction is noted, participant should be managed according to Section 7.4.8.

Participants should receive relatlimab and nivolumab until progression, unacceptable toxicity, withdrawal of consent/assent by the participant, or the study ends, whichever occurs first. Participants should begin study treatment within 3 calendar days of treatment assignment.

Doses of immunotherapy may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment according to Section 7.4.1.

Dosing visits must not be skipped, only delayed. See Section 7.4 and Section 8.1.

If a participant meets criteria for discontinuation and the Investigator is unable to determine whether the event is related to all or any one study drug, the participant should discontinue all study drugs and be taken off the treatment phase of the study.

The study drug injections can be infused undiluted or diluted. All infusions must be promptly followed by a diluent flush to clear the line of IP before starting infusion(s) of any additional treatment. Instruction for dilution and infusion of study drug injections will be provided in the Pharmacy Manual. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent. For details on prepared drug storage, preparation, and administration, please refer to the IBs and/or Pharmacy Manual. The selection and timing of dose for each participant is provided in Table 7.1-1.

Study treatment will be dispensed by interactive response technology (IRT) at the study visits as listed in Section 2 (Schedule of Activities). Further details regarding preparation and administration will be provided separately in site/pharmacy training materials.

7.1.2 BMS-986205 Administration

BMS-986205 will be dispensed to participants in Part 1A and Part 2A at each Day 1 visit within a cycle. Participants will be instructed that BMS-986205 is to be administered once a day in the morning (approximately 24 hours apart) following a meal.

On the study days when relatlimab and nivolumab are also administered, participants will take BMS-986205 in the morning and then report to the clinic for relatlimab and nivolumab infusions (except for Day 1 of Cycle 1, where BMS-986205 is administered in the clinic; see Section 7.1.1). Study procedures, and [redacted]

Further details regarding preparation and administration of BMS-986205 will be provided separately in site/pharmacy training materials.

At the time of original protocol finalization, BMS-986205 will be available in a tablet formulation only; therefore, participants must be able to swallow intact tablets to enroll in the study. Ongoing clinical pharmacology studies may expand the options available. Full details can be found in the IB and Pharmacy Manual, which will be updated throughout the study. Please contact the Medical Monitor with any queries.

Participants will be provided with pill diaries and instructed to record intake of BMS-986205 in the diary after each daily administration.

[redacted] Participants should begin study treatment within 3 calendar days of treatment assignment. Doses of BMS-986205 may be modified or interrupted, depending on how well the participant tolerates the treatment. See Section 7.4.3 for dose modifications. If the dose of BMS-986205 is reduced, re-escalation will not be permitted. Skipped doses during interruptions should not be administered within the same cycle.

For details on prepared drug storage, preparation, and administration, please refer to the BMS-986205 IB and/or Pharmacy Manual. The selection and timing of dose for each participant is provided in Section 7.1.

7.1.3 Ipilimumab Administration

[redacted] There will be no dose modifications allowed.

Participants should be carefully monitored for infusion reactions during administration. If an acute infusion reaction is noted, participants should be managed according to Section 7.4.8.

Doses of immunotherapy may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment according to Section 7.4.1.

Dosing visits must not be skipped, only delayed. See Section 7.4 and Section 8.1.

Participants should receive ipilimumab until progression, unacceptable toxicity, withdrawal of consent/assent by the participant, or the study ends, whichever occurs first. Participants should begin study treatment within 3 calendar days of treatment assignment.

All infusions must be promptly followed by a diluent flush to clear the line of IP before starting infusion(s) of any additional treatment. Instruction for dilution and infusion of study drug injections will be provided in the Pharmacy Manual. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic

agent. For details on prepared drug storage, preparation, and administration, please refer to the IBs and/or Pharmacy Manual. The selection and timing of dose for each participant is provided in Table 7.1-1.

7.2 Method of Treatment Assignment

All participants will be centrally assigned using an Interactive Response Technology (IRT) system; until this system is activated, enrollment may be manually managed by the Sponsor. Before the study is initiated, each user will receive log in information and directions on how to access the IRT.

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

During the screening visit, the investigative site will call into the enrollment option of the IRT designated by BMS for assignment of a 5-digit participant number that will be unique across all sites. Enrolled participants, including those not dosed, will be assigned sequential participant numbers starting with [redacted] The PID number will ultimately be comprised of the site number and participant number. For example, the first participant screened (ie, enrolled) at site number 1, will have a PID of [redacted]. Once it is determined that the participant meets the eligibility criteria following the screening visit, the investigative site will call the IRT to assign the participant into the open dose level.

Treatment assignments for participants eligible for both Part 1A and Part 1B or for melanoma participants in Part 2A or Part 2B will alternate among the parts, with consecutively screened participants assigned to different parts through IRT. If a treatment arm becomes overly enrolled because of screen failures in the alternate arm, it can be temporarily closed to allow enrollment in the alternate arm only. Once balance is achieved, the temporary hold can be lifted. If there are no openings available in the part to which the participant would be assigned by this algorithm, the participant will be assigned to the next open part/cohort until respective dose levels or cohorts have completed accrual according to principles outlined in Section 5.1.2.

Participants will not be replaced if they are discontinued from the study secondary to an AE unless the AE can be determined to be unrelated to treatment.

Participants not evaluable for DLT will be replaced. Participants not evaluable for PD endpoints may be replaced at the discretion of the Sponsor.

7.3 Blinding

As this is an open-label study, blinding procedures are not applicable; however, the specific treatment to be taken by a participant will be assigned using an IRT. The site will contact the IRT prior to the start of study treatment administration for each participant. The site will record the treatment assignment on the applicable case report form (CRF), if required. BMS personnel may have access to treatment information during the course of the trial to help with internal decision making and for disclosure of preliminary scientific results.

7.4 Dosage Modification

7.4.1 Relatlimab Dose Modification

No dose modifications for relatlimab are permitted.

There will be no dose escalations or reductions of relatlimab allowed. Doses of relatlimab may be interrupted, delayed, or discontinued according to Section 7.4.5 and Section 8.1. Dosing visits are not skipped, only delayed.

7.4.2 Nivolumab Dose Modification

No dose modifications for nivolumab are permitted.

There will be no dose escalations or reductions of nivolumab allowed. Doses of nivolumab may be interrupted, delayed, or discontinued according to Section 7.4.5 and Section 8.1. Dosing visits are not skipped, only delayed.

7.4.3 BMS-986205 Dose Modification

[redacted]

The dose of BMS-986205 should be reduced for the following AEs attributable to study therapy that do not otherwise meet criteria for discontinuation:

- [redacted]

Dose modification and interruption of BMS-986205 may occur in the setting of lower grade AEs and/or be more conservative than indicated above based on the clinical judgment of the Investigator and in consultation with the BMS Medical Monitor/designee. For an AE requiring dose modification, BMS-986205 should be interrupted to allow improvement of the AE, even if the AE does not otherwise meet criteria for dose modification (see Section 7.4.5).

Re-escalation of BMS-986205 will not be permitted once the dose of BMS-986205 has been reduced for a participant.

7.4.4 Ipilimumab Dose Modification

No dose modifications for ipilimumab are permitted.

There will be no dose escalations or reductions of ipilimumab allowed. Doses of ipilimumab may be interrupted, delayed, or discontinued according to Section 7.4.5 and Section 8.1. Dosing visits are not skipped, only delayed.

7.4.5 Dose Modification Criteria for IO Therapies

Dose delay criteria apply only for drug-related AEs. Delay administration of relatlimab, nivolumab, and ipilimumab (and interrupt dosing of BMS-986205) if any of the delay criteria in [redacted] are met, or if [redacted] infection is either confirmed or suspected. Delay relatlimab, nivolumab, and ipilimumab dosing (and interrupt dosing of BMS-986205) for any AE, laboratory abnormality, or intercurrent illness which, in the judgement of the Investigator, warrants delaying the dose of study medication.

For participants who require delay of relatlimab, nivolumab, and ipilimumab (or interrupt BMS-986205 dosing), re-evaluate weekly, or more frequently, if clinically indicated, and resume dosing when criteria to resume treatment are met (refer to Section 8.1.2).

[redacted]

Participants who experience the following toxicities must have all study treatment(s) withheld:

- Potential DLTs, until DLT relatedness is defined.
- [redacted] infection either confirmed or suspected.

Criteria for participants who are required to permanently discontinue study treatments are listed in Section 8.1. [redacted]

Participants not meeting guidelines for permanent discontinuation will be permitted to resume therapy based on the criteria specified in Section 8.1.2 and Section 8.1.3. Participants eligible to resume study therapy will resume study therapy at the nominal treatment visit after their last received study medication dose.

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

In extenuating circumstances in which the participant cannot make the dose administration schedule within the dosing window, the BMS Medical Monitor/designee should be contacted.

Participants who require delay of any study treatment should be re-evaluated weekly or more frequently if clinically indicated and resume dose administration when criteria to resume treatment are met.

[redacted]

If BMS-986205 administration is delayed, dose reduction may be necessary (see Section 7.4.3).

If dose administration is resumed after a delay, BMS-986205 may be resumed as soon as the criteria to resume treatment are met (see Section 8.1.2). [redacted] Participants who require delay of any study treatment should be re-evaluated weekly or more frequently if clinically indicated and resume dose administration when retreatment criteria are met.

7.4.6 Dose-limiting Toxicities

For the purpose of guiding dose selection, DLTs will be defined based on the incidence, intensity, and duration of AEs that are possibly related to study treatment. The DLT period will be [redacted] in Part 1A and Part 1B. Any toxicities that occur beyond the DLT period will be accounted for in making final dose level decisions.

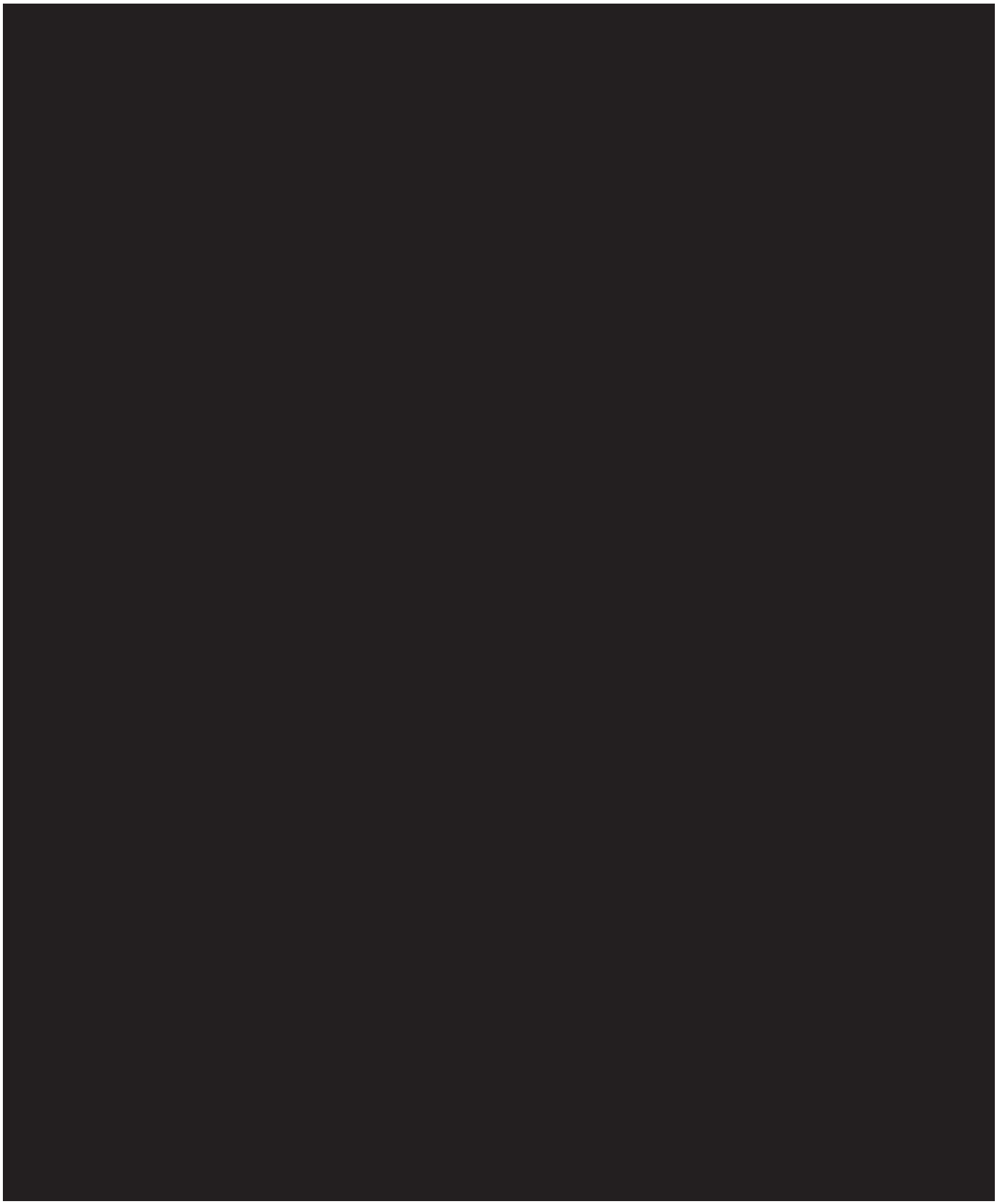
The DLT evaluation interval begins on the first day of treatment and continues for [redacted].

[redacted]

For the purpose of guiding decisions regarding dose escalation in Part 1A and Part 1B, DLT will be determined based on the incidence, intensity, and duration of AEs that are related to study drug and that occur within [redacted] of initiation of study drug (ie, the DLT evaluation interval through the completion of Cycle 1). The severity of AEs will be graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

For the purpose of participant management, potential DLTs that occur at any time, will result in all study drug(s) being held pending evaluation of the event's relatedness to study drug, severity, and duration, and in accordance with Section 7.4.5. Participants must meet criteria for retreatment prior to reinitiation of study treatment (see Section 8.1.2).

[redacted]



7.4.7 Management Algorithms for Immuno-oncology Agents

IO agents are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Relatlimab, nivolumab, ipilimumab, and BMS-986205 are considered as IO agents in this protocol. Early recognition and management of AEs associated with IO agents may mitigate severe toxicity. Management algorithms have been developed to assess and manage the following groups of IMAEs:

- Gastrointestinal
- Renal
- Pulmonary (for participants with dyspnea, complete blood count [CBC] should be measured)
- Hepatic
- Endocrinopathy

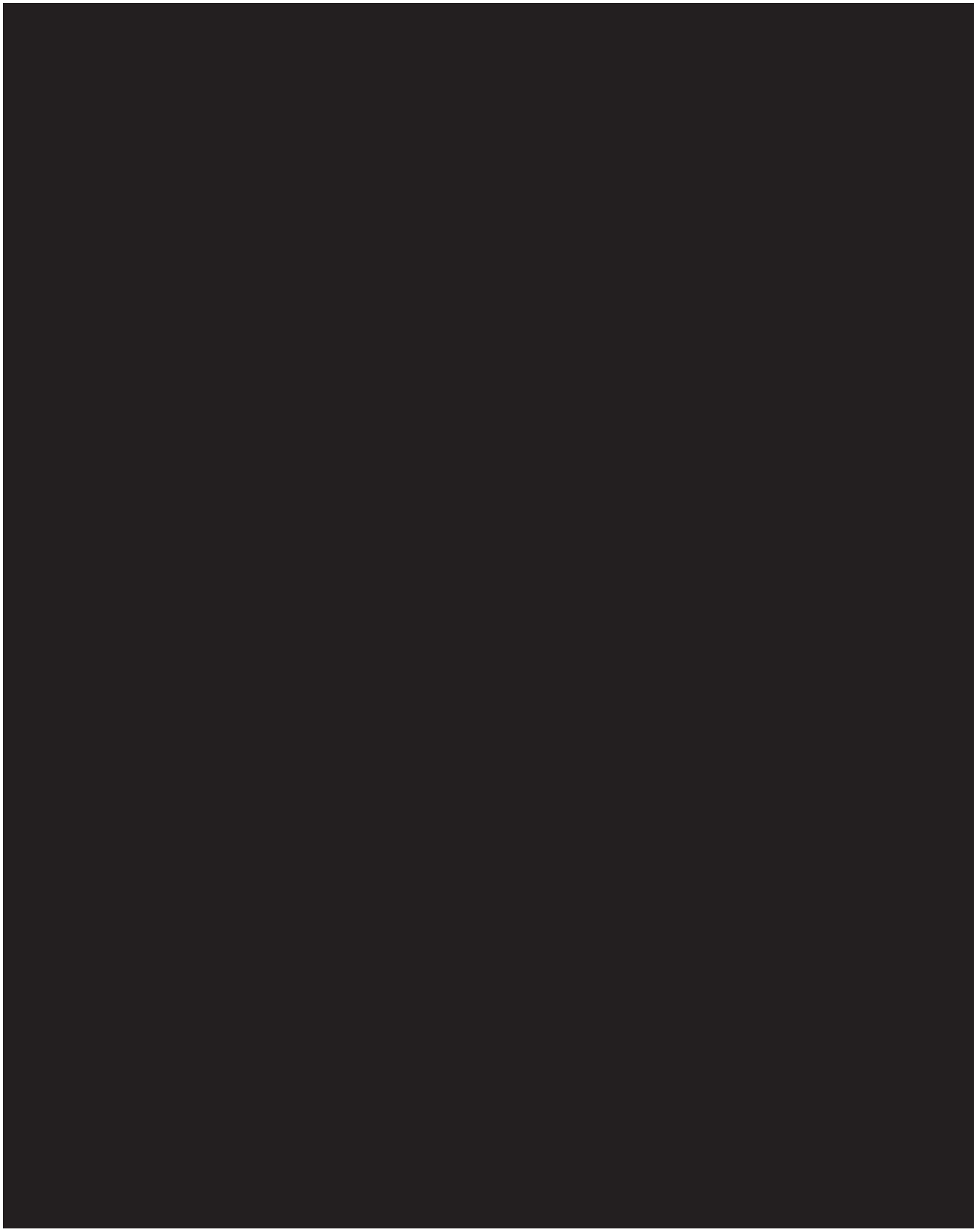
- Skin
- Neurological
- Myocarditis

The algorithms recommended for the management of IMAEs in this protocol are in Appendix 5.

7.4.8 Management of Drug-related Infusion Reactions

Since relatlimab, nivolumab, and ipilimumab contain only human immunoglobulin protein sequences, they are unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. Report all Grade 3 or 4 infusion reactions within 24 hours as an SAE if it meets the criteria.

Treatment recommendations are provided below based on CTCAE v5.0 grading definitions and may be modified based on local treatment standards and guidelines, as appropriate.



7.5 Preparation/Handling/Storage/Accountability

For relatlimab, nivolumab, ipilimumab, and BMS-986205, refer to the current version of the IBs and/or Pharmacy Manual for complete storage, handling, dispensing, and infusion information.

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

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

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

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

- Further guidance and information for final disposition of unused study treatment are provided in Appendix 2 and the Pharmacy Manual.

7.5.1 Retained Samples for Bioavailability/Bioequivalence

Not applicable.

7.6 Treatment Compliance

All IV infusion study treatments will be administered to the participant in the clinical facility. Trained medical personnel will dispense study treatments to the participants. Treatment compliance for participants administered BMS-986205 orally will be monitored by drug accountability, as well as by recording study treatment administration in the participant pill diary, medical record, and CRF. Participants should bring all drug containers to each study visit for drug reconciliation.

7.7 Concomitant Therapy

7.7.1 Prohibited Treatments

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

- Immunosuppressive agents.
- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 6.2).
- Any concurrent antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive non-palliative radiation therapy, or standard or investigational agents for the treatment of cancer).
- Prior exposure to relatlimab or other LAG-3-targeting agents.
- For participants to be treated with BMS-986205: prior exposure to IDO1 targeting agents.
- [redacted]
- Use of any medicinal herbal preparations within 2 weeks of the first dose of study treatment and during study treatment unless prescribed by a treating physician.
- Treatment with any live/attenuated vaccine within [redacted] of first study treatment, during treatment, and up to [redacted] post last dose.

7.7.1.1 Restricted Treatments for Participants Treated with BMS-986205

Restricted therapies are not prohibited but are not recommended; consult the BMS Medical Monitor/designee if the following are clearly medically indicated:

- Avoid coadministration of traditional Chinese medicines with any of the study treatments, unless with Sponsor approval. [redacted]

7.7.2 Other Restrictions and Precautions

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

[redacted]

7.7.2.1 Imaging Restriction and Precautions

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

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

7.7.3 Permitted Therapy

Participants are permitted the use of the following treatments:

- Topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption).
- Adrenal replacement steroid doses > 10 mg daily prednisone equivalent.
- A brief (less-than-3-week) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of nonautoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen).

7.7.4 Palliative Local Therapy

Palliative and supportive care for disease-related symptoms may be offered to all participants on the trial; however, Investigators should consult with the BMS Medical Monitor prior to initiating palliative radiation in participants who have not yet completed the DLT evaluation period. Limited radiation therapy or surgery to control isolated lesions is permitted for participants who have Investigator-assessed clinical benefit following consultation with the BMS Medical Monitor. Participants should not receive study drug treatment during radiation, as the potential for overlapping toxicities with radiotherapy and the triplet combinations is currently not known. Anecdotal data suggest that radiotherapy administered to participants while receiving nivolumab therapy is tolerable; however, because concurrent radiotherapy and immunotherapies in cancer have not been formally evaluated, in cases where palliative radiotherapy is required for a tumor lesion, study treatment should be withheld for at least 1 week before, during, and 1 week after radiation. Participants should be closely monitored for any potential toxicity during and after receiving radiotherapy, and AEs related to radiotherapy should resolve to Grade 1 prior to resuming study drug.

7.8 Treatment After the End of the Study

At the conclusion of the study, participants who continue to demonstrate clinical benefit will be eligible to receive BMS-supplied study treatment. Study treatment will be provided via an

extension of the study, a rollover study requiring approval by responsible health authority and Ethics Committee, or through another mechanism at the discretion of BMS.

BMS reserves the right to terminate access to BMS-supplied study treatment if any of the following occur: a) the study is terminated due to safety concerns; b) the development of relatlimab or BMS-986205 is terminated for other reasons, including but not limited to lack of efficacy and/or not meeting the study objectives; c) the participant can obtain medication from a government-sponsored or private health program. In all cases BMS will follow local regulations.

8 DISCONTINUATION CRITERIA

8.1 Discontinuation from Study Treatment

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

- If a participant receiving relatlimab, nivolumab, and ipilimumab combination meets criteria for discontinuation per [redacted], they must discontinue all study drugs and be taken off the treatment phase of the study.
- Any drug-related AE occurring at any time that meets DLT criteria as outlined in Section 7.4.6 will require permanent discontinuation. Exceptions to permanent discontinuation are listed in Section 8.1.3.
- Documented disease progression as defined by RECIST v1.1 (Appendix 11), unless participants meet criteria for treatment beyond progression [redacted]
- Clinical deterioration while receiving active study therapy that, in the opinion of the Investigator, indicates that continued participation in the study is not in the best interest of the participant.
- Any clinical AE, laboratory abnormality, or intercurrent illness which, in the opinion of the Investigator, indicates that continued participation in the study is not in the best interest of the participant.
- Participant's request to stop study treatment. Participants who request to discontinue study treatment will remain in the study and must continue to be followed per protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by the participant to provide this information.
- Termination of the study by BMS.
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness. (Note: Under specific circumstances, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply and BMS approval is required.)
- Inability to comply with the protocol.
- Discretion of the Investigator.
- Pregnancy.
- [redacted]

BMS Medical Monitor/designee in settings where benefit-risk justifies discontinuation of [redacted]

In the case of pregnancy, the Investigator must notify, within 24 hours of the awareness of the pregnancy, the BMS Medical Monitor/designee of this event. In most cases, the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). Please contact the Sponsor or designee within 24 hours of awareness of the pregnancy. Refer to Section 9.2.6 Pregnancy.

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

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

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

8.1.1 Relatlimab, Nivolumab, BMS-986205, and Ipilimumab Dose Discontinuation

Relatlimab, nivolumab, BMS-986205, and ipilimumab treatment should be permanently discontinued for the following:

- If a participant receiving relatlimab, nivolumab, and ipilimumab combination meets criteria for discontinuation per Table 7.4.5-1, they must discontinue all study drugs and be taken off the treatment phase of the study.
- [redacted]
- In most cases of Grade 3 AST or ALT elevation (defined as AST or ALT > 5 x ULN, regardless of baseline value), study treatment(s) will be permanently discontinued. If the Investigator determines a possible favorable benefit-risk ratio that warrants continuation of study

treatment(s), a discussion between the Investigator and the BMS Medical Monitor/designee must occur.

- [redacted]
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the participant with continued dose administration.
- [redacted]

8.1.2 Criteria to Resume Treatment

Participants experiencing AEs not meeting criteria for permanent discontinuation as outlined in Section 7.4.5 and Section 8.1.1 may resume treatment with study drug under the following criteria:

- Participants may resume treatment with study drug if they have completed AE management (ie, corticosteroid taper) or are on ≤ 10 mg prednisone or equivalent, and meet the requirements per Table 7.4.5-1.
- [redacted]
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved according to Management Algorithms (Appendix 5) and meeting the criteria for resumption per Table 7.4.5-1. Participants with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by the BMS Medical Monitor or designee.

- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- If the criteria to resume treatment are met, the participant should restart treatment at the next scheduled time point per protocol.
- [redacted]

8.1.3 Exceptions to Permanent Discontinuation

Any drug-related AE occurring at any time that meets DLT criteria as outlined in Section 7.4.6 [redacted]

- [redacted]
- Any AE, laboratory abnormality, or concurrent illness, which, in the judgment of the Investigator, presents a substantial clinical risk to the participant with continued dose administration.

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

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

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

[redacted]

[redacted]

8.1.5 Post Study Treatment Study Follow-up

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

In this study, participants who complete or discontinue study treatment will continue to be followed.

8.2 Discontinuation from the Study

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

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

8.3 Lost to Follow-Up

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

9 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the Schedule of Activities (see Section 2).
- Protocol waivers or exemptions are not allowed.
- All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.
- Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before treatment assignment. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before the signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Schedule of Activities.

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

If a participant shows pulmonary-related signs (hypoxia, fever) or symptoms (eg, dyspnea, cough, fever) consistent with possible pulmonary AEs, the participant should be immediately evaluated to rule out pulmonary toxicity, according to the suspected pulmonary toxicity management algorithm in Appendix 5.

The troponin elevations will require the participant to undergo a cardiac evaluation. Following this evaluation, determination of further treatment will be based on the discretion of the Investigator.

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

9.1 Efficacy Assessments

9.1.1 Imaging Efficacy Assessments

Screening images should be acquired as outlined in Table 2-1. On-study images should be acquired as outlined in Table 2-2 and Table 2-3 from the date of first dose until participant is off-study as defined in Section 8.1. For participants continuing in the Follow-up period, imaging will continue as defined in Table 2-4. Any additional imaging that may demonstrate tumor response or progression (including scans performed at unscheduled time points and/or at an outside institution) [redacted]

9.1.2 Imaging Assessment for the Study

Images will be submitted to [redacted] on a rolling basis, preferably within 7 days of scan acquisition. Sites should be qualified prior to scanning the first study participant. Image acquisition guidelines and submission process will be outlined in the CA224048 Imaging Manual to be provided by [redacted]

9.1.3 Imaging Methods of Measurement

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

Should a participant have contraindication for CT intravenous contrast, a non-contrast CT of the chest and a contrast-enhanced MRI of the neck (if required), abdomen, pelvis, and other known/suspected sites of disease should be obtained.

Should a participant have contraindication for both MR and CT intravenous contrasts, a non-contrast CT of the chest and a non-contrast MRI of the neck (if required), abdomen, pelvis, and other known/suspected sites of disease should be obtained.

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

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

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

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

9.2 Adverse Events

The definitions of an AE or serious adverse event (SAE) can be found in Appendix 3.

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

The Investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that

are serious, considered related to the study treatment or the study, or that caused the participant to discontinue before completing the study.

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

Contacts for SAE reporting are specified in Appendix 3.

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

The collection of non-serious AE information (with the exception of non-serious AEs related to [redacted]) should begin at initiation of study treatment until the time points specified in the Schedule of Activities (Section 2). Non-serious 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 participants.

Section 5.6.1 and 5.6.2 in the IBs for relatlimab, nivolumab, BMS-986205, and ipilimumab, represent the Reference Safety Information, to determine expectedness of SAEs for expedited reporting. Following the participant's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures.

All SAEs must be collected that occur during the screening period and within [redacted] of the last dose of study treatment. For participants assigned to treatment and never treated with study drug, SAEs should be collected for [redacted] from the date of treatment assignment. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy). All SAEs, and all AEs (SAEs and non-serious AEs) associated with confirmed or suspected [redacted] infection must be collected from the date of the participant's written consent until [redacted] following discontinuation of dosing.

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

- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the appropriate section of the eCRF section.
- All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix 3.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of updated information being available.

Investigators are not obligated to actively seek AEs or SAEs in former study participants; however, if the Investigator learns of any SAE, including a death, at any time after a participant has been

discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the Investigator must promptly notify the Sponsor.

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

9.2.2 Method of Detecting AEs and SAEs

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

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

9.2.3 Follow-up of AEs and SAEs

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

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 9.2) and AEs (SAEs and non-serious AEs) associated with confirmed or suspected [redacted] will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, the event is deemed irreversible, or until the participant is lost to follow-up (as defined in Section 8.3).

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

9.2.4 Regulatory Reporting Requirements for SAEs

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

The Sponsor or designee will be reporting AEs to regulatory authorities and Ethics Committees according to local applicable laws, including European Directive 2001/20/EC and FDA Code of

Federal Regulations 21 CFR Parts 312 and 320. Suspected, unexpected serious adverse reactions (SUSARs) are a subset of SAEs and will be reported to the appropriate regulatory authorities and Investigators following local and global guidelines and requirements.

9.2.6 Pregnancy

If, following initiation of the study treatment, it is subsequently discovered that a participant is pregnant or may have been pregnant at the time of study exposure, including during at least 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 or designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Appendix 3.

If the Investigator determines a possible favorable benefit-risk ratio that warrants continuation of study treatment, or reinitiation of study treatment, a discussion between the Investigator and the BMS Medical Monitor/designee must occur. If, for whatever reason, the pregnancy has ended, confirmed by negative serum pregnancy test, treatment may be resumed (at least 3 weeks and not greater than 6 weeks after the pregnancy has ended), following approvals of participant/Sponsor/IRB/EC, as applicable.

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 the Sponsor or designee. In order for the Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an ICF for disclosure of this information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

9.2.7 Laboratory Test Result Abnormalities

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

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

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

9.2.8 Potential Drug Induced Liver Injury

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

Potential DILI is defined as:

1) Aminotransaminase (AT; ALT or AST) elevation >3 × ULN.

AND

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

AND

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

9.2.9 Other Safety Considerations

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

9.3 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. Overdose, as a verbatim term (as reported by the investigator), should not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae and should specify "intentional overdose" as the verbatim term (see Section 9.2).

For this study, any dose of relatlimab, nivolumab, BMS-986205, or ipilimumab greater than the planned dose will be considered an overdose.

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

1) Contact the Medical Monitor immediately.
2) Closely monitor the participant for AEs/SAEs and laboratory abnormalities until study treatment can no longer be detected systemically (at least [redacted]
3) Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

9.4 Safety

Planned time points for all safety assessments are listed in the Schedule of Activities (see Section 2).

9.4.1 Physical Examinations

Refer to Schedule of Activities.

9.4.2 Vital signs

Refer to Schedule of Activities.

9.4.3 Electrocardiograms

Refer to Schedule of Activities.

9.4.4 Clinical Safety Laboratory Assessments

- Investigators must document their review of each laboratory safety report.
- Local laboratory tests may be used to guide clinical decisions and determine eligibility for dose administration once eligibility to participate in this study has been confirmed by central laboratory results.

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

During screening and treatment, unless otherwise indicated in Table 9.4.4-1, results of clinical laboratory tests must be reviewed prior to dose administration.

Table 9.4.4-1: Laboratory Assessments

Hematology	
Hemoglobin	
Hematocrit	
Total leukocyte count, including differential	
Platelet count	
Methemoglobin; if elevated, draw reticulocyte count, lactate dehydrogenase (LDH), and haptoglobin. Methemoglobin is assessed on arterial or venous blood sample	
G6PD levels; prior to treatment assignment only, if indicated	
Serum Chemistry	
Aspartate aminotransferase (AST)	Total Protein
Alanine aminotransferase (ALT)	Albumin
Total bilirubin	Sodium
Direct bilirubin; reflex if total is abnormal	Potassium
Alkaline phosphatase	Chloride
Lactate dehydrogenase	Calcium
Creatinine	Phosphorus
[redacted]) (**see below**)	Magnesium
Blood urea nitrogen (BUN)	Creatinine clearance; screening only; Cockcroft-Gault formula
Uric acid	Cardiac troponin T (cTnT) or I (cTnI); see below
Glucose	Amylase
C-reactive protein	Thyroid-stimulating hormone (TSH), free T3 and free T4 - screening; see below
Lipase	
Gamma glutamyl transferase; reflex when alkaline phosphatase is Grade ≥ 2	
HbA1c; obtain during screening to establish baseline in participants with type 2 diabetes, then as clinically indicated	
Endocrine Panel	
TSH with reflex to free T3 and free T4 as applicable on-treatment	
Participants with controlled hyperthyroidism must be negative for thyroglobulin and thyroid peroxidase antibodies and thyroid stimulating immunoglobulin; screening only.	

[redacted]

Table 9.4.4-1: Laboratory Assessments

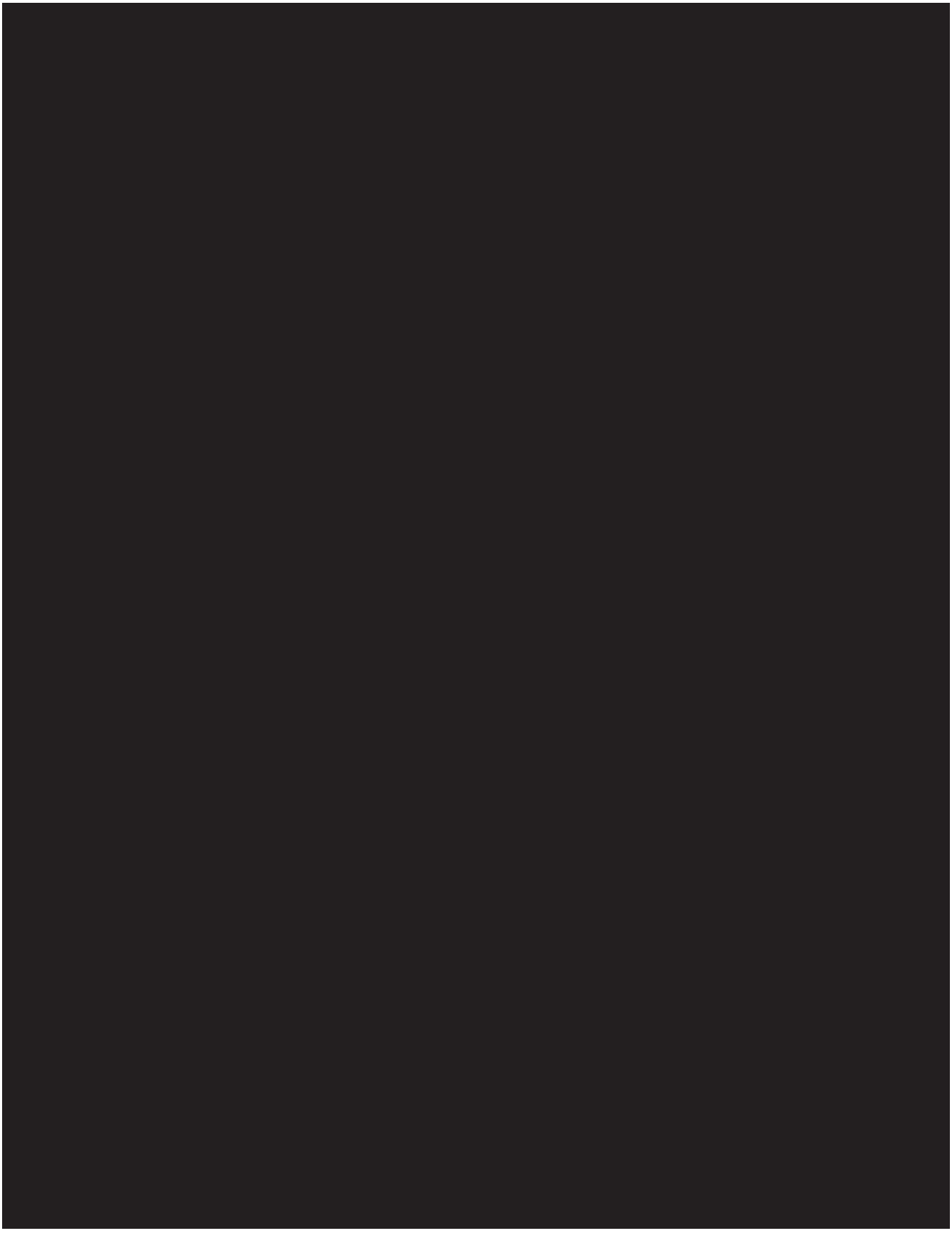
Urinalysis
Protein
Glucose
Blood
Leukocyte esterase
pH
Microscopic examination of the sediment if blood, protein or leukocytes esterase are positive on the dipstick
Serology (at screening only)
Hepatitis A antibody
Hepatitis C antibody; if hepatitis C antibody is positive, reflex to hepatitis C RNA
Hepatitis B surface antigen (HBsAg) and/or hepatitis B core antigen
HIV-1, and -2 antibody where mandated by local requirements
Other Analyses
Pregnancy test (WOCBP only: minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [hCG])
Follicle stimulating hormone (FSH) screening - only required to confirm menopause in women < age 55) as defined in Appendix 4
Serologic tumor marker for gastric cancer, carcinoembryonic antigen (CEA)

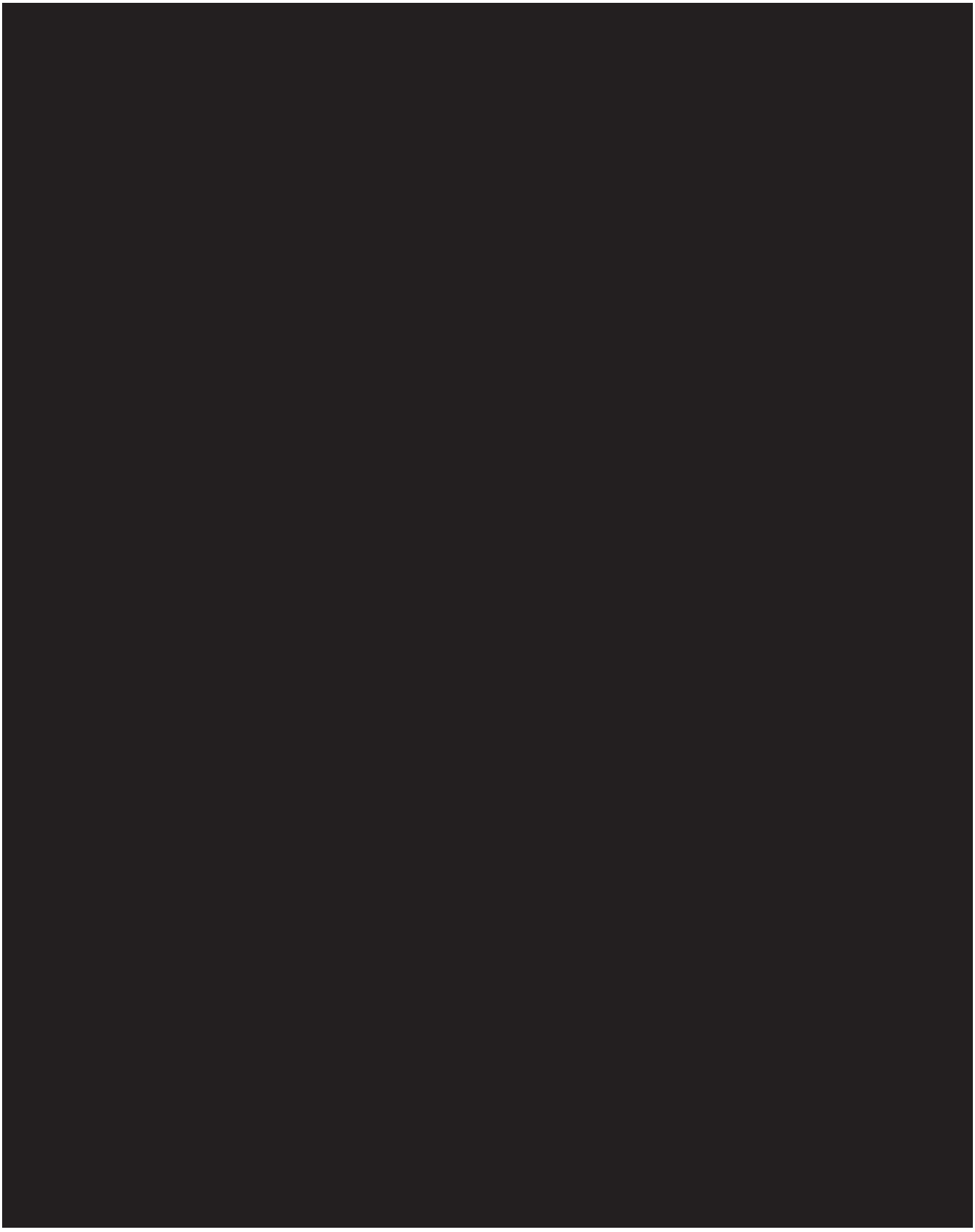
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CEA = carcinoembryonic antigen; [redacted] T; FSH = follicle stimulating hormone; GP6D = glucose-6-phosphate dehydrogenase; HbA1c = glycated hemoglobin; HBSAg = hepatitis B surface antigen; HCG = human chorionic gonadotropin; HIV-1 = human immunodeficiency virus-1; HIV-2 = human immunodeficiency virus-2; LDH = lactate dehydrogenase; RNA = ribonucleic acid; TSH = thyroid-stimulating hormone WOCBP = women of child bearing potential.

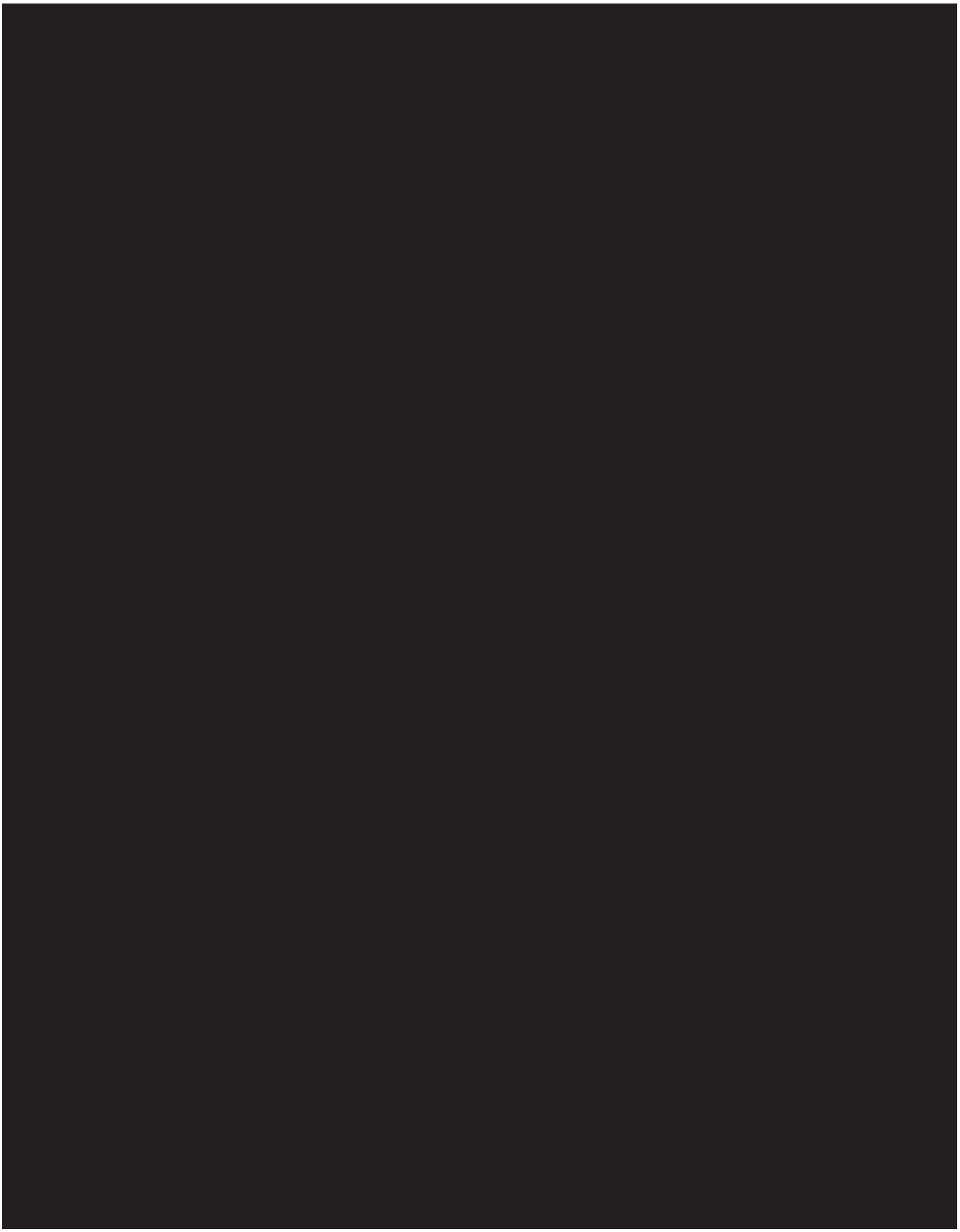
9.4.5 Imaging Safety Assessment

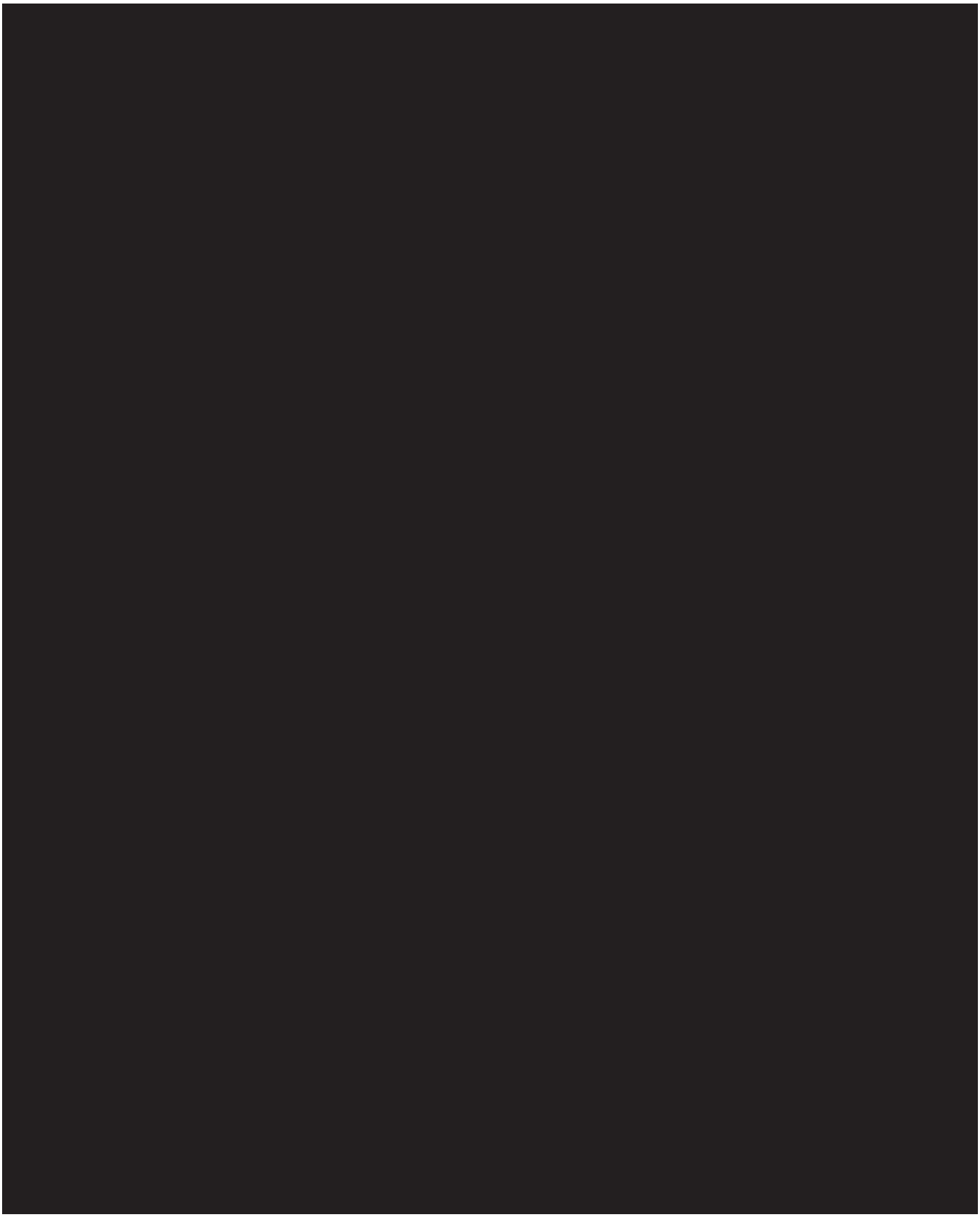
Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the study Investigator per standard medical/clinical judgment.

[redacted]









9.8.3 Additional Research Collection

This protocol will include residual sample storage for additional research.

For All US Sites:

Additional research participation is required for all investigational sites in the U.S.

For Non-US Sites:

Additional research is optional for all study participants, except where retention and/or collection is prohibited by local laws or regulations, ethics committees, or institutional requirements.

This retention for additional research is intended to expand the translational Research and Development capability at BMS, and will support as yet undefined research aims that will advance our understanding of disease and options for treatment. It may also be used to support health authority requests for analysis, and advancement of pharmacodiagnostic development to better

target drugs to the right patients. This may also include genetic/genomic exploration aimed at exploring disease pathways, progression and response to treatment, etc.

Sample Collection and Storage

All requests for access to samples or data for additional research will be vetted through a diverse committee of the study Sponsor's senior leaders in Research and Development (or designee) to ensure the research supports appropriate and well-defined scientific research activities.

- [redacted]

Samples kept for future research will be stored at the BMS Biorepository in [redacted] or an independent, BMS-approved storage vendor.

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

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

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

Further details of sample collection and processing will be provided to the site in the Procedure Manual.

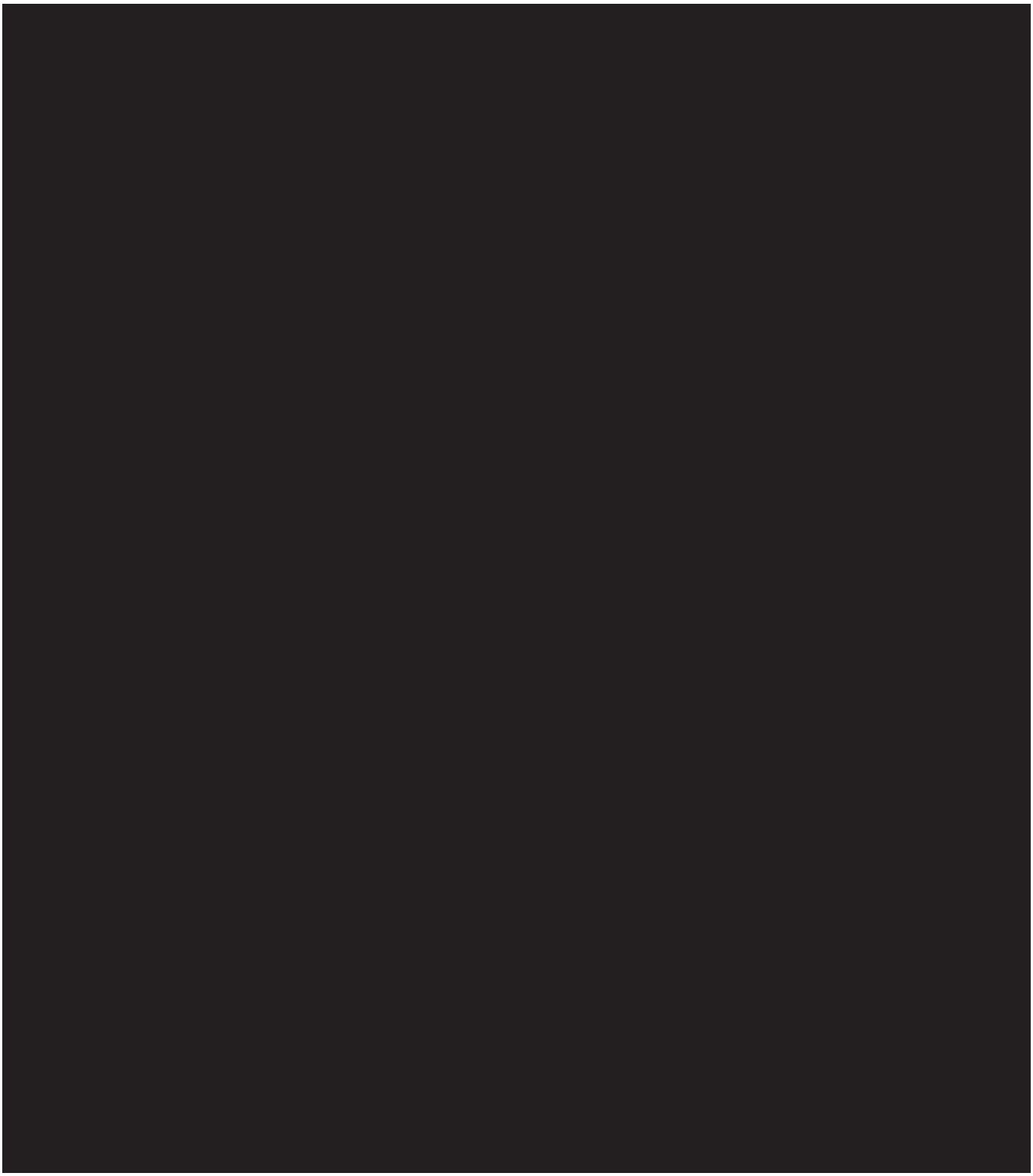
[redacted]

[redacted]

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

[redacted]



10.2 Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign informed consent and are registered into the IRT
Treated	All participants who take at least 1 dose of study treatment
Response-evaluable	All treated participants with measurable disease at baseline and 1 of the following: a) at least 1 post-baseline tumor assessment; b) clinical progression, or c) death
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Abbreviations: IRT = interactive response technology; [redacted].

10.3 Statistical Analyses

Final analysis will be performed after all participants are enrolled and have been followed for the minimum time to evaluate the primary endpoint. The statistical analysis plan will be developed and finalized before the database lock for the final analysis. A description of the participant population will be included in the statistical output reported, including subgroup of age, gender, and race. Below is a summary of planned statistical analyses of the primary and secondary endpoints. In general, summaries will be performed by dose level, cohort, and indication. If sufficient data are not available such that adequate interpretation of the result is not warranted, some summaries may not be performed and only listings will be presented.

[redacted]

10.3.1 Efficacy Analyses

The primary efficacy analyses will be performed on the treated population for the final analysis. Efficacy analyses based on the response-evaluable population may be performed for interim analyses when the minimum follow-up period is less than sufficient to warrant adequate interpretation of the result. Efficacy analyses may be performed on selected subgroups, including biomarker-selected subgroups. Efficacy analyses will be performed using the RECIST v1.1 criteria. Additional details on efficacy analyses are provided in Table 10.3.1-1.

Table 10.3.1-1: Overview of Efficacy Analysis Methods

Endpoint	Statistical Analysis Methods
ORR is defined as the proportion of participants whose BOR is either CR or PR. DCR is defined as the proportion of participants whose BOR includes CR, PR, and SD. Best overall response per RECIST v1.1 is defined as the best response designation recorded between the date of first dose and the date of first objectively documented progression per RECIST v1.1 or the date of subsequent therapy, whichever occurs first. For participants who continue treatment beyond progression per RECIST v1.1 or begin subsequent therapy, the BOR should be determined based on response designations recorded up to the time of the initial progression or subsequent therapy, whichever occurs first. For participants without documented progression or subsequent therapy, all available response designations should contribute to the BOR assessment.	Estimate of ORR and DCR and corresponding 2-sided exact 95% CI using the Clopper-Pearson method.
mDOR DOR for a participant with a BOR of CR or PR is defined as the time between the date of first response and the date of the first objectively documented tumor progression per RECIST v1.1 or death, whichever occurs first. For those participants who neither progress nor die, the duration of objective response will be censored at the same time they will be censored for the primary definition of PFS.	Estimate by the Kaplan-Meier method and corresponding 2-sided 95% CI using Brookmeyer and Crowley methodology (using log-log transformation).
mPFS and PFSR at 6 and 12 months PFS is defined as the time from first dose to the date of first objectively documented progression, per RECIST v1.1, or death due to any cause, whichever occurs first. Clinical deterioration in the absence of objectively documented progression per RECIST v1.1 is not considered progression for the purpose of determining PFS. Participants who die without a reported progression will be considered to have progressed on the date of their death. Participants who did not progress or die will be censored on the date of their last evaluable tumor assessment. Participants who did not have any on study tumor assessments and did not die will be censored on the date of first dose. Participants who started any subsequent anticancer therapy, including tumor-directed radiotherapy and tumor-directed surgery, without a prior reported progression will be censored at the last evaluable tumor assessment prior to initiation of the subsequent anticancer therapy. The PFSR at time T is defined as the probability that a participant has not progressed and is alive at time T following first dose.	Estimate by the Kaplan-Meier method and corresponding 2-sided 95% CI using Brookmeyer and Crowley methodology (using log-log transformation) for the median and Greenwood formula for the rate.
[redacted]	

Abbreviations: BOR = best overall response; CI = confidence interval; CR = complete response; DCR = disease control rate; DOR = duration of response; mDOR = median duration of response; mPFS = median progression-free survival; [redacted] ORR = overall response rate; [redacted] PFS = progression-free survival; PFSR = progression-free survival rate; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease; T= time.

10.3.2 Safety Analyses

All safety analyses (see Table 10.3.2-1) will be performed on the treated population.

Table 10.3.2-1: Overview of Safety Analysis Methods

Endpoint	Statistical Analysis Methods
Incidence of AEs, SAEs, AEs meeting protocol-defined DLT criteria, AEs leading to discontinuation and deaths AEs will be graded according to CTCAE v5.0	DLT rate by dose level; frequency distribution of treated participants with AE using the worst CTC grade. Participants will only be counted (1) once at the PT level, (2) once at the SOC level, and (3) once in the "total participant" row at their worst CTC grade, regardless of SOC or PT.
Incidence of clinical laboratory test abnormalities Laboratory values will be graded according to CTCAE v5.0	Laboratory shift table using the worst CTC grade on treatment per participant.

Abbreviations: AE = adverse event; CTC = Common Terminology Criteria; CTCAE = Common Terminology Criteria for Adverse Events; DLT = dose-limiting toxicity; PT = preferred term; SAE = serious adverse event; SOC = system organ class.

[redacted]

10.3.4 Interim Analyses

The Statistical Analysis Plan will further describe the planned interim analyses.

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12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
1L	first-line
2L	second-line
ACLS	advanced cardiac life support
ADA	anti-drug antibody
AE	adverse event
AESOI	adverse events of special interest
AI	accumulation index
AI_AUC	AUC Accumulation Index; ratio of AUC(TAU) at steady state to AUC(TAU) after the first dose
AI_Cmax	Cmax Accumulation Index; ratio of Cmax at steady state to Cmax after the first dose
AI_Ctau	Ctau Accumulation Index; ratio of Ctau at steady state to Ctau after the first dose
AIDS	acquired immunodeficiency syndrome
[redacted]	[redacted]
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANOVA	analysis of variance
AST	aspartate aminotransferase
AT	aminotransaminase
AUC	area under the concentration-time curve
AUC(INF)	area under the concentration-time curve from time zero extrapolated to infinite time
AUC(0-T)	area under the concentration-time curve from time zero to the time of the last quantifiable concentration
AUC(TAU)	area under the concentration-time curve in one dosing interval
A-V	atrioventricular
β-hCG	beta-human chorionic gonadotrophin
BICR	blinded independent clinical review
BID, bid	bis in die, twice daily
BLQ	below limit of quantification

Term	Definition
[redacted]	[redacted]
BMI	body mass index
BMS	Bristol-Myers Squibb Company
BOR	best overall response
BP	blood pressure
BUN	blood urea nitrogen
C	cycle
C12	concentration at 12 hours
C24	concentration at 24 hours
Ca^{++}	calcium
Cavg	average concentration
Cavgss	time-averaged steady-state concentration
CBC	complete blood count
CD	cluster of differentiation
CEA	carcinoembryonic antigen
Cexpected-tau	expected concentration in a dosing interval
CFR	Code of Federal Regulations
CI	confidence interval
$C1^-$	chloride
CL	clearance
CL/F	apparent clearance
CLss	clearance at steady-state
cm	centimeter
Cmax	maximum observed concentration
Cmaxss	maximum observed steady-state concentration
Cmin	minimum observed concentration
Cminss	minimum observed steady-state concentration
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019

Term	Definition
[redacted]	[redacted]
CR	complete response
CRC	colorectal cancer
CrCl	creatinine clearance
CRF	Case Report Form, paper or electronic
CT	computed tomography
CTAg	clinical trial agreement
CTC	common terminology criteria
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
CTLA-4	cytotoxic T-lymphocyte-associated protein-4
cTnI	cardiac troponin I
cTnT	cardiac troponin T
Ctrough	trough observed plasma concentration
CV	coefficient of variation
CYP	cytochrome p-450
D	day
DCR	disease control rate
D/C	discontinue
DIL	Dear Investigator Letter
DILI	drug-induced liver injury
dL	deciliter
DLT	dose limiting toxicity
DMC	data monitoring committee
DoR	duration of response
DRESS	drug reaction with eosinophilia and systemic symptoms
DSM IV	Diagnostic and Statistical Manual of Mental Disorders (4^{th} Edition)
EA	extent of absorption
EC50	half-maximal effective concentration
ECG	electrocardiogram

Term	Definition
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EEG	electroencephalogram
eg	exempli gratia (for example)
eGFR	estimated glomerular filtration rate
[redacted]	[redacted]
ELISA	enzyme-linked immunosorbent assay
EOI	end of infusion
EOT	end of treatment
ESR	Expedited Safety Report
F	bioavailability
FDA	Food and Drug Administration
FDC	Fixed-dose combination
[redacted]	[redacted]
FSH	follicle stimulating hormone
FU/FUP	follow-up
g	gram
G6PD	glucose-6-phosphate dehydrogenase
GBS	Guillain-Barre syndrome
[redacted]	[redacted]
GCP	Good Clinical Practice
Geo.	geometric
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
h	hour
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
hCG	human chorionic gonadotropin

Term	Definition
HCV	hepatitis C virus
HCO_3^-	bicarbonate
HIV	human immunodeficiency virus
[redacted]	[redacted]
HPV	human papillomavirus
HR	heart rate
HRT	hormone replacement therapy
HuMAb	human monoclonal antibody
hWB	human whole blood
IB	Investigator's Brochure
IC50	half-maximal inhibitory concentration
ICD	International Classification of Diseases
ICF	informed consent form
ICH	International Conference on Harmonisation
IDO1	indoleamine 2,3-dioxygense 1
ie	id est (that is)
IEC	Independent Ethics Committee
Ig	immunoglobulin
IgG	immunoglobulin G
IHC	immunohistochemistry
IMAE	immune-mediated adverse event
[redacted]	[redacted]
IMP	investigational medicinal products
IND	Investigational New Drug Exemption
IO	immuno-oncology
IP	investigational product
IPI	ipilimumab
IQR	interquartile range
IRB	Institutional Review Board
IRT	Interactive Response Technology

Term	Definition
IU	International Unit
IV	intravenous
K	slope of the terminal phase of the log concentration-time curve
K_3EDTA	potassium ethylenediaminetetraacetic acid
K^+	potassium
Kd	dissociation constant
kg	kilogram
L	liter
LAG-3	lymphocyte activation gene 3
LAM	Lactation amenorrhea method
LCMS	liquid chromatography mass spectrometry
LDH	lactate dehydrogenase
ln	natural logarithm
LVEF	left ventricular ejection fraction
MAD	maximum administered dose
mDOR	median duration of response
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
Mg^{++}	magnesium
MG	myasthenia gravis
MHC	major histocompatibility complex
MI	myocardial infarction
min	minute
mL	milliliter
MLR	mixed lymphocyte reaction
mmHg	millimeters of mercury
[redacted]	[redacted]
mPFS	median progression-free survival
MR	medical research
MRI	magnetic resonance imaging

Term	Definition
MS	mass spectrometry
MTD	maximum tolerated dose
MUGA	multiple-gated acquisition
µg	microgram
n	number of participants or observations
Na^+	sodium
NA	not applicable
NCI	National Cancer Institute
ng	nanogram
NIVO	nivolumab
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
ORR	overall response rate
[redacted]	[redacted]
[redacted]	[redacted]
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
[redacted]	[redacted]
PD-1	programmed death 1
PD-L1	programmed death-ligand 1
PD-L2	programmed death-ligand 2
PE	physical examination
PET	positron emission tomography
PFS	progression-free survival
PFSR	progression-free survival rate
PID	participant identification
[redacted]	[redacted]
PO	per os (by mouth route of administration)
[redacted]	[redacted]
PR	partial response

Term	Definition
PT	preferred term
[redacted]	
QD	quaque die, once daily
Q2W	every 2 weeks
Q3W	every 3 weeks
Q4W	every 4 weeks
Q6W	every 6 weeks
Q8W	every 8 weeks
Q12W	every 12 weeks
R^2	coefficient of determination
RBC	red blood cell
RCC	renal cell cancer
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	ribonucleic acid
RO	receptor occupancy
[redacted]	[redacted]
RP2D	recommended Phase 2 dose
RT-PCR	reverse transcriptase-polymerase chain reaction
SAE	serious adverse event
[redacted]	[redacted]
[redacted]	[redacted]
SD	stable disease
SJS	Stevens-Johnson syndrome
[redacted]	
SNP	single nucleotide polymorphism
SOC	system organ class
SOP	Standard Operating Procedures
sp.	species
SUSAR	suspected, unexpected serious adverse reaction
t	temperature

Term	Definition
T	time
T.Bili	total bilirubin
TAO	Trial Access Online, the BMS implementation of an EDC capability
TEN	toxic epidermal necrolysis
TID	ter in die, three times a day
Tmax	time to achieve maximum drug concentration
TnI	troponin I
TnT	troponin T
TRAE	treatment-related adverse event
TSH	thyroid-stimulating hormone
TTE	transthoracic echocardiogram
ULN	upper limit of normal
US	United States
UV	ultraviolet
VS	vital signs
Vss	volume of distribution at steady state
W	washout
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential
WNOCBP	women **not** of childbearing potential
WWPS	Worldwide Patient Safety

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

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

REGULATORY AND ETHICAL CONSIDERATIONS

This study will be conducted in accordance with:

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

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

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

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

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

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

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

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

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

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

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

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

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

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

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

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

FINANCIAL DISCLOSURE

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information, in accordance with regulations, to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate Health Authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

INFORMED CONSENT PROCESS

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

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

The investigator or his/her representative must:

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

Obtain an ICF signed and personally dated by participant or his/her legally acceptable representative and by the person who conducted the informed consent discussion.

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

Revise the ICF whenever important new information becomes available that is relevant to the participant's consent. The investigator, or a person designated by the investigator, should fully inform the participant or his/her legally acceptable representative of all pertinent aspects of the study and of any new information relevant to the participant's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify participants must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the participant's signed ICF, and, in the US, the participant's signed HIPAA Authorization.

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

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

If informed consent is initially given by a participant's legally acceptable representative or legal guardian and the participant subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the participant.

For minors, according to local legislation, one or both parents or a legally acceptable representative must be informed of the study procedures and must sign the ICF approved for the study prior to clinical study participation. The explicit wish of a minor, who is capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the clinical study at any time, should be considered by the investigator.

Minors who are judged to be of an age of reason must also give their written consent. Minors who reach the age of majority (legal adulthood) during the clinical trial must give their written consent.

Participant unable to give their written informed consent (eg, stroke or participants with severe dementia) may only be enrolled in the study with the consent of a legally acceptable representative. The participant must also be informed about the nature of the study to the extent compatible with his or her understanding, and should this participant become capable, he or she should personally sign and date the ICF as soon as possible. The explicit wish of a participant who is unable to give his or her written consent, but who is capable of forming an opinion and assessing information to refuse participation in, or to be withdrawn from, the clinical study at any time, should be considered by the investigator.

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

BMS COMMITMENT TO DIVERSITY IN CLINICAL TRIALS

The mission of BMS is to transform patients' lives through science by discovering, developing, and delivering innovative medicines that help them prevail over serious diseases.

BMS is committed to doing its part to ensure that patients have a fair and just opportunity to achieve optimal health outcomes.

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

DATA PROTECTION, DATA PRIVACY, AND DATA SECURITY

BMS collects and processes personal data of study participants, patients, health care providers, and researchers for biopharmaceutical research and development to advance innovative, high-quality medicines that address the medical needs of patients. BMS ensures the privacy, protection, and confidentiality of such personal data to comply with applicable laws. To achieve these goals, BMS has internal policies that indicate measures and controls for processing personal data. BMS adheres to these standards to ensure that collection and processing of personal data are limited and

proportionate to the purpose for which BMS collects such personal data. This purpose is clearly and unambiguously notified to the individual at the time of collection of personal data. In the true spirit of science, BMS is dedicated to sharing clinical trial information and data with participants, medical/research communities, the media, policy makers, and the general public. This is done in a manner that safeguards participant privacy and informed consent while respecting the integrity of national regulatory systems. Clinical trial data, health-related research, and pharmacovigilance activities on key-coded health data transferred by BMS across national borders is done in compliance with the relevant data protection laws in the country and GCP requirements.

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

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

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

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

SOURCE DOCUMENTS

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

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

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

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

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

STUDY INTERVENTION RECORDS

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

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

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

CASE REPORT FORMS

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents, or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

For sites using the Sponsor or designee electronic data capture (EDC) tool, eCRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be

reported on the electronic SAE form and Pregnancy Surveillance Form, respectively. If the electronic SAE form is not available, a paper SAE form can be used. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by the Sponsor or designee.

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

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

The completed CRF and SAE/pregnancy CRFs must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a sub-investigator and who is delegated this task on the Delegation of Authority Form. Sub-investigators in Japan may not be delegated the CRF approval task. For eCRFs, 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 eCRFs must meet Sponsor or designee training requirements and must only access the BMS EDC tool using the unique user account provided by the Sponsor or designee. User accounts are not to be shared or reassigned to other individuals.

MONITORING

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

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

Certain CRF pages and/or electronic files may serve as the source documents.

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

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities and promptly forward copies of inspection reports to the Sponsor or designee.

RECORDS RETENTION

The investigator (or head of the study site in Japan) must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS or its designee, whichever is longer.

The investigator (or head of the study site in Japan) must contact BMS prior to destroying any records associated with the study.

BMS or its designee will notify the investigator (or head of the study site in Japan) when the study records are no longer needed.

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

RETURN OF STUDY TREATMENT

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

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

It is the investigator's or designee's responsibility to arrange for disposal of study interventions, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The following minimal standards must be met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's standard operating procedures and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal (eg, incinerator, licensed sanitary landfill, or licensed waste-disposal vendor) must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Study Monitor to review throughout the clinical trial period.

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

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

STUDY AND SITE START AND CLOSURE

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

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

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

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

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

DISSEMINATION OF CLINICAL STUDY DATA

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

CLINICAL STUDY REPORT

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

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

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

SCIENTIFIC PUBLICATIONS

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

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

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

1) Substantial intellectual contribution to the conception or design of the work; or the acquisition of data (ie, evaluable participants with quality data), analysis, or interpretation of data for the work (eg, problem solving, advice, evaluation, insights and conclusion); AND
2) Drafting the work or revising it critically for important intellectual content; AND

3) Final approval of the version to be published; AND
4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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

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

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

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

ADVERSE EVENTS

Adverse Event Definition:

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

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

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or results from other safety assessments (eg, electrocardiograms, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Note that abnormal lab tests or other safety assessments should only be reported as AEs if the final diagnosis is not available. Once the final diagnosis is known, the reported term should be updated to be the diagnosis.
- Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration, even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose, as a verbatim term (as reported by the investigator), should not be reported as an AE/serious adverse event (SAE) unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae and should specify "intentional overdose" as the verbatim term.

Events NOT Meeting the AE Definition

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

DEFINITION OF SAE

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

SERIOUS ADVERSE EVENTS

A serious adverse event (SAE) is defined as any untoward medical occurrence that, at any dose:
Results in death.
Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
Requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below). NOTE: The following hospitalizations are not considered SAEs in Bristol-Myers Squibb (BMS) clinical studies: • A visit to the emergency room or other hospital department < 24 hours that does not result in admission (unless considered an important medical or life-threatening event). • Elective surgery, planned prior to signing consent. • Admissions as per protocol for a planned medical/surgical procedure. • Routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy). • Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases. • Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason). • Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols).
Results in persistent or significant disability/incapacity.
Is a congenital anomaly/birth defect.
Is an important medical event (defined as a medical event[s] that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm and blood dyscrasias or convulsions that do not result in hospitalization. Potential drug-induced liver injury (DILI) is also considered an important medical event. (See Section 9.2.7 for the definition of potential DILI.)

Pregnancy and DILI must follow the same transmission timing and processes to BMS as used for SAEs. (See Section 9.2.6 for reporting pregnancies.)

EVALUATING AES AND SAES

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the Investigator's Brochure and/or product information for marketed products in his/her assessment.
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

- **Assessment of Intensity or Severity**

The NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 is a descriptive terminology which can be utilized for AE reporting. A grading (severity) scale is provided for each AE term. The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL*.
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE

Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the

telephone, managing money, etc.

**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event, and both AEs and SAEs can be assessed as severe.

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

Follow-up of AEs and SAEs

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

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

All SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

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

SAE Email Address: worldwide.safety@BMS.com

SAE Facsimile Number: Refer to Contact Information List.

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

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

Appendix 4 provides general information and definitions related to Woman of Childbearing Potential and methods of contraception that can be applied to most clinical trials. For information specific to this study regarding acceptable contraception requirements for female and male participants, refer to Section 6.1 of the protocol. Only the contraception methods as described in Section 6.1 are acceptable for this study.

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP:

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

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

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

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

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

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

End of Relevant Systemic Exposure

End of relevant systemic exposure is the timepoint where the Investigational Medicinal Product (IMP) or any active major metabolites have decreased to a concentration that is no longer considered to be relevant for human teratogenicity or fetotoxicity. This should be evaluated in context of safety margins from the no-observed-adverse-effect level or the time required for 5 half-lives of the IMP to pass.

METHODS OF CONTRACEPTION

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

Note: Hormone-based contraceptives are <u>not</u> considered highly effective methods of contraception for WOCBP participants treated with BMS-986205.

Highly Effective Contraceptive Methods That Are <u>User Dependent</u> *Failure rate of < 1% per year when used consistently and correctly.*[a]
• **Not in BMS-986205 treated participants:** Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation and/or implantation. (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol.)[b] – Oral (birth control pills) – Intravaginal (rings) – Transdermal • **Not in BMS-986205 treated participants:** Combined (estrogen-and progestogen-containing) hormonal contraception must begin at least 30 days prior to initiation of study therapy.
• **Not in BMS-986205 treated participants:** Progestogen-only hormonal contraception associated with inhibition of ovulation. (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol.)[b] – Oral – Injectable • **Not in BMS-986205 treated participants:** Progestogen-only hormonal contraception must begin at least 30 days prior to initiation of study therapy.

Highly Effective Methods That Are User Independent
• **Not in BMS-986205 treated participants:** Implantable progestogen-only hormonal contraception associated with inhibition of ovulation and/or implantation. (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol.)[b] • Intrauterine device. • **Not in BMS-986205 treated participants:** Intrauterine hormone-releasing system (IUS). (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol.)[b,c] • Bilateral tubal occlusion.
• Vasectomized partner Having a vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. **For BMS-986205 treated participants:** Male participants will be required to always use a latex or other synthetic condom during any sexual activity (eg, vaginal, anal, oral) with WOCBP, even if the participants have undergone a successful vasectomy or if their partner is already pregnant or breastfeeding.
• Sexual abstinence. *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.* • Continuous abstinence must begin at least 30 days prior to initiation of study therapy. • It is not necessary to use any other method of contraception when complete abstinence is elected. • WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2. • Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participant chooses to forego complete abstinence. • Periodic abstinence (including, but not limited to, calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception for this study.

NOTES:

[a] Typical use failure rates may differ from failure rates when contraceptive methods are used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

[b] Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized. For information specific to this study regarding permissibility of hormonal contraception, refer to Sections 6.1 INCLUSION CRITERIA and 7.7.1 PROHIBITED AND/OR RESTRICTED TREATMENTS of the protocol.

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

Less Than Highly Effective Contraceptive Methods That Are User Dependent

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

- Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously.
- Diaphragm with spermicide.
- Cervical cap with spermicide.
- Vaginal sponge with spermicide.
- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action. (This method of contraception cannot be used by WOCBP participants in studies where hormonal contraception is prohibited.)

Unacceptable Methods of Contraception

- Periodic abstinence (calendar, symptothermal, postovulation methods).
- Withdrawal (coitus interruptus).
- Spermicide only.
- LAM.

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of pregnancy information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 9.2.6 and Appendix 3.

APPENDIX 5 MANAGEMENT ALGORITHMS FOR STUDIES UNDER CTCAE VERSION 5.0

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

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

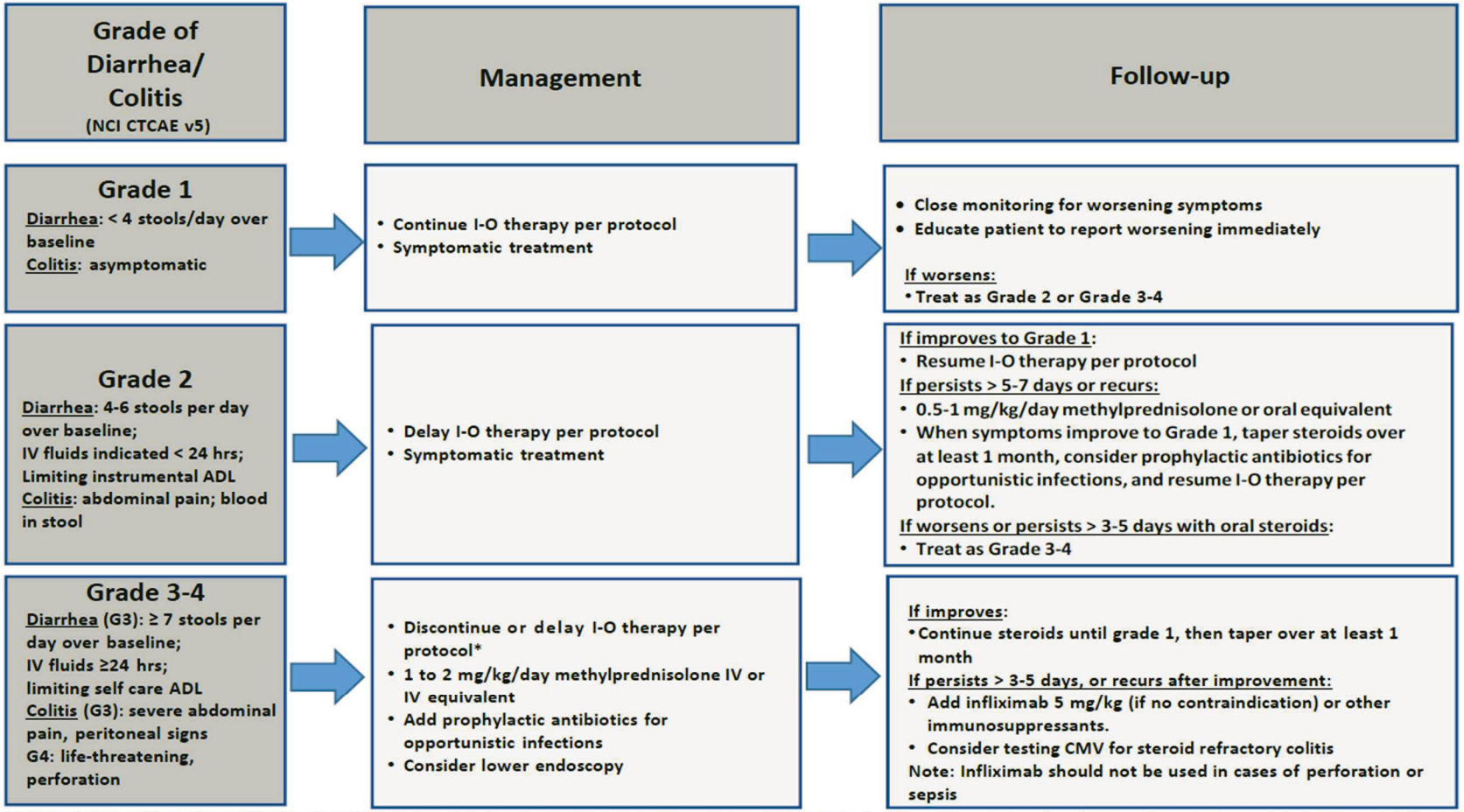
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the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

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or 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.



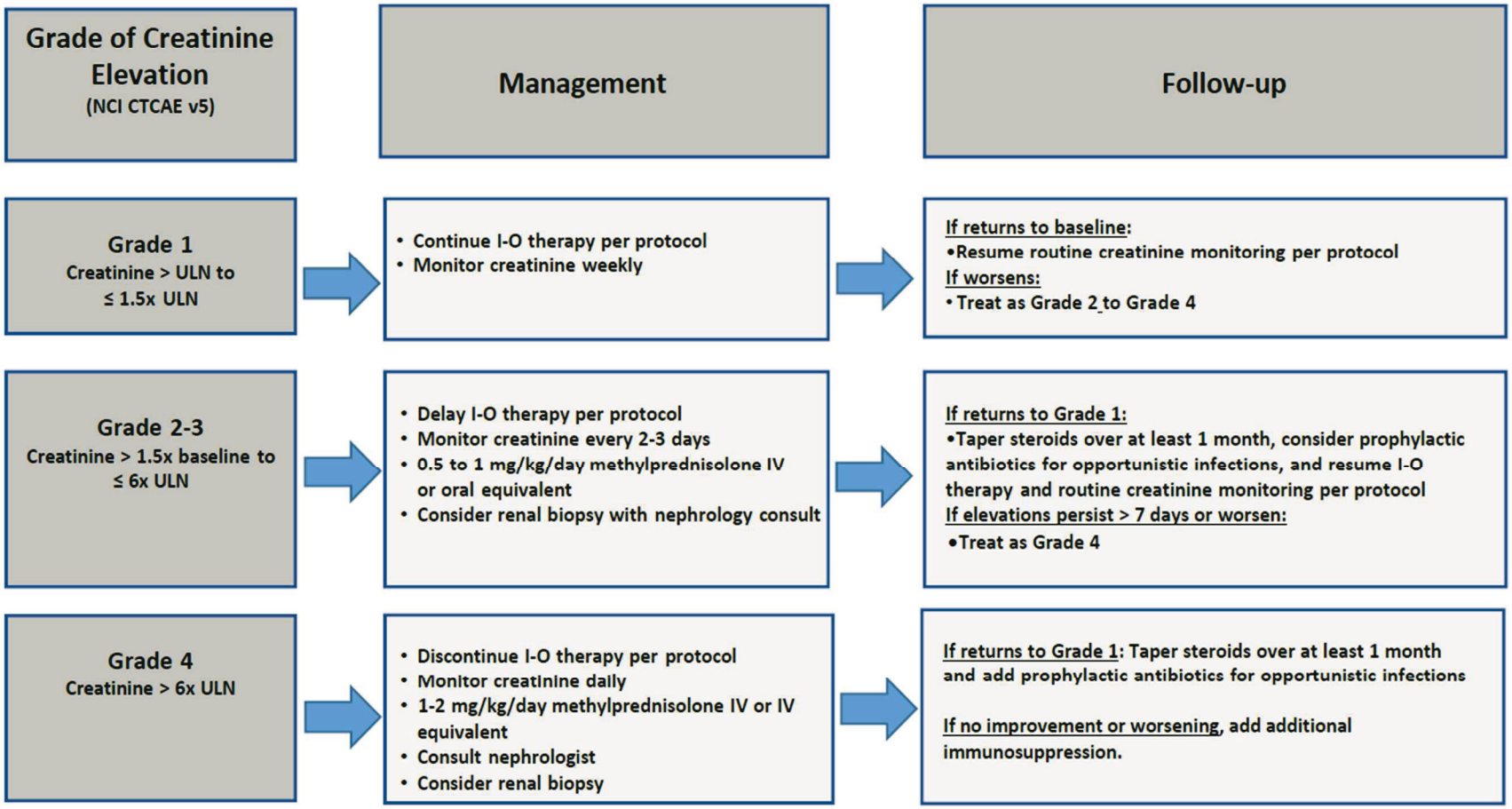
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

28-Sep-2020

Renal Adverse Event Management Algorithm

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

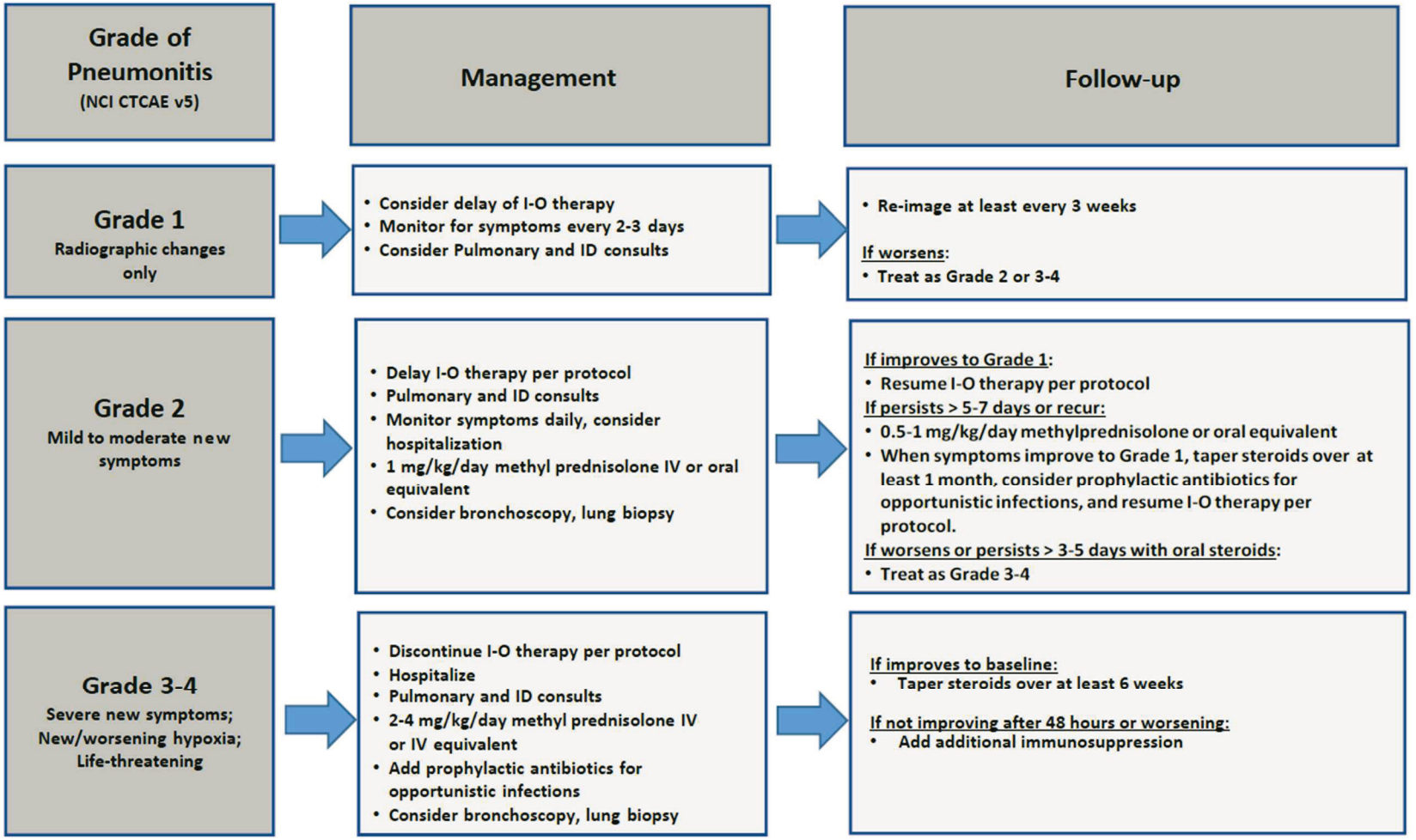


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

28-Sep-2020

Pulmonary Adverse Event Management Algorithm

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

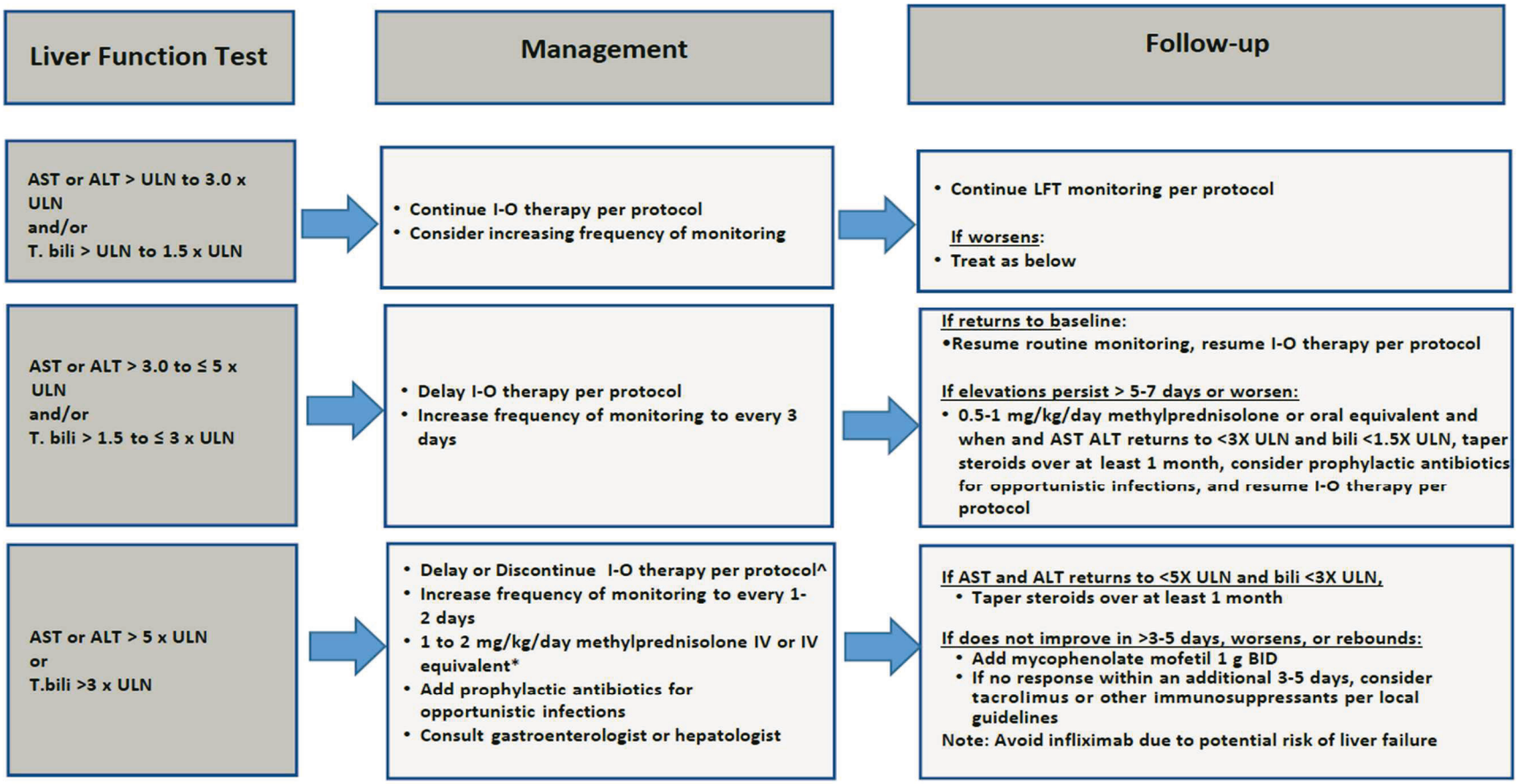


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

28-Sep-2020

Hepatic Adverse Event Management Algorithm

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

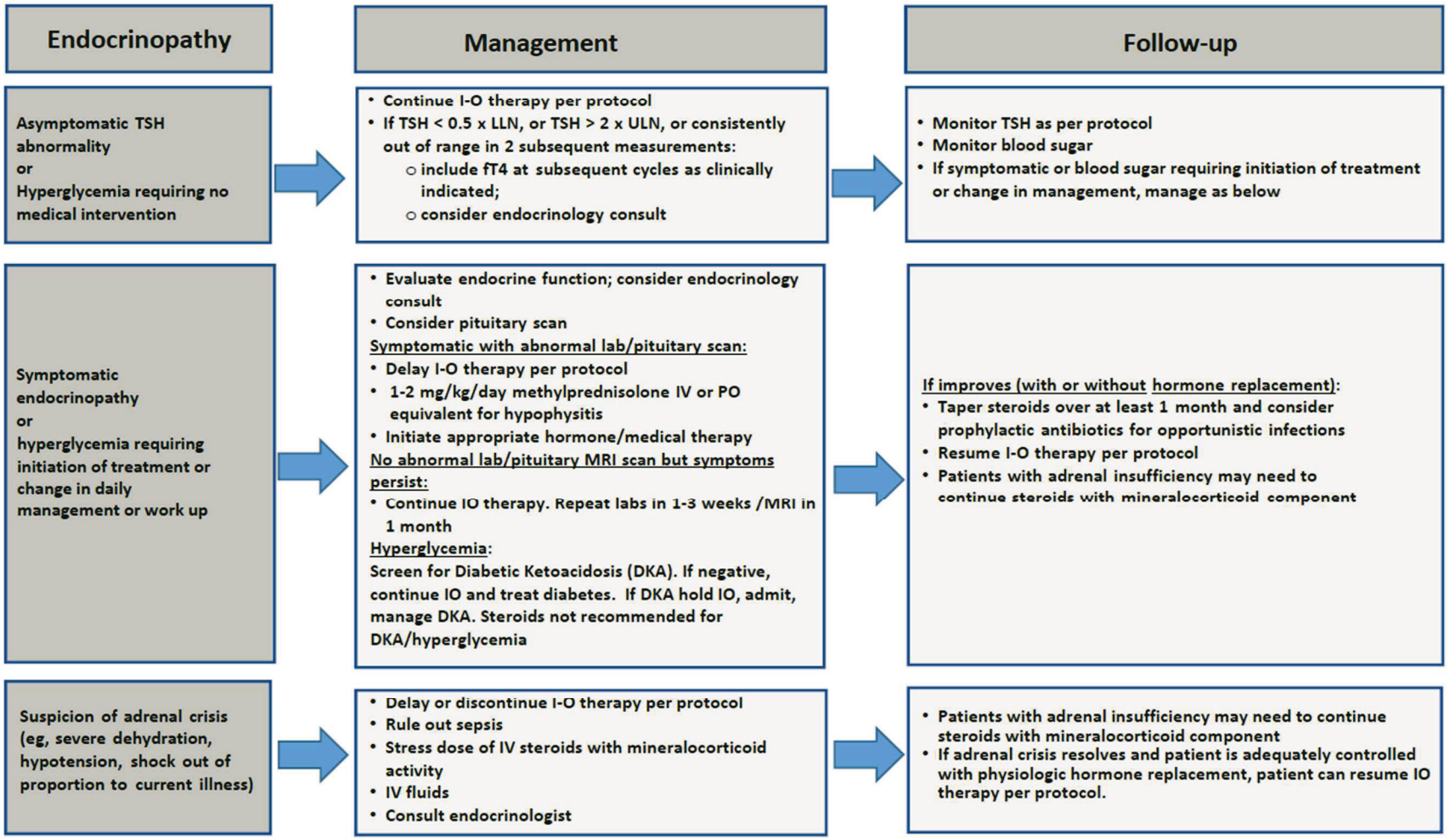


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

28-Sep-2020

Endocrinopathy Adverse Event Management Algorithm

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

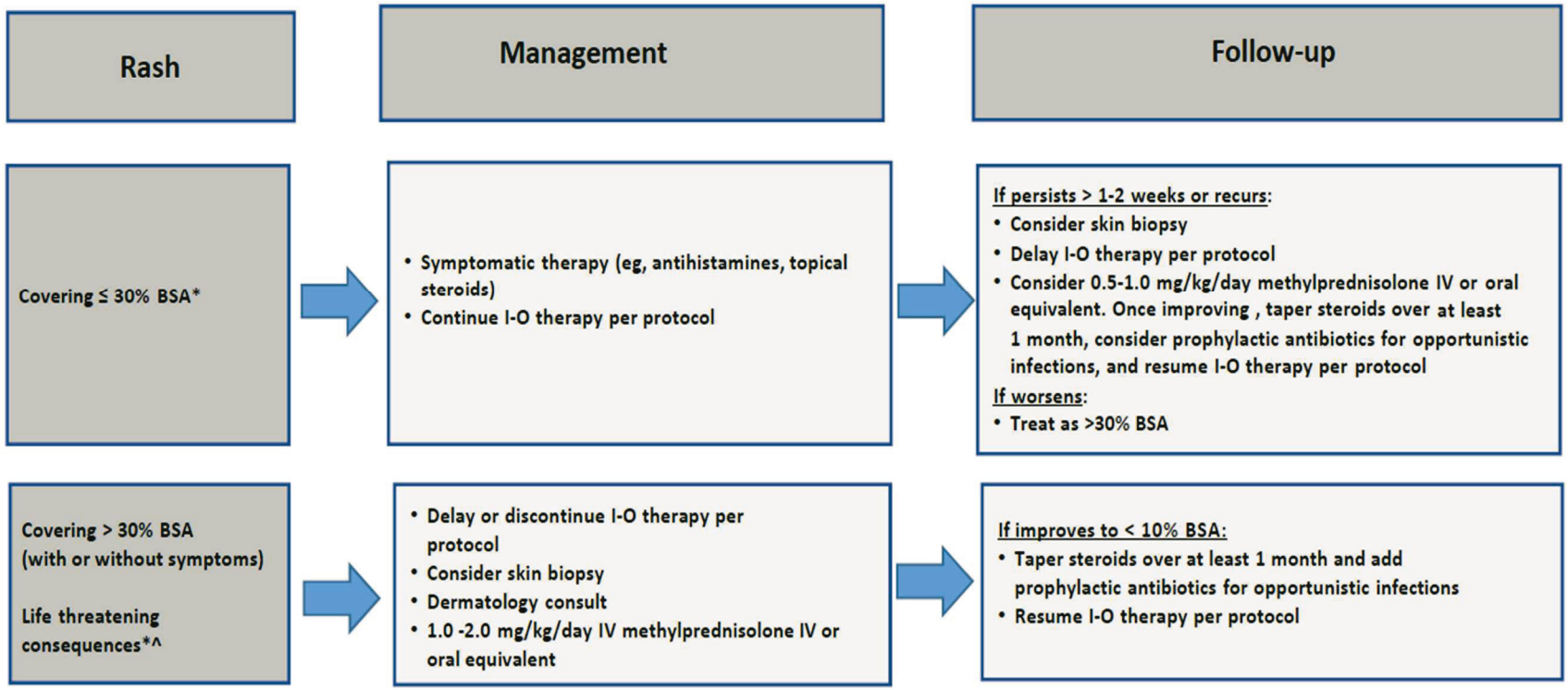


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

28-Sep-2020

Skin Adverse Event Management Algorithm

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



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

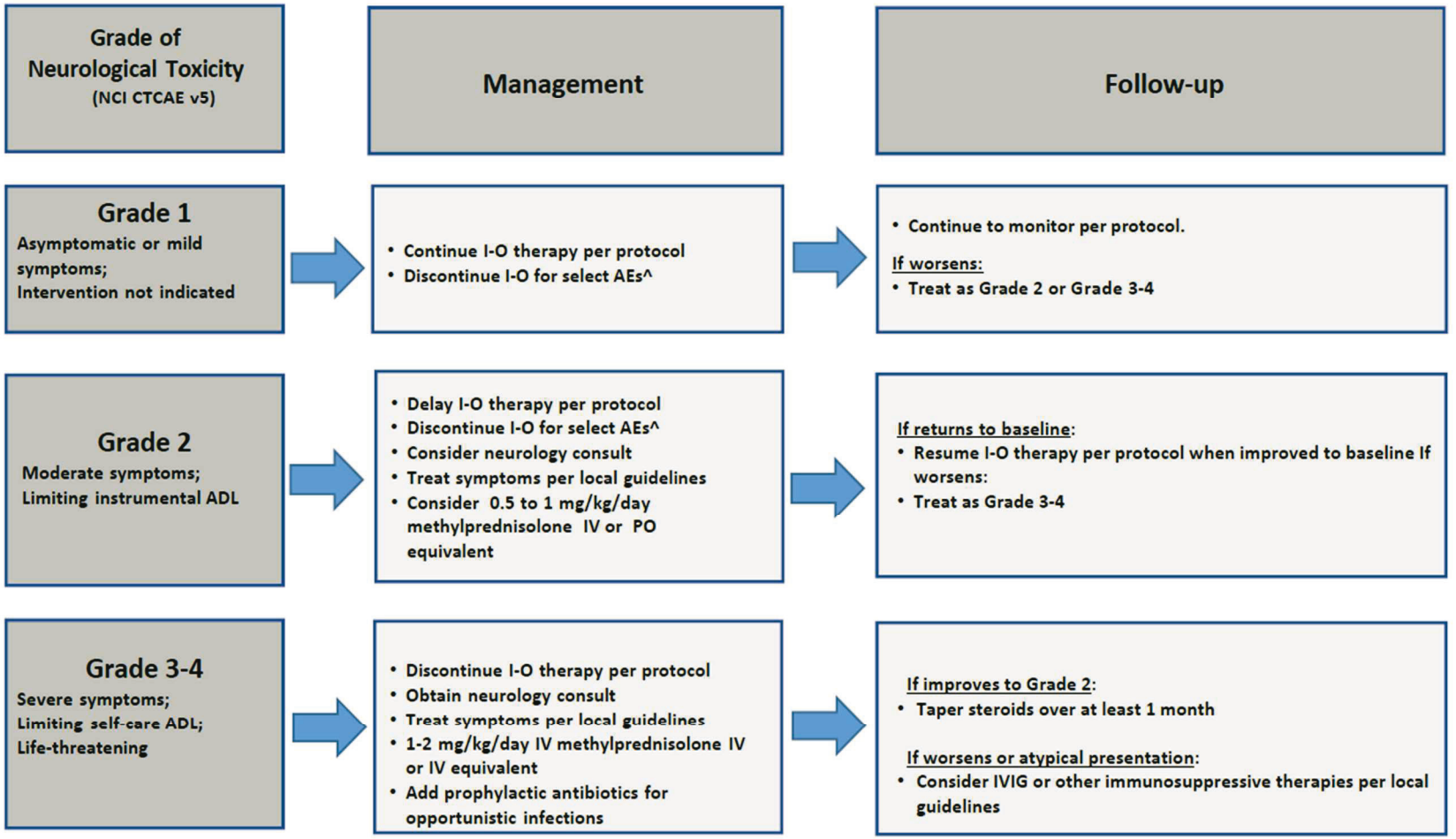
*Refer to NCI CTCAE v5 for term-specific grading criteria.

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

28-Sep-2020

Neurological Adverse Event Management Algorithm

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

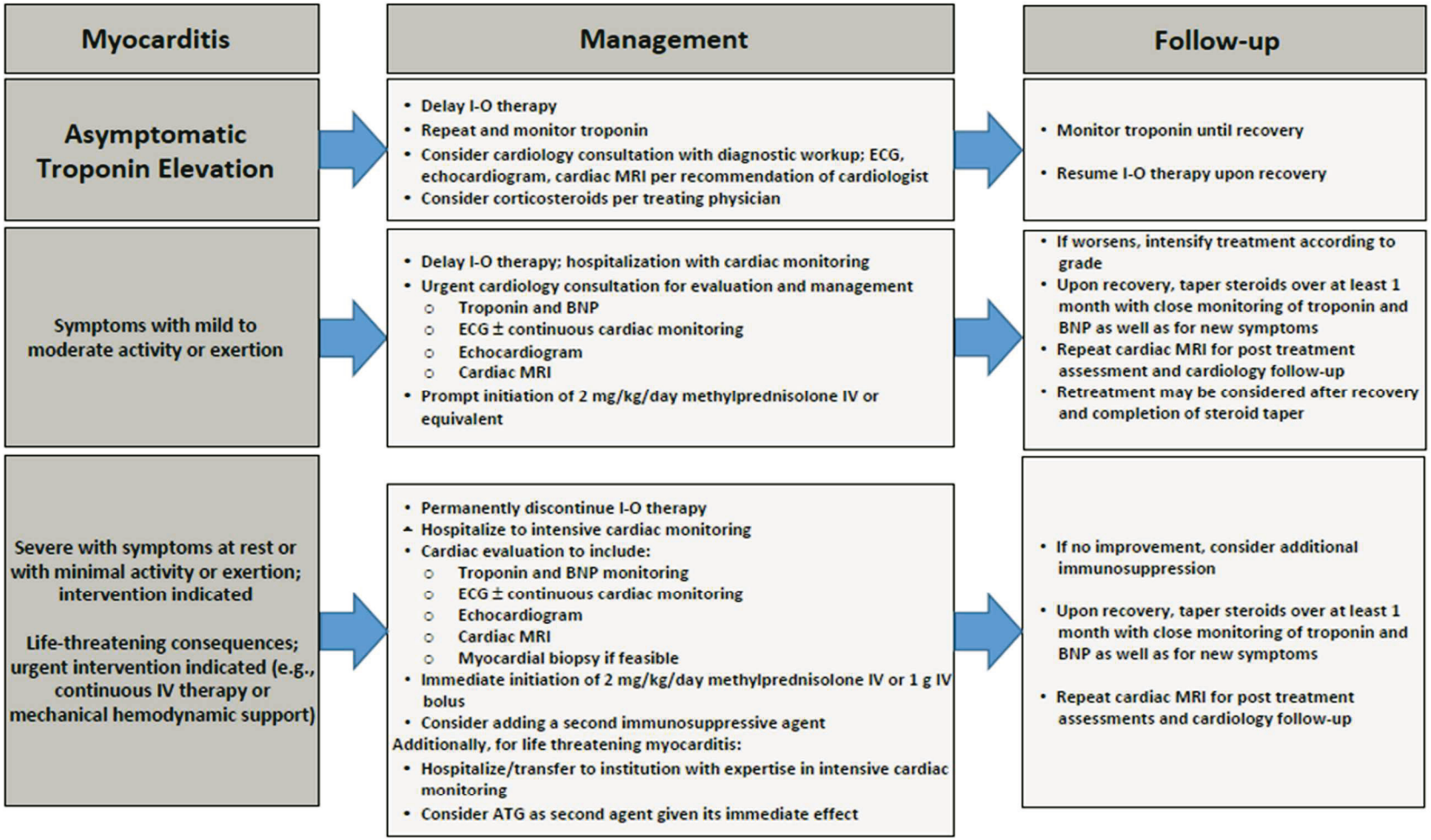


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

28-Sep-2020

Myocarditis Adverse Event Management Algorithm

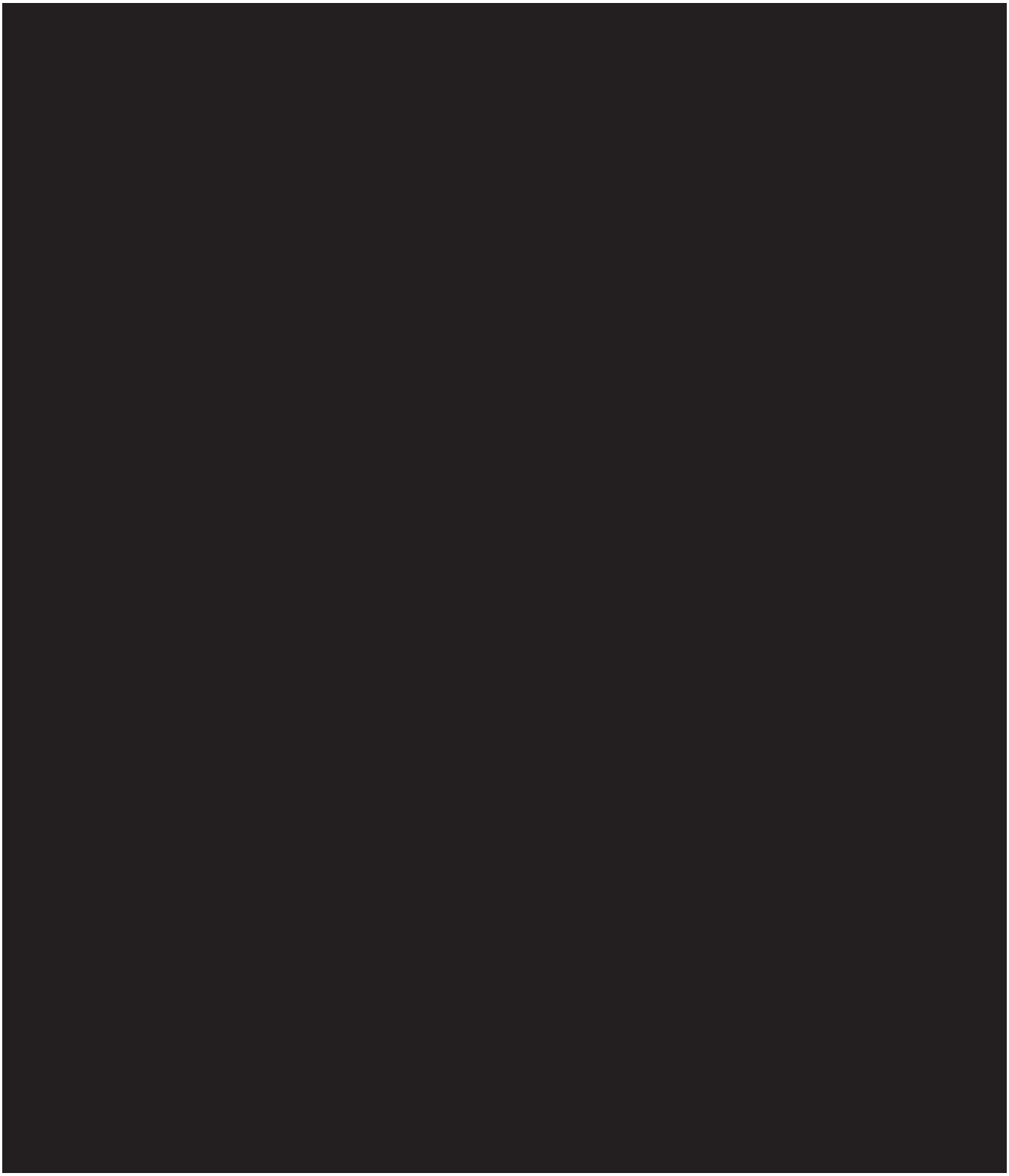


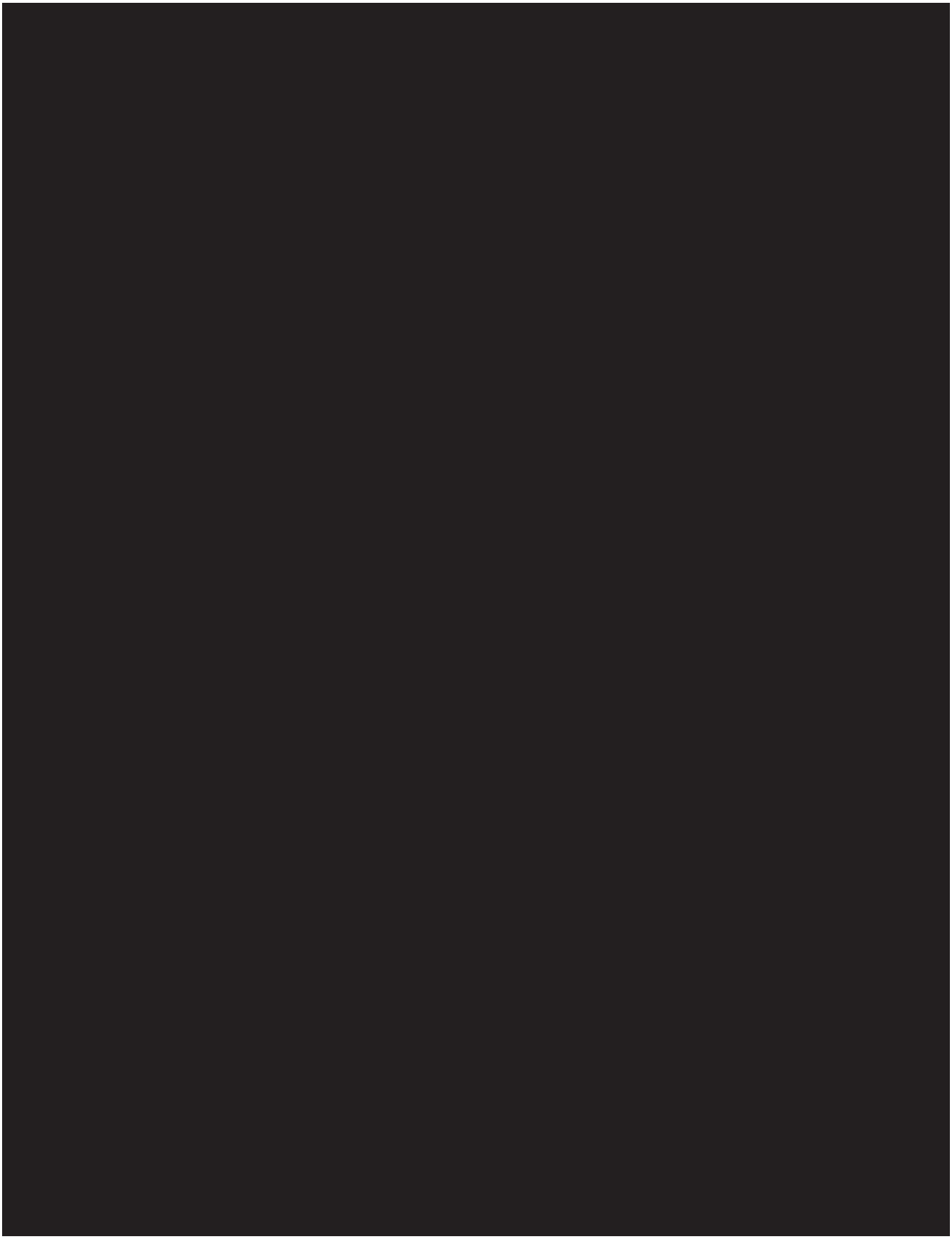
For the protocols under CTCAE version 5.0. Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids. Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.
ATG = anti-thymocyte globulin; BNP = B-type natriuretic peptide; ECG = electrocardiogram; IV = intravenous; MRI = magnetic resonance imaging

11-Sep-2020

APPENDIX 6 ECOG PERFORMANCE STATUS

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





APPENDIX 11 RESPONSE EVALUATION CRITERIA IN SOLID TUMORS GUIDELINES (VERSION 1.1) WITH BMS MODIFICATIONS

1 EVALUATION OF LESIONS

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

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

1.1 Measurable

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

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

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

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

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

1.2 Non-Measurable

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

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

1.3 Special considerations regarding lesion measurability

1.3.1 Bone lesions

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

1.4 Baseline DOCUMENTATION OF 'TARGET' AND 'NON-TARGET' LESIONS

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

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

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

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

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

2 RESPONSE CRITERIA

2.1 Evaluation of Target Lesions

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

2.1.1 Special Notes on the Assessment of Target Lesions

2.1.1.1 Lymph nodes

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

2.1.1.2 Target lesions that become 'too small to measure'

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

default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

2.1.1.3 Lesions that split or coalesce on treatment

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

2.2 Evaluation of Non-Target Lesions

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

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

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

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

2.2.1.1 When the patient also has measurable disease

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

2.2.1.2 When the patient has only non-measurable disease

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

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

2.2.2 New Lesions

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

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

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

1. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
2. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up

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

2.3 Response Assessment

2.3.1 Evaluation of Best Overall Response

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

2.3.2 Time Point Response

At each protocol specified time point, a response assessment occurs. Table 5 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline. When patients have non-measurable (therefore non-target) disease only, Table 6 is to be used.

Table 5: Time Point Response: Patients With Target (± Non-Target) Disease

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

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease and NE = inevaluable

Table 6: Time Point Response: Patients with Non-target Disease Only

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

Table 6: Time Point Response: Patients with Non-target Disease Only		
Non-Target Lesions	**New Lesions**	**Overall Response**
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD
CR = complete response, PD = progressive disease and NE = inevaluable		

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

2.3.3 Best Overall Response

Best response determination of complete or partial response requires confirmation: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point of ≥ 4 weeks (28 days) later. In this circumstance, the best overall response can be interpreted as in Table 7. When SD is believed to be best response, it must meet the protocol specified minimum time from the date of first treatment or randomization date.

For example, if the first scheduled follow-up imaging visit is Week 8 (± 7 days) for a particular protocol, a Best Response of SD can only be made after the subject is on-study for a minimum of 8 weeks (56 days) minus 7 days, for an absolute minimum time on-study of 49 days from the reference start date (reference date is considered Day 1 on study). If the subject is not on-study for at least this amount of time, any tumor assessment indicating stable disease before this time period will have a Best Response of NE unless PD is identified.

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

Table 7: Best Overall Response (Confirmation of CR and PR Required)		
Overall Response First Time Point	**Overall Response Subsequent Time Point**	**Best Overall Response**
CR	CR	CR
CR	PR	SD, PD OR PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE

Table 7:	Best Overall Response (Confirmation of CR and PR Required)	
Overall Response First Time Point	**Overall Response Subsequent Time Point**	**Best Overall Response**
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable

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

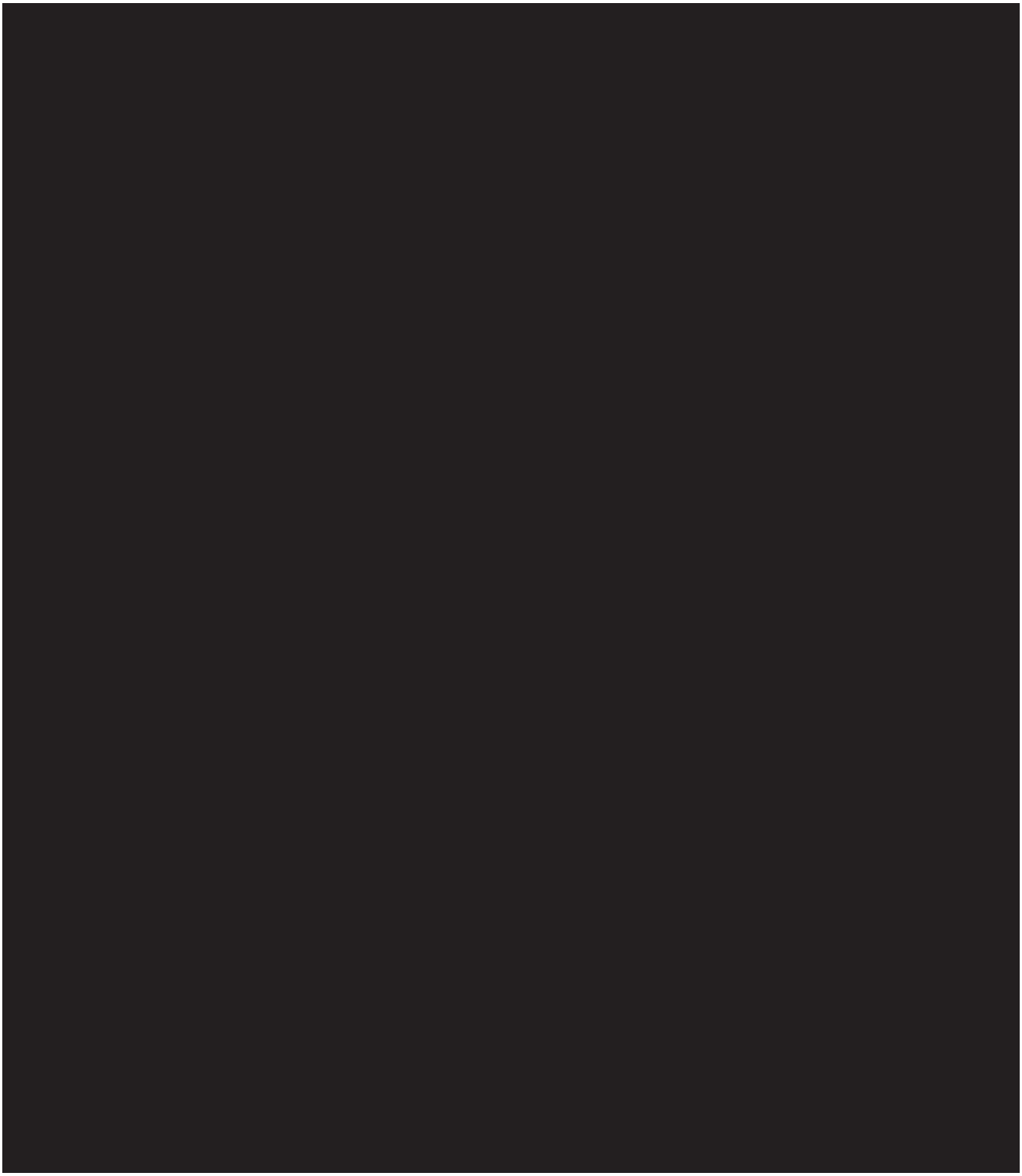
2.3.4 Confirmation Scans

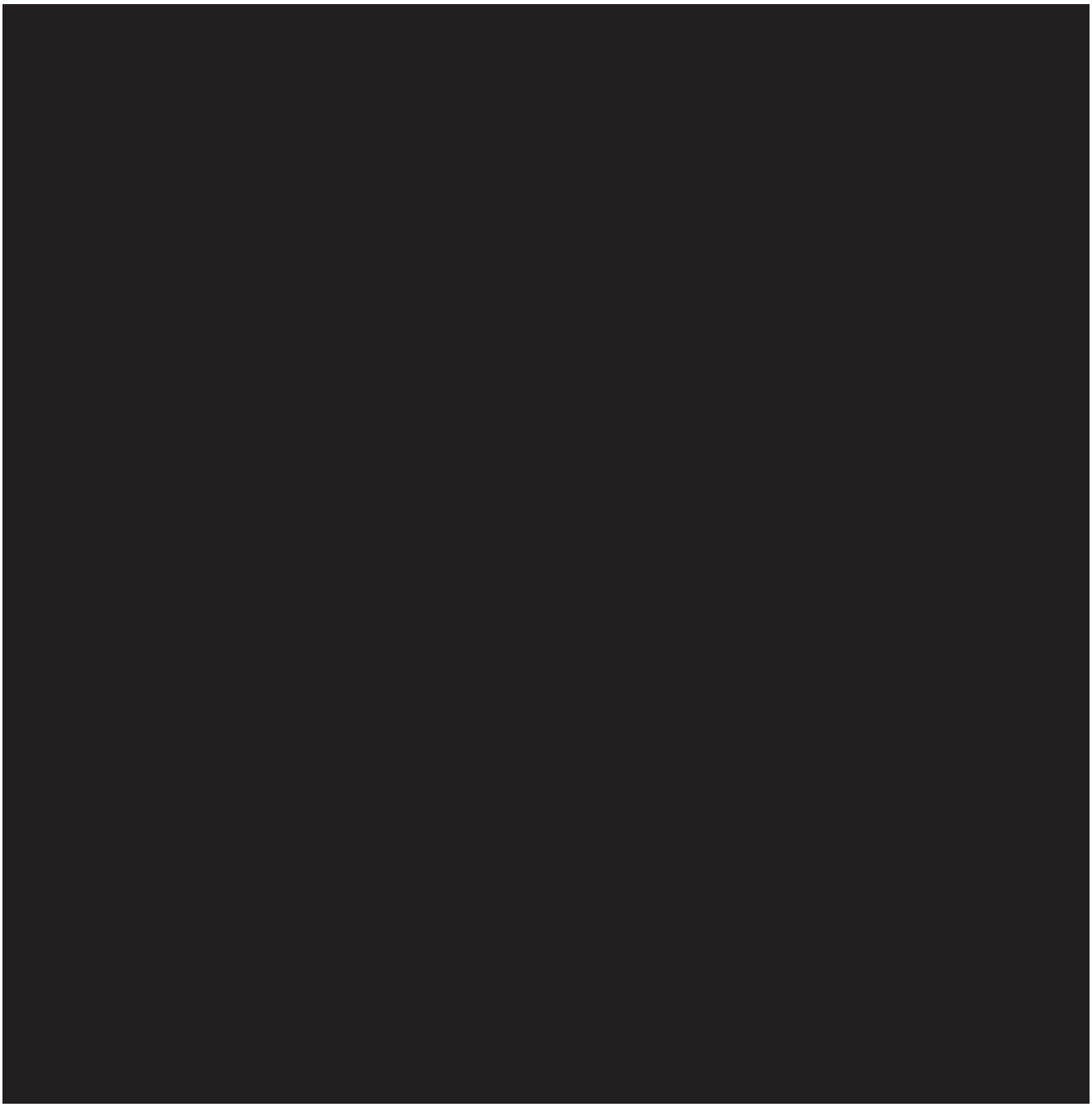
Verification of Response: To be assigned a status of CR or PR, changes in tumor measurements must be confirmed by consecutive or subsequent repeat assessments that should be performed no less than 28 days after the criteria for response are first met. Subsequent documentation of a CR may provide confirmation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

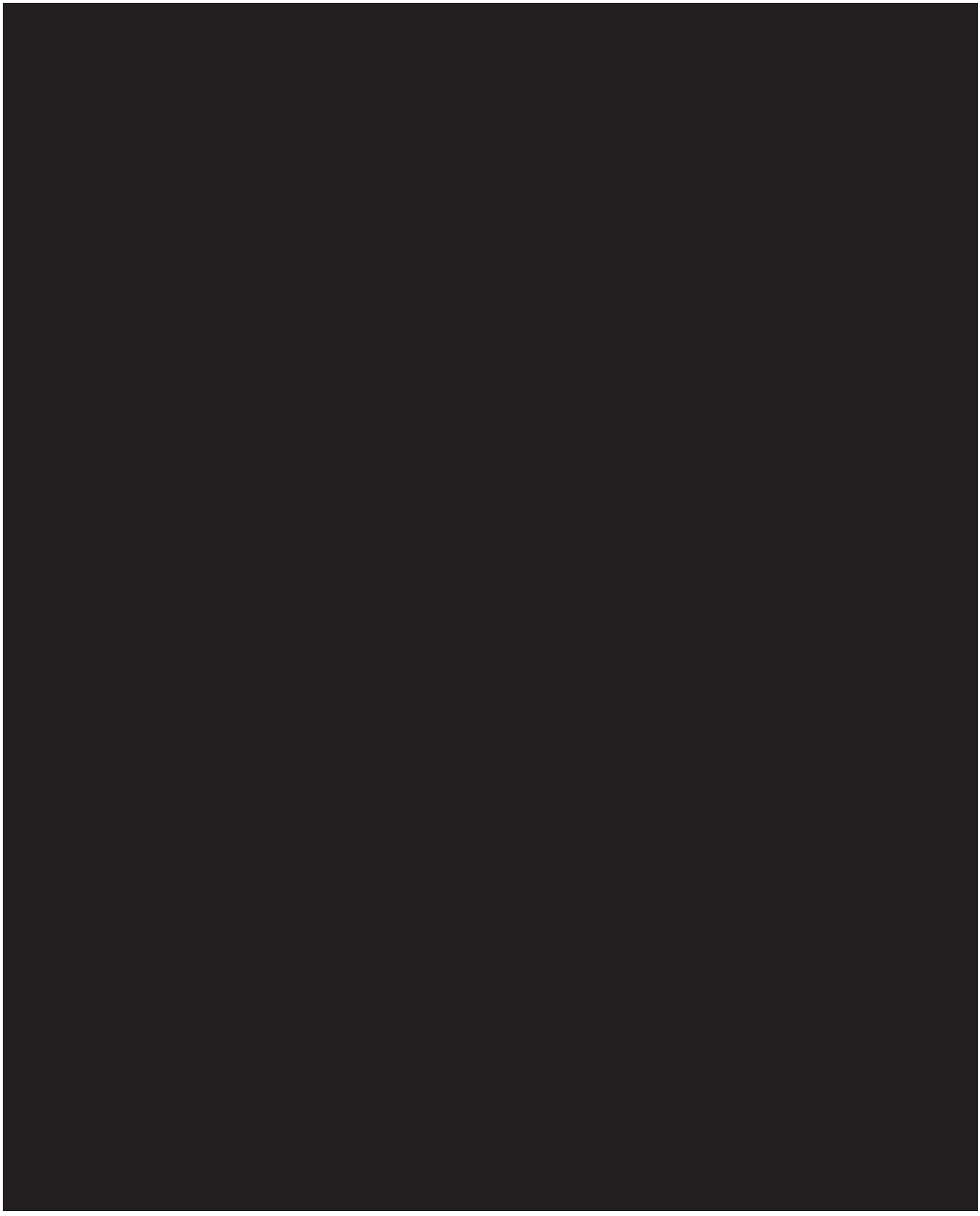
Verification of Progression: Progression of disease should be verified in cases where progression is equivocal. If repeat scans confirm PD, then progression should be declared using the date of the initial scan. If repeat scans do not confirm PD, then the subject is considered to not have progressive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

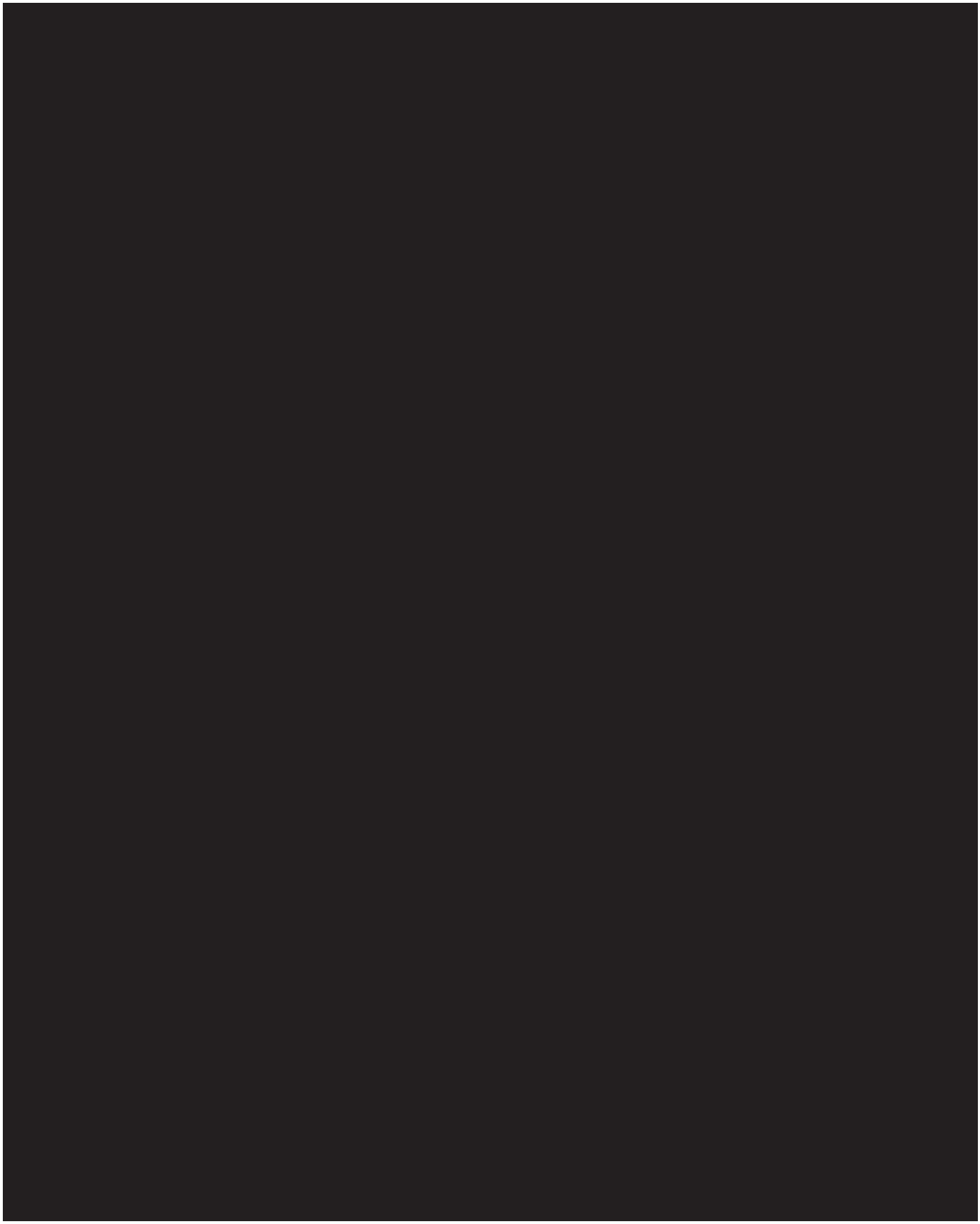
REFERENCE FOR APPENDIX 11

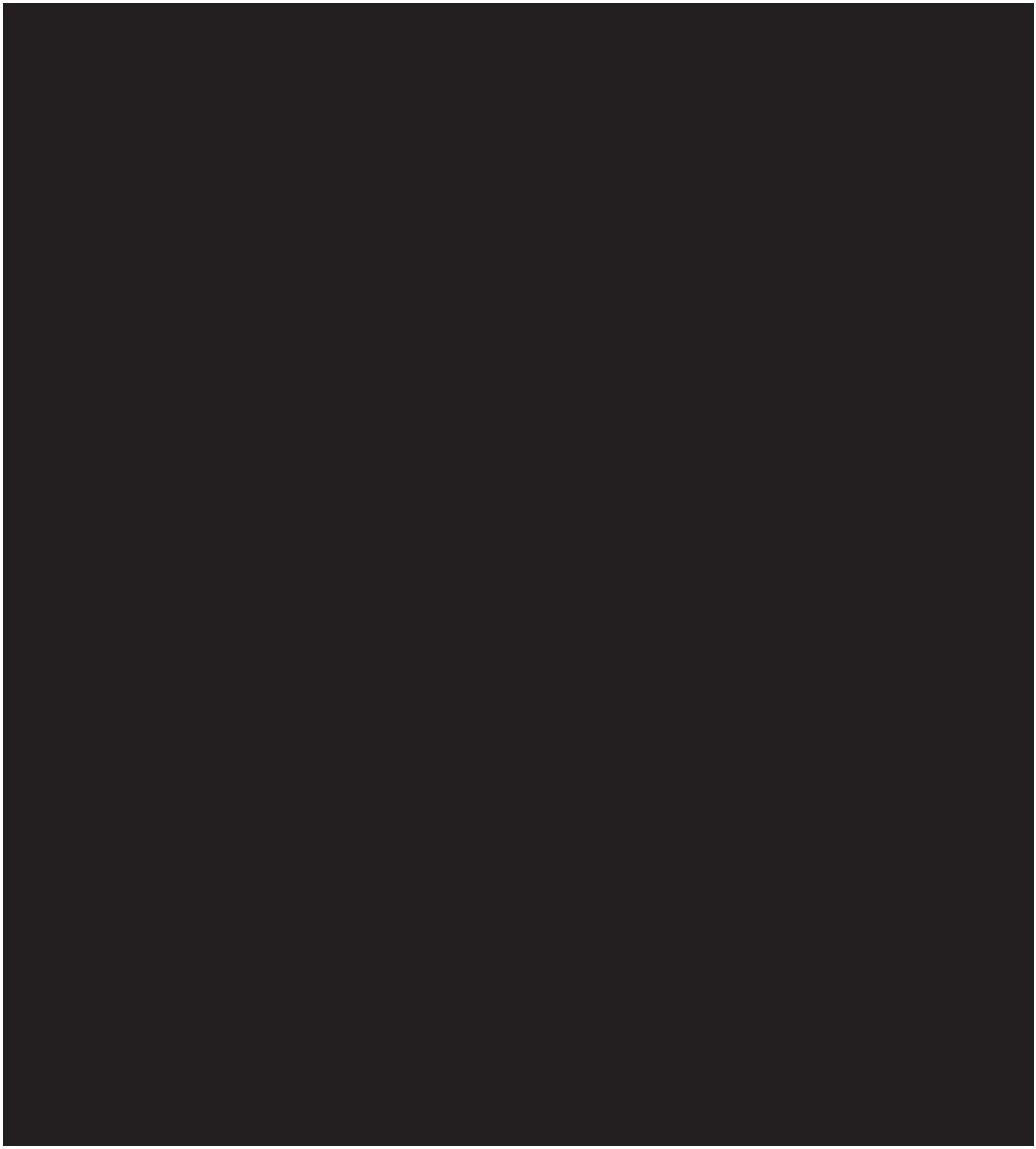
[1] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45: 228-47.

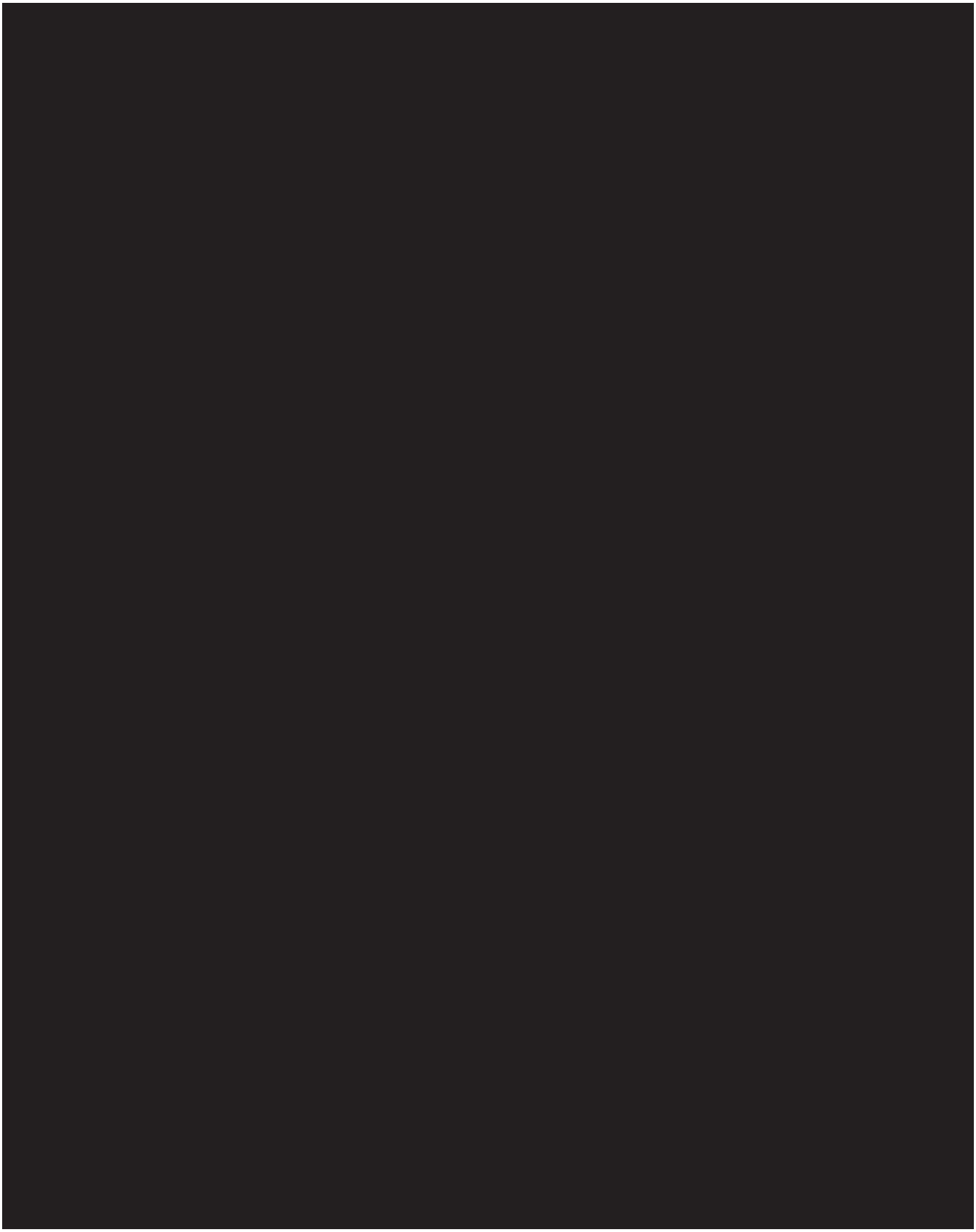


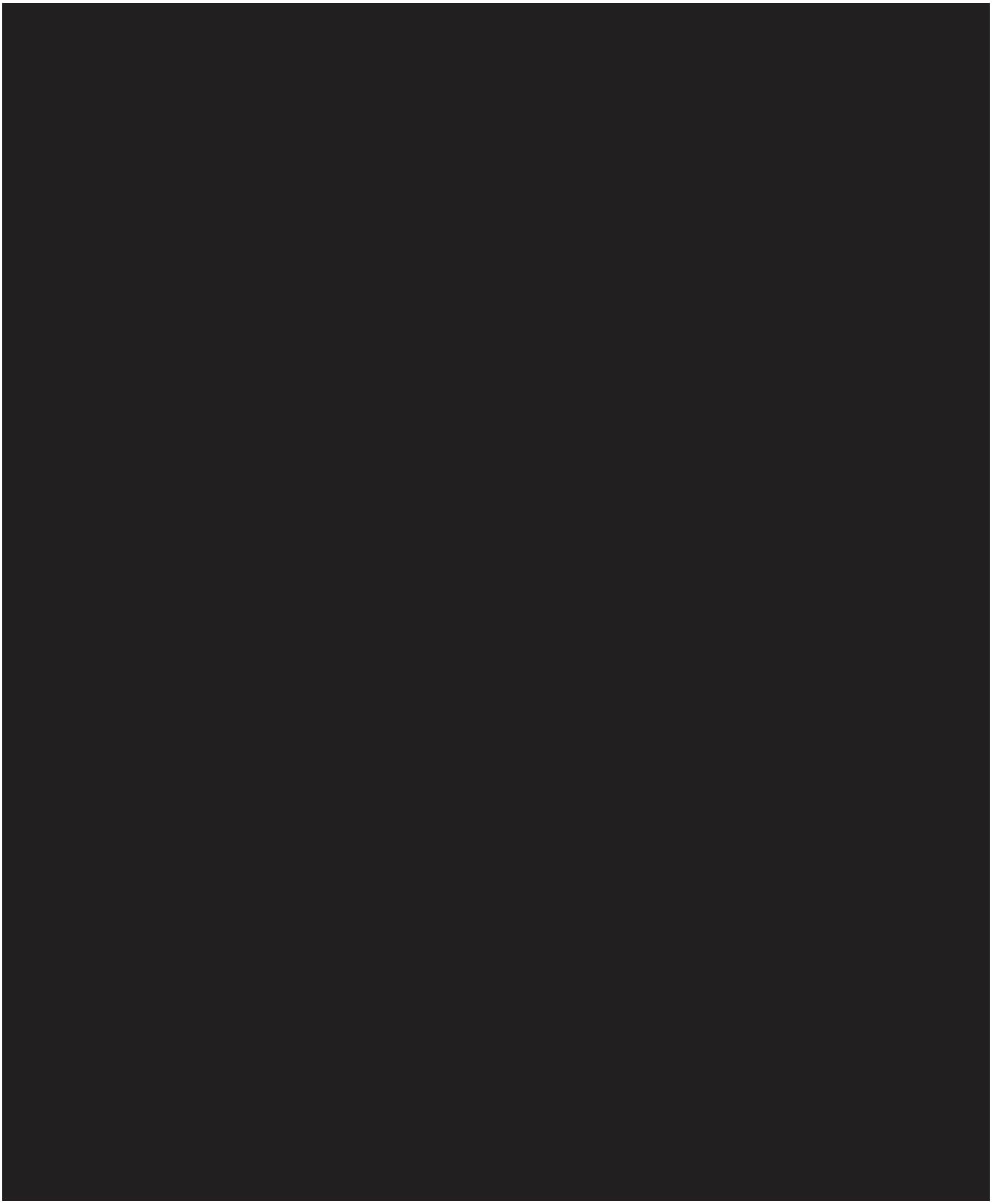


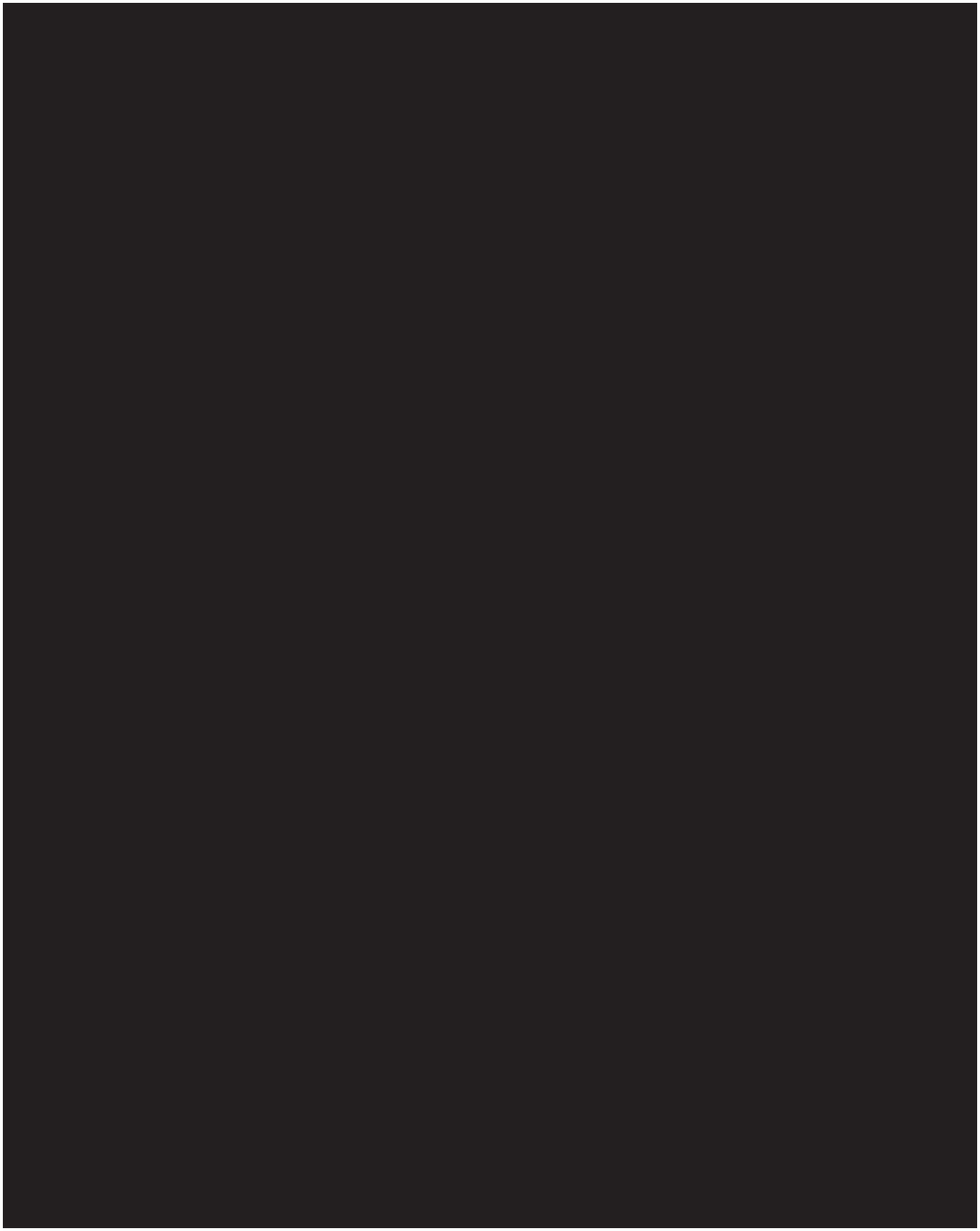


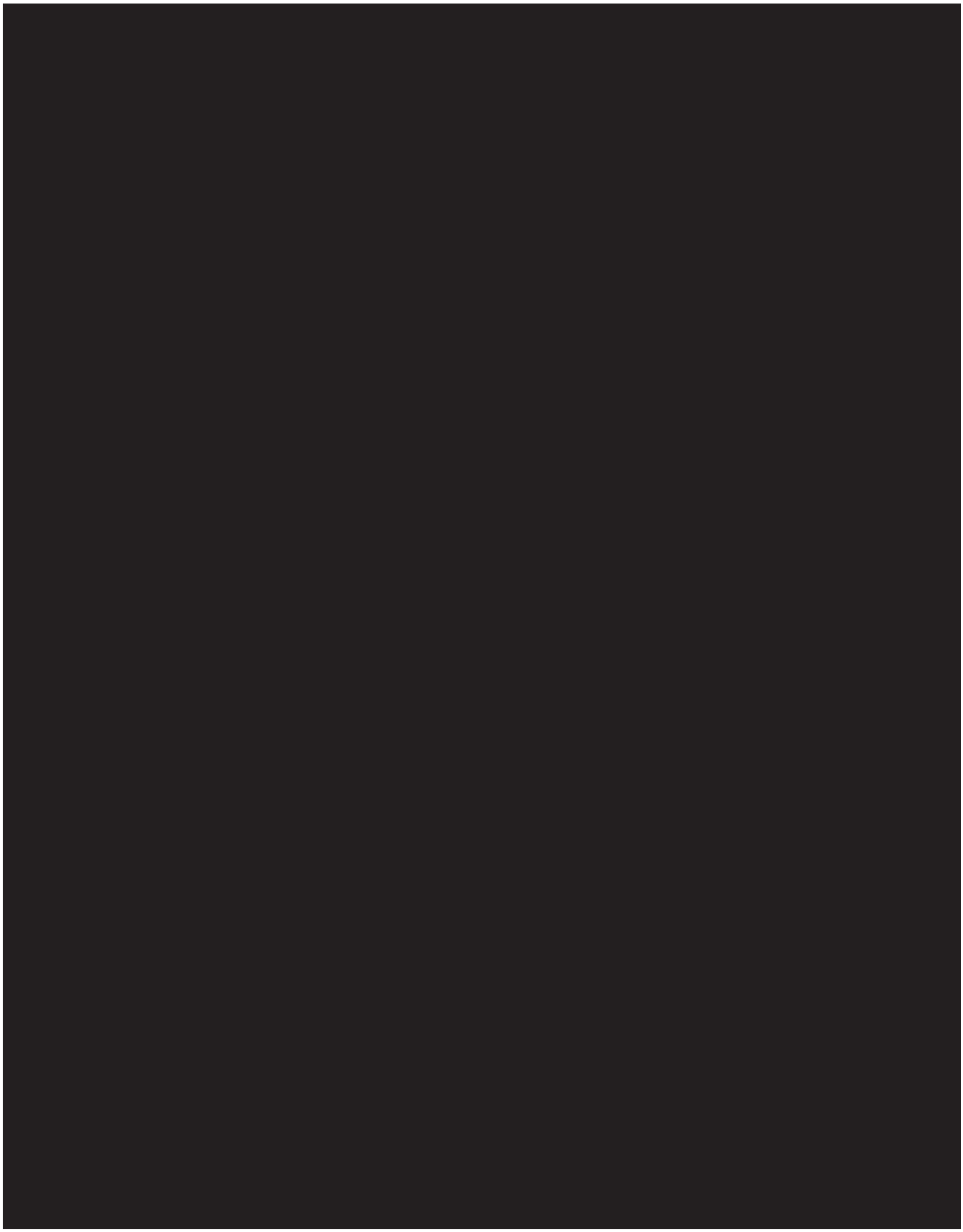


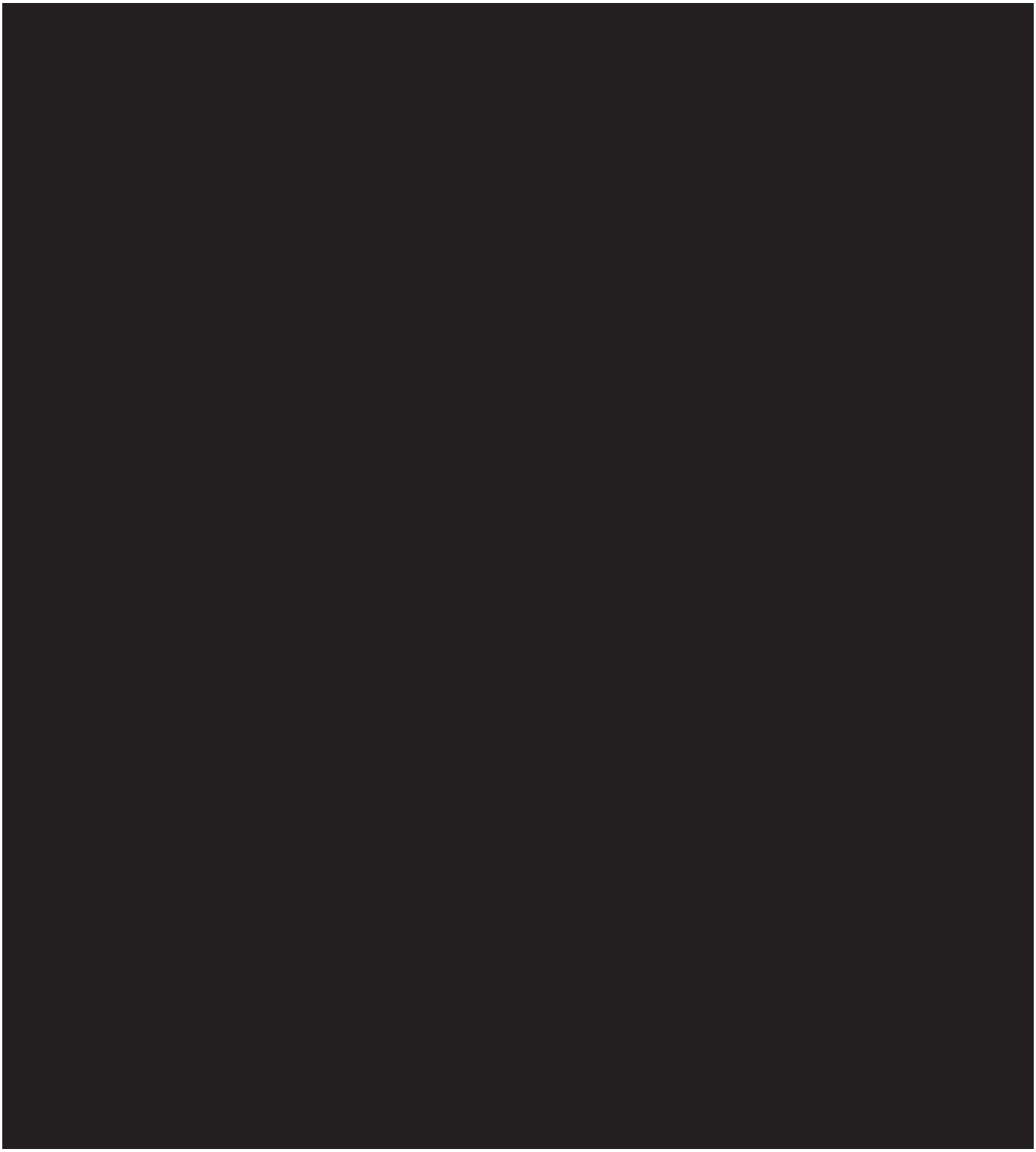


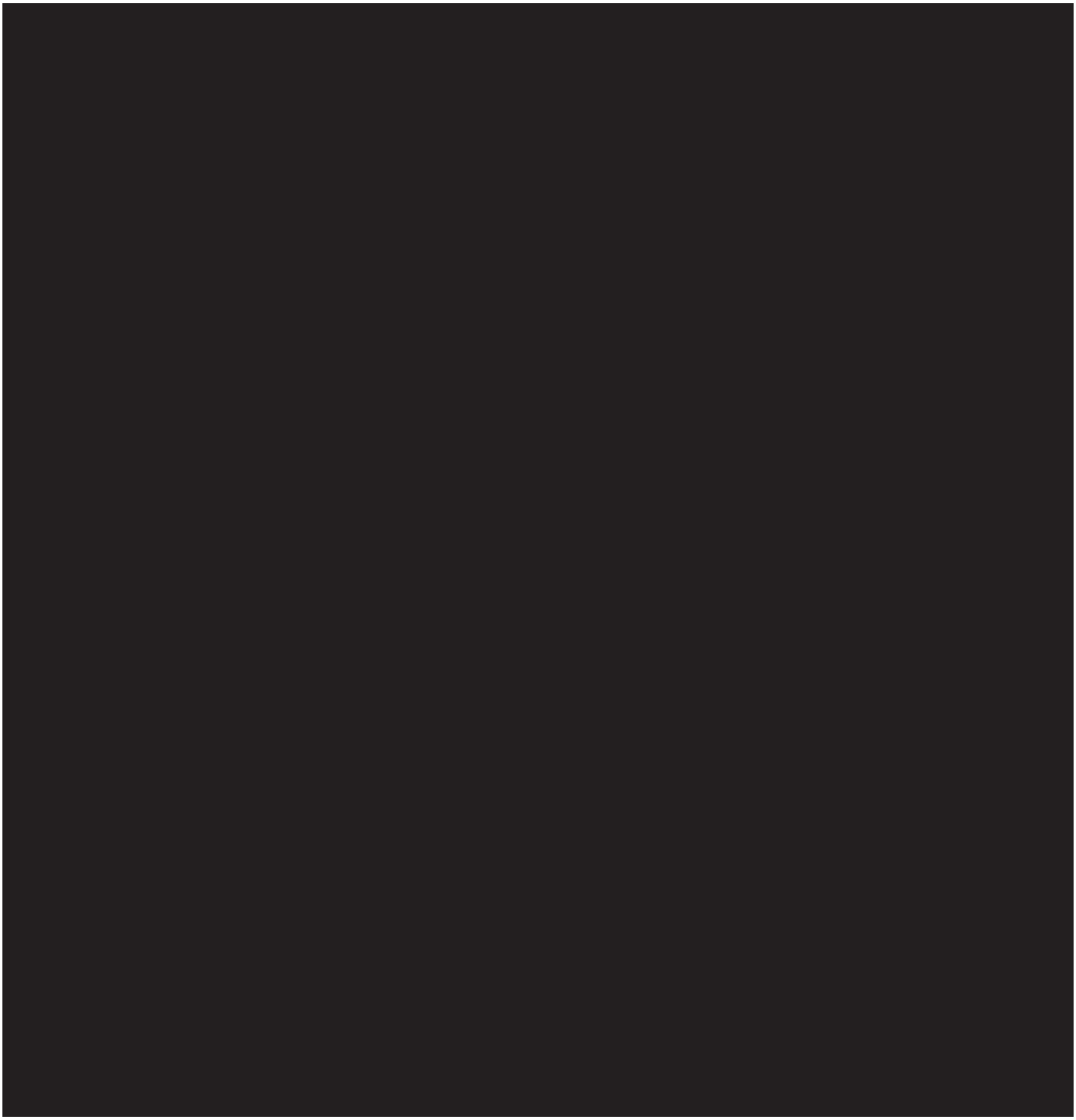


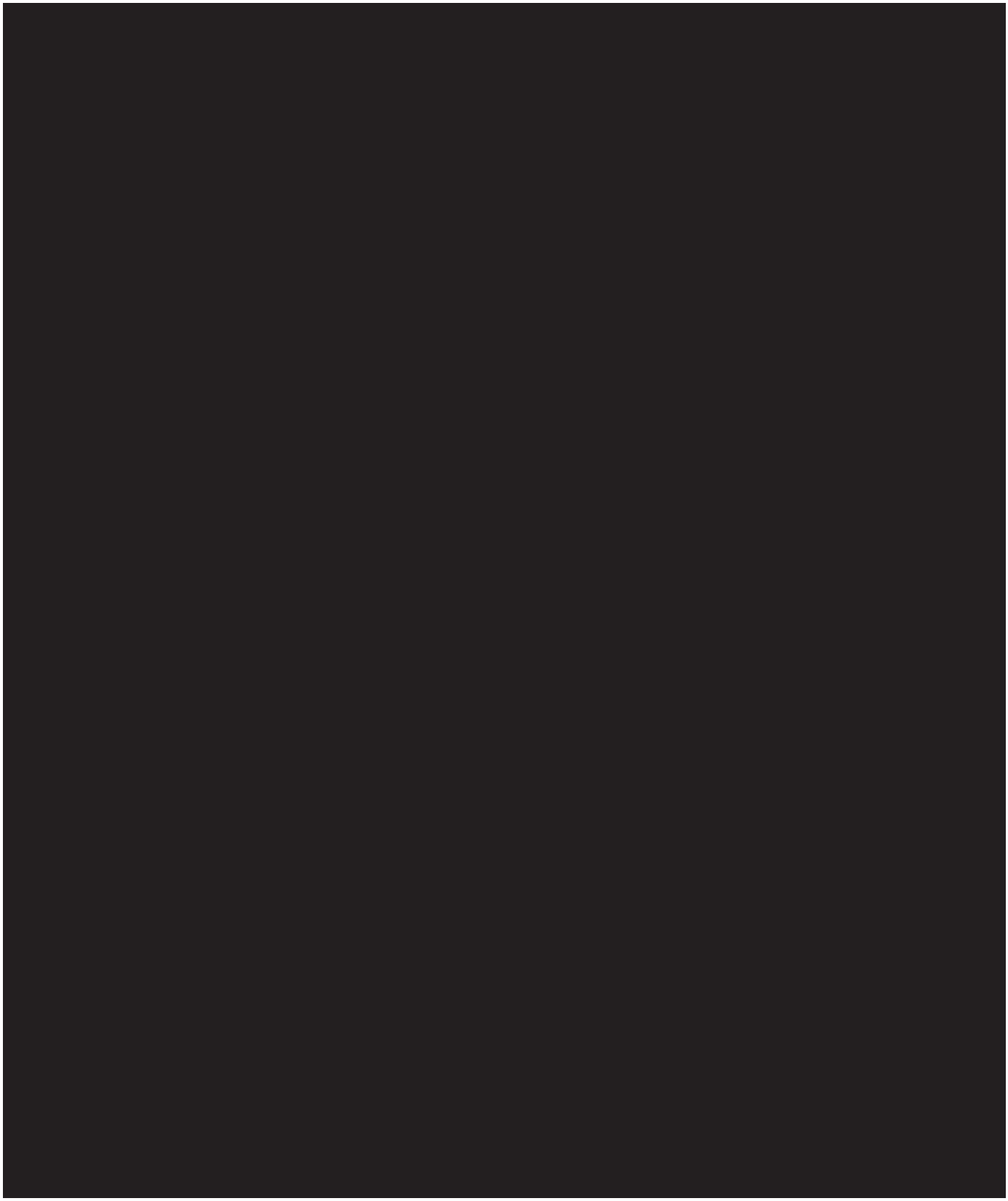


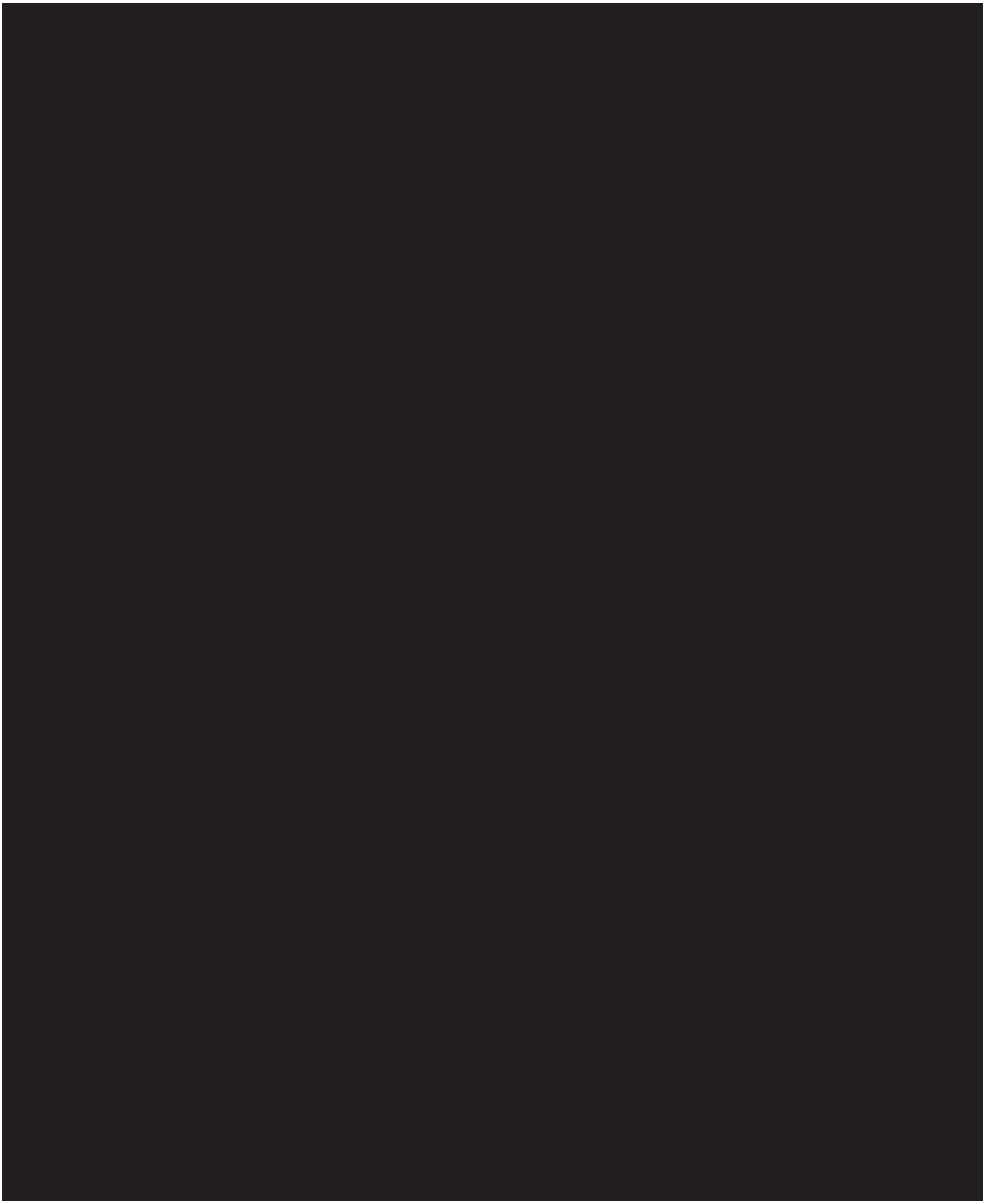












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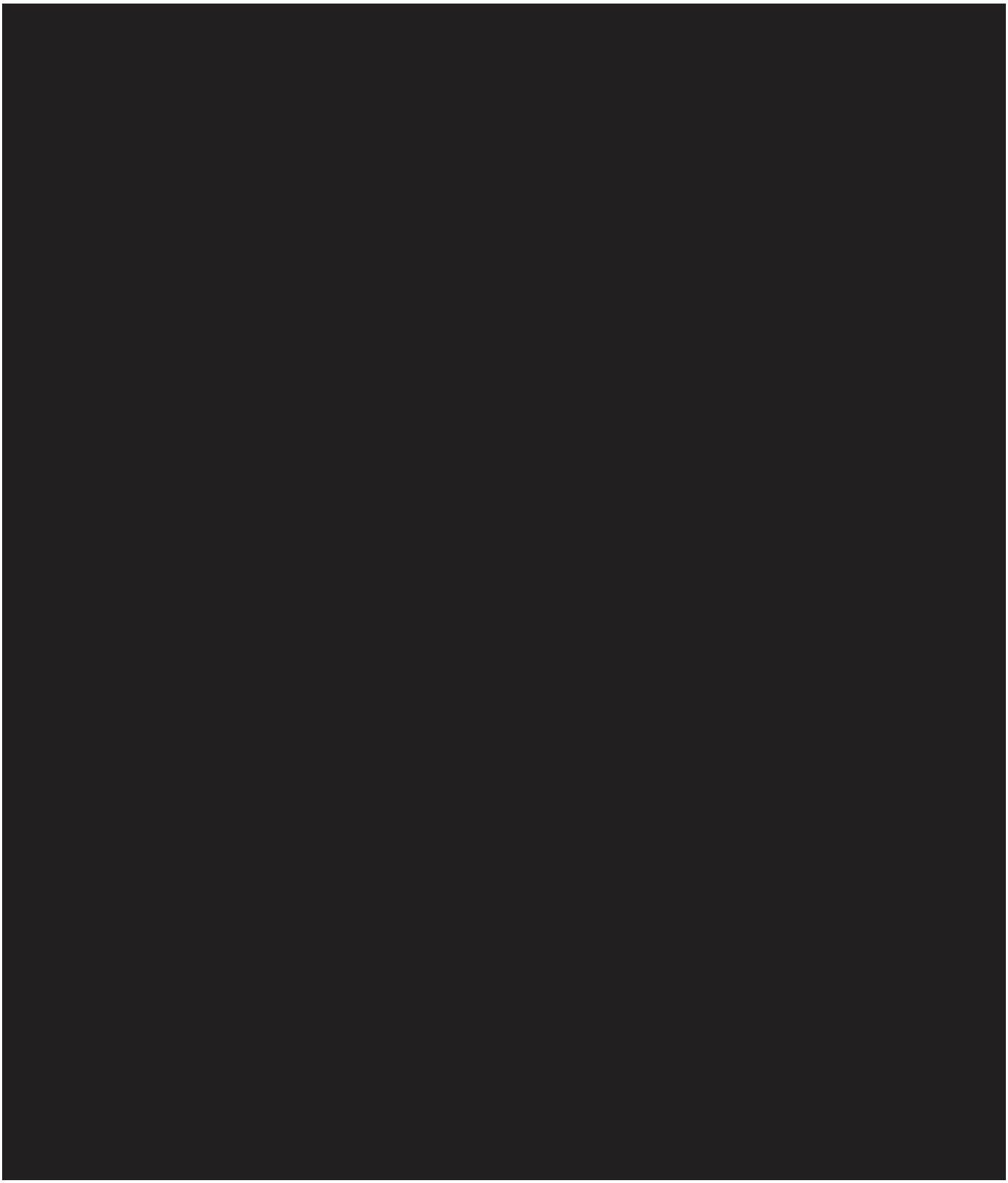
APPENDIX 14 PROTOCOL AMENDMENT SUMMARY OF CHANGE HISTORY



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Summary of Key Changes for Protocol Amendment 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 2 Schedule of Activities	Table 2-1: • Added language describing consent for current and new participants for Protocol Amendment 05. • [redacted]	These changes were made to: • Provide expectations for participant consent for Protocol Amendment 05. • [redacted]
	Table 2-2: • Updated Laboratory Tests Notes to: ○ [redacted] ○ Include text regarding safety laboratory collections	To provide clarification; [redacted]
	Table 2-2: • [redacted]	[redacted]
	Table 2-2: Added Clinical Observation row	
	Table 2-3: • Updated Laboratory Tests Notes to: ○ [redacted]	To provide clarification; increase safety monitoring

Summary of Key Changes for Protocol Amendment 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
	collections	
	Table 2-3: [redacted]	[redacted]
Section 3.3 Benefit/Risk Assessment	[redacted]	These changes were made to align with updated clinical experience
Section 6.1 Inclusion Criteria	[redacted]	Provide expectations for participants consent for Protocol Amendment 05
Section 9.4.4 Clinical Safety Laboratory Assessments	[redacted]	[redacted]

Overall Rationale for Protocol Amendment 04, 23-Jul-2021

The primary reasons for the changes are to align dose modification criteria and IO agent management algorithms (Appendix 5) with the current Common Terminology Criteria for Adverse Event (CTCAE) version 5 (v5); [redacted] vaccination and washout periods; and incorporate additional updates to improve alignment across protocol sections and/or clarify expectations for eligibility, assessments, tumor tissue collections, and treatment administration. Study personnel information updates have been included.

Summary of Key Changes for Protocol Amendment 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Synopsis, Rationale	Updated to match language in the body of the protocol.	For consistency in the document.
Synopsis, Study Population	[redacted] Clarified that women of childbearing potential (WOCBP) must have a negative pregnancy test at screening and within 24 hours prior to administering study drug.	[redacted] te tissue are not excluded. Pregnancy testing language updated for consistency in the document.
Synopsis, Objectives and Endpoints; Section 4: Objectives and Endpoints	[redacted]	[redacted]
Synopsis, Overall Design (Treatment Period)	[redacted]	[redacted]
Synopsis, Overall Design (Clinical Safety Follow-up Period)	[redacted] .	For clarity and consistency within the protocol.
Synopsis, Overall Design (Response Follow-up);	[redacted]	Added for clarity and consistency with the

Summary of Key Changes for Protocol Amendment 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.1: Overall Design	[redacted].	protocol summary and Section 2.
[redacted]		
Synopsis, Overall Design (Treatment Groups and Duration [Table 2: Treatments Administered]); Table 7.1-1: Treatments Administered	[redacted]	Update made for clarification.
Synopsis, Overall Design (Treatment Groups and Duration); Section 5.1.2: Treatment Period; Section 7.1: Treatments Administered	Added the RP2D selected for Part 2.	Update made to clarify the RP2D which has been selected since the last protocol amendment.
Synopsis, Number of Participants; Section 5.2: Number of Participants	[redacted]	[redacted]
Synopsis, Safety Analyses	[redacted]	[redacted]
Synopsis, Study Assessments and Analyses (Efficacy Assessments)	[redacted]	Imaging language clarified to ensure adequate data collection for efficacy assessments.
Section 2, Schedule of Activities (Table 2-1: Screening Procedural Outline for All Study Parts [CA224048])	Removed the Day -1 Visit time point and added a footnote in the "Notes" column that some of the assessments referred to in this section may not be captured as data in the CRF.	Removed to avoid duplication with the "Notes" column.
	[redacted]	For clarification and consistency across the document.

Summary of Key Changes for Protocol Amendment 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
	[redacted]	Removed to reduce subjectivity to the interpretation of the screening criteria.
	[redacted]	For clarification and consistency across the document.
	[redacted]	Added for clarification and consistency across the document, as cardiac troponin is a screening criterion for eligibility in Section 6.2.
	Under "Genetic Mutation Status" added activating mutation statuses to be collected.	Added for clarification.
	The "Notes" for "Serology" was updated to include human immunodeficiency virus (HIV) and [redacted]	[redacted] HIV status positivity is an exclusion criterion for study participation in Section 6.2.
	Added that all AEs (SAEs or non-serious AEs) associated with [redacted] infection are collected from time of consent in the row "Monitor for Serious Adverse Events"	[redacted] .
Section 2, Schedule of Activities (Table 2-2: On-treatment Procedural Outline Part 1A [Relatlimab + Nivolumab + BMS-986205] and Part 1B [Relatlimab + Nivolumab + Ipilimumab])	[redacted]	Added to ensure that cardiac troponin is assessed prior to first dose administration and clarified the required time points for assessment.
	[redacted]	[redacted]
	Added [redacted] to the table.	[redacted]

Summary of Key Changes for Protocol Amendment 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
		[redacted]
	[redacted]	Imaging language clarified to ensure adequate data collection for efficacy assessments.
	[redacted]	Response assessment language clarified to ensure adequate data collection for efficacy assessments.
	Added a row for IRT Drug Assignment and Study Drug Dispensation	Added for clarity and consistency.
	In the notes for the row for [redacted]	Added for clarity and consistency.
	Added the following language in the BMS-986205 pill diary notes: Collect at completion of each cycle, "or earlier" and at EOT.	Added to enable IP reconciliation earlier if the participant does not complete a full cycle of therapy, if applicable.
	Footnotes "a" and "c" were updated to clarify the end of treatment (EOT) visit.	Added to clarify that the EOT visit takes place when the participant discontinues study therapy to ensure safety procedures and data collection in the eCRF are performed at this time point appropriately.
	Footnotes "d" and "e" were added.	Added to clarify trial procedure requirements for participant safety and efficacy assessment, some of which may not be collected in the eCRF.
Section 2, Schedule of Activities (Table 2-3: On-treatment Procedural Outline: Part 2A [Relatlimab + Nivolumab + BMS-986205] and Part 2B [Relatlimab + Nivolumab + Ipilimumab])	[redacted]	Typographical error was corrected.

Summary of Key Changes for Protocol Amendment 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
	Footnotes “d” and “e” were added.	Added to clarify trial procedure requirements for participant safety and efficacy assessment, some of which may not be collected in the eCRF.
	Time points for “Cardiac Troponin” testing were clarified.	Added to ensure that cardiac troponin is assessed prior to first dose administration and clarified the required time points for assessment.
	[redacted]	[redacted]
	Added [redacted] to the table.	[redacted]
	The “Notes” for “Body Imaging” was updated.	Imaging language clarified to ensure adequate data collection for efficacy assessments.
	In the “Notes” for “Brain Imaging”, a window of ± 7 days was added.	Added for clarity and consistency.
	[redacted]	To clarify tumor imaging and response assessment requirements for efficacy assessments.
	[redacted]	Clarified that the IPs will be co-administered because no intra-patient dose de-escalation is permissible in Part 2 and sequential administration is only permissible for de-escalated doses.
	Footnotes “a”, “b”, and “c” were updated to clarify the EOT visit.	Added to clarify that the EOT visit takes place when the participant discontinues study therapy to ensure safety procedures and data collection in the eCRF are performed at this time point

Summary of Key Changes for Protocol Amendment 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
		appropriately.
Section 2, Schedule of Activities (Table 2-4: Follow-Up Procedural Outline CA224048)	Clarified when the response follow-up begins for participants with complete response (CR), partial response (PR), or stable disease (SD) at EOT and the duration of this follow-up.	[redacted]
	Clarified when the survival/Long-term follow-up begins for all participants and the duration of this follow-up.	[redacted]
	Added rows for "Pregnancy Test" and to "Assess Adequate Contraceptive Use"	Added per requirements for pregnancy testing after study drug discontinuation for consistency and participant safety.
	Added [redacted] to the table.	[redacted]
	Under "Notes" for "Adverse Event Assessment" added language for AE/SAE collection including those associated with [redacted]	[redacted]
Section 3: Introduction; Section 7: Treatment	Added the generic name for BMS-986205.	Compound generic name introduced.
Section 3.1: Study Rationale	Clarified that Study CA017003 was a first in human dose-finding and cohort expansion study	Clarified type of study.
Section 3.2.5: Nivolumab Combined with Ipilimumab Clinical Activity	Added data from Phase 3 CheckMate 227 study.	Clinical data relevant to the expansion cohort (non-small cell lung cancer) in Part 2 added.
Section 3.2.6: Relatlimab Combined with	Added data from the Phase 2/3 CA224047 study.	Clinical data relevant to the expansion cohort

Summary of Key Changes for Protocol Amendment 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Nivolumab Clinical Activity		(melanoma) in Part 2 added.
Section 3.2.8: Relatlimab Combined with Nivolumab Clinical Safety	New section added.	Clinical safety data updated.
Section 3.3: Benefit/Risk Assessment	Updated the section with the safety profile of nivolumab in combination with ipilimumab, relatlimab, or BMS-986205.	Benefit-risk assessment updated based on emergent clinical efficacy and safety data of the IO therapy combinations.
Section 5.1.1: Screening Period; Section 6.4.1: Retesting During Screening or Lead-In Period	Added language for participant eligibility if they develop suspected or confirmed [redacted]	[redacted]
Section 5.1.4: Clinical Safety Follow-up Period	Clarified EOT visit for participants who complete all scheduled cycles of therapy and participants who did not complete all scheduled cycles of therapy.	For clarity and consistency within the protocol.
Section 5.1.5: Response Follow-up	[redacted]	Added for clarity and consistency with the protocol summary and Section 2.
Section 5.1.6: Survival Follow-up Period	[redacted]	Added for clarity and consistency with the protocol summary and Section 2.
	Added abbreviations for Figure 5.1.6-1.	To correct an omission.
Section 6.1: Inclusion Criteria	[redacted]	[redacted]
	[redacted]	Existing language supplemented to ensure participant can comply with trial procedures and

Summary of Key Changes for Protocol Amendment 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
	[redacted]	treatment.
	Added that age is in "years" in criterion "3.a"	Minor editorial change.
	Updated the contraceptive language for females and males in criteria "3.d" and "3.e", respectively.	Duration of contraception for females, males, and their partners changed in accordance with the Investigator Brochure updates for relatlimab, nivolumab, ipilimumab and BMS-986205.
Section 6.2: Exclusion Criteria	Updated criterion "1.d" to say that all participants will be screened for methemoglobin levels prior to treatment assignment.	Updated as there is no randomization in this study.
	Criterion "1.f" was updated to define eligibility in case of concurrent malignancy.	Updated exclusion criterion to permit participants with a history of concurrent malignancy or prior malignancy within 2 years. Previous language restricted participation of participants with a history of active malignancy within 3 years.
	Updated criterion "1.m" with eligibility in case of [redacted]	[redacted]
	Added clarification to criterion "2.a.ii" that participants must have recovered from radiation-related toxicities prior to first study treatment.	Language added for participant safety.
	Updated criterion "2.a.iii" to add that herbal supplements or traditional Chinese medicines are permitted if they are used as supportive care.	Language added to clarify eligibility based on prior therapy with complementary medicines, including herbal supplements and traditional Chinese medicines.
	Criterion "2.c.i" was updated to include treatment with any live/attenuated vaccine within [redacted]s of first study treatment, during treatment, and up to [redacted] post last dose.	Language added to clarify eligibility and wash-out period for participants receiving prior treatment with live/attenuated vaccine(s).
	Criterion "2.g" was newly added to provide guidance related to coronavirus disease 2019 (COVID-19) eligibility.	Language added to clarify eligibility of participants enrolled on other interventional studies, including COVID-19 trials.

Summary of Key Changes for Protocol Amendment 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
	Laboratory hemoglobin levels were updated to < 9.0 g/dL in criterion "3.d".	Language updated for patient safety (eligibility criterion is more conservative than the previous requirement).
	Exclusion criteria based on out-of-range troponin was revised in criterion "3.i".	Language updated to remove the requirement for Medical Monitor discussion for out-of-range troponin, for eligibility and replaced with Investigator judgement. The Medical Monitor has to be notified of this decision.
	Updated criterion "3.j" to state that participants with positive HCV antibody and an undetectable HCV-RNA are eligible to enroll.	Previous language clarified.
Section 7.1.1: Relatlimab Combined with Nivolumab Administration	Revised language for the administration of nivolumab combined with relatlimab.	Updated language to provide more clarity for the administration of relatlimab in combination with nivolumab to improve adherence to trial procedures and patient safety.
Section 7.1.2: BMS-986205 Administration	Added that participants should begin study treatment within 3 calendar days of treatment assignment.	Updated language for clarity and consistency between Sections 2 and 7.1.2.
Section 7.1.3: Ipilimumab Administration	Revised language for the administration of ipilimumab in combination of relatlimab and nivolumab.	Updated language to provide more clarity for the administration of ipilimumab plus relatlimab in combination with nivolumab to improve adherence to trial procedures and participant safety.
Section 7.4.1: Relatlimab Dose Modification	Added that there will be no dose escalations or reductions of relatlimab allowed, and doses of relatlimab may be interrupted, delayed, or discontinued.	Updated language to clarify dosing of relatlimab.
Section 7.4.2: Nivolumab Dose Modification	Added that there will be no dose escalations or reductions of nivolumab allowed, and doses of nivolumab may be interrupted, delayed, or discontinued.	Updated language to clarify dosing of nivolumab.
Section 7.4.3: BMS-986205 Dose Modification	Added "Grade 3 AEs (eg, hypoxia, dyspnea, confusion) associated to sustained elevations of methemoglobin"	Updated to provide further clarity to guide dose reduction of BMS-986205.

Summary of Key Changes for Protocol Amendment 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 7.4.4: Ipilimumab Dose Modification	Added that there will be no dose escalations or reductions of ipilimumab allowed, and doses of ipilimumab may be interrupted, delayed, or discontinued.	Updated language to clarify dosing of ipilimumab.
Section 7.4.5: Dose Modification Criteria for IO Therapies	[redacted]	[redacted]
[redacted]	[redacted]	Correction of prior inconsistent language.
	[redacted]	[redacted]
Section 7.4.8: Management of Drug-related Infusion Reactions	Reporting requirements of Grade 3 and 4 infusion related reactions updated and other minor clarifications for consistency with CTCAE version 5.0.	Removed requirement for reporting of Grade 3 and 4 infusion-related reactions to the Medical Monitor, as these only have to be reported as an SAE.
Section 7.7.1: Prohibited Treatments	Added "treatment with any live/attenuated vaccine within [redacted] of first study treatment, during treatment, and up to [redacted] post last dose" to the list of prohibited treatments	Language added based on recommendations of prohibited treatments for IO therapies.
Section 7.7.1.1: Restricted Treatments for Participants Treated with BMS-986205	[redacted]	[redacted].
Section 8.1: Discontinuation from Study Treatment; Section 8.1.1: Relatlimab, Nivolumab, BMS-986205, and Ipilimumab Dose Discontinuation	Added a bullet point that participants receiving relatlimab, nivolumab, and ipilimumab combination, who meet criteria for discontinuation per Table 7.4.5-1 must discontinue all study drugs and be taken off the treatment phase of the study.	Language updated for consistency with Section 7.4.5.
Section 8.1.1: Relatlimab, Nivolumab, BMS-986205, and Ipilimumab Dose Discontinuation	Section updated and language for discontinuation subsumed in Table 7.4.5-1.	Language updated for consistency with Table 7.4.5-1.
Section 8.1.2: Criteria to Resume Treatment	Section updated and criteria to resume treatment subsumed into Table 7.4.5-1. Guidance provided on	Language updated for consistency with Table

Summary of Key Changes for Protocol Amendment 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
	the criteria to resume treatment after suspected or confirmed [redacted]	[redacted]
Section 8.1.3: Exceptions to Permanent Discontinuation	Section updated and exceptions for permanent discontinuation criteria were subsumed into Table 7.4.5-1.	Language updated for consistency with Table 7.4.5-1.
Section 9: Study Assessments and Procedures	Replaced "randomization" with "treatment assignment"	Language corrected as there is no randomization in this Phase 1/2 open-label trial.
	[redacted]	[redacted]
Section 9.1.1: Imaging Efficacy Assessments	Updated the text to state that imaging should continue until disease progression or treatment discontinuation, whichever occurs later, participant withdrawal of consent, start of subsequent therapy, or death.	Imaging language clarified to ensure adequate data collection for efficacy assessments.
Section 9.2.1: Time Period and Frequency for Collecting AE and SAE Information	Clarified that with the exception of non-serious AEs related to [redacted], collection of nonserious AEs should begin at initiation of study treatment until the time points specified in the Schedule of Activities.	[redacted]
	Added that all SAEs, and all AEs (SAEs and non-serious AEs) associated with confirmed or suspected [redacted] must be collected from the date of the participant's written consent until [redacted] following discontinuation of dosing.	[redacted]
Section 9.2.2: Method of Detecting AEs and SAEs	Added that every AE must be assessed by the investigator with regard to whether it is considered immune-mediated and additional information for those potentially immune-mediated, will be collected on the case report form.	Added to ensure the assessment, reporting, and data collection of potential immune-mediated AEs is performed.
Section 9.2.3: Follow-up of AEs and SAEs	Added that AEs associated with confirmed or suspected [redacted] will be followed until resolution, until the condition stabilizes, until	[redacted]

Summary of Key Changes for Protocol Amendment 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
	the event is otherwise explained, the event is deemed irreversible, or until the participant is lost to follow-up.	[redacted]
Table 9.4.4-1: Laboratory Assessments	Clarified that thyroid-stimulating hormone (TSH), free T3 and free T4 will be assessed at Screening and as applicable On Treatment.	Added for clarification.
	[redacted]	Language for management [redacted]
	Added pregnancy test having a minimum sensitivity of 25 IU/L or equivalent units of hCG in WOCBP and follicle stimulating hormone (FSH) at screening to confirm menopause in women < age 55.	Language added for clarity of criteria of pregnancy tests.
Section 9.4.6: Echocardiogram (ECHO)/Multiple-gated Acquisition (MUGA) Testing	Added this new section.	Added as ECHO/MUGA is a screening procedure in the Schedule of Activities table.
[redacted]		
	[redacted]	[redacted]

Summary of Key Changes for Protocol Amendment 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
	[redacted]	
Section 10.1.2: Dose Expansion (Part 2)	Sample size determination for Part 2 was revised based on [redacted]	[redacted]
Section 10.3.3: Other Analyses	[redacted] will be described in the Statistical Analysis Plan.	[redacted].
Appendix 1: Abbreviations and Trademarks	Abbreviation list was updated.	For consistency within the protocol.
Appendix 2: Study Governance Considerations	Appendix was updated with standard language.	To align with current standards.
Appendix 3: Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting	Appendix was updated with standard language.	To align with current standards.
Appendix 4: Women of Childbearing Potential Definitions and Methods of Contraception	Appendix was updated with standard language.	To align with current standards.
Appendix 5: Management Algorithms for Studies Under CTCAE Version 5.0	Algorithms were updated.	To align to most current version.
Appendix 11: Response Evaluation Criteria in Solid Tumors Guidelines (Version 1.1) with BMS Modifications	In Section 2.3.3 (Best Overall Response), the timelines for best overall response for stable disease was updated.	Clarified that the required minimum period for stable disease evaluable in this protocol is 56 days (minus 7 days), based on an 8-week cycle.
All	Minor formatting and typographical corrections.	Minor, therefore have not been summarized.

Overall Rationale for the Revised Protocol 03, [redacted]

[redacted]

Summary of Key Changes for Revised Protocol 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Synopsis	[redacted]	Correction of text concerning survival follow-up to ensure uniformity throughout the protocol.
Table 2-1 Screening Procedural Outline Section 6.2 Exclusion Criteria Table 9.4.4-1 Laboratory Assessments	[redacted]	[redacted]
Section 6.1 Inclusion Criteria, 2) Type of Participant and Target Disease Characteristics, j) [redacted]	[redacted]	Correction of irregularities in language for targeted mutations.

Summary of Key Changes for Revised Protocol 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]	[redacted]	[redacted]
Appendix 3 Adverse Events and Serious Adverse Events: definitions and procedures for recording, evaluating, follow up and reporting	Previous version of Appendix 3 was replaced with most recent version.	Appendix was replaced to align with the latest BMS standards.
Appendix 5 Management Algorithms; Section 7.4.7 Management Algorithms for Immuno-oncology Agents	[redacted]	[redacted].
All	Minor corrections	Corrections for clarity and consistency within the document were minor, and therefore have not been summarized.

Overall Rationale for the Revised Protocol 02, [redacted]

The primary reasons for these changes include: updating the starting dose of BMS-986205 to 25 mg once daily (QD) in Part 1A of the dose-finding phase of the study; clarifying details, scenarios, and/or timing for some assessments and follow-up; updating contraceptive requirements for males; adding information on adverse events (AEs) of special interest; updating the [redacted]; and updating guidance on concomitant therapies. Additional amendments, including to sections of the Synopsis, have been made to align the protocol with respect to these changes.

Summary of Key Changes for Revised Protocol 02

Section Number & Title	Description of Change	Brief Rationale
Title Page	Replaced Study Director and Medical Monitor contact information with: Medical Monitor [redacted]	Updated contact information.
Title Page; Section 1 Synopsis	Short Title added.	Short Title added for clarity and alignment with Short Title provided on ClinicalTrials.gov.
Table 2-1 Screening Procedural Outline for All Study Parts (CA224048); Table 2-3 On-treatment Procedural Outline Part 2A and Part 2B; Section 6.2 Exclusion Criteria; [redacted] Table 9.4.4-1 Laboratory Assessments	[redacted]	[redacted]
Table 2-1 Screening Procedural Outline for All Study Parts (CA224048); Table 9.4.4-1 Laboratory Assessments; Section 6.2 Exclusion Criteria	[redacted]	[redacted]

Summary of Key Changes for Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-2 On-treatment Procedural Outline Part 1A and Part 1B; Table 2-3 On-treatment Procedural Outline Part 2A and Part 2B; [redacted]	[redacted]	[redacted]
Table 2-2 On-treatment Procedural Outline Part 1A and Part 1B; Table 2-3 On-treatment Procedural Outline Part 2A and Part 2B	Removed qualifying text "able to reproduce" from notes in Assess Adequate Contraceptive Use row.	Clarified that contraceptive use for males applies to all male participants who are sexually active with WOCBP, for consistency with the related update made to Section 6.1.
Table 2-4 Follow-up Procedural Outline CA224048	[redacted]	[redacted]
Section 3.3 Benefit/Risk Assessment	[redacted]	Updated information related to the safety profile of BMS-986205 to align with currently available safety and PK/PD data.
Section 5.1 Overall Design	Added sentence to second paragraph: "Part 2A and Part 2B may be initiated independently from each other based on the timing of data evaluation in Part 1."	Clarified timing of initiating Part 2A and Part 2B following evaluation of data in Part 1A and Part 2B, respectively.
Section 5.1 Overall Design; Figure 5.1-1 Study Design Schematic; Section 5.1.2 Treatment Period; Table 7.1-2 Part 1A; Section 10.1.1 Dose Finding (Part 1)	Modified the treatment/dose administration scheme and related text for Part 1A: Dose Finding.	Information related to the treatment/dose administration scheme for Part 1A of the study updated to reflect a change to the starting dose of BMS-986205 to 25 mg QD.

Summary of Key Changes for Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.1.2 Treatment Period; Section 10.1.1 Dose Finding (Part 1)	Added text to related to the number of study participants to clarify that: • [redacted]	Clarified the planned number of participants in Part 1 of the study.
Section 5.1.2 Treatment Period; [redacted] Section 10.1 Sample Size Determination	Modified description of Part 1 of the study from "safety evaluation" to "dose finding."	Updated description of Part 1 of the study to "dose finding" for consistency with the updated treatment/dose-administration scheme for Part 1A.
Section 5.5.3 Justification for BMS-985205 Dose	Modified the text in this section to: • [redacted]	Updated nonclinical PK and safety information to support use of a starting BMS-986205 dose of 25 mg QD.
Section 5.5.5 Justification for Relatlimab, Nivolumab, and BMS-986205 Combination Dose (Part 1A and Part 2A)	Modified text related to Part 1A to: • Update starting dose of BMS-986205 to 25 mg QD. • [redacted]	Modified dose information for BMS-986205 to align with the updated starting dose of 25 mg QD.
Section 6.1 Inclusion Criteria	Updated criteria 3) e) and 3) f) related to male contraceptive requirements to require condom use for all males (even azoospermic males).	Male contraceptive requirements modified to require condom use for all males who are sexually active with WOCBP based on recent preclinical data.
Section 6.2 Exclusion Criteria	Modified text as follows: • Updated criterion 1) d) to include prior history of [redacted] • Added new exclusion criterion 3) n) for [redacted]	Updated Exclusion Criteria related to [redacted]

Summary of Key Changes for Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 7.2 Method of Treatment Assignment	Added text to provide method for achieving balance among treatment groups in Part 1 and Part 2 if 1 treatment group becomes overly enrolled due to screen failures.	Modified text to clarify method for balancing enrollment among treatment groups.
Section 7.3 Blinding	Added the following text: "BMS personnel may have access to treatment information during the course of the trial to help with internal decision-making and for disclosure of preliminary scientific results."	Updated blinding information to clarify when treatment information may be available to BMS.
Section 7.4.3 BMS-986205 Dose Modification	Added text to clarify that for BMS-986205: • [redacted]	Clarified dose modification information for BMS-986205 to align with the updated starting dose of 25 mg QD.
Section 7.4.6 Dose-limiting Toxicities; Section 7.4.8 Management of Drug-related Infusion Reactions; Table 10.3.2-1 Overview of Safety Analysis Methods	Updated Common Terminology Criteria for Adverse Events (CTCAE) used for grading AEs from v4.0 to v5.0.	Updated method for grading AEs to be according to CTCAE v5.0.
Section 7.7.1 Prohibited Treatments; [redacted]	Added information related to concomitant use of [redacted]	Updated information for concomitant therapies to include [redacted]
Section 7.7.2 Other Restrictions and Precautions	Added paragraph related to development and monitoring of [redacted]	Added information related to the development and monitoring of [redacted]
Section 8.1 Discontinuation from Study Treatment	Modified text related to pregnancy cases to: • Add that BMS/Medical Monitor must be notified within 24 hours of a pregnancy event. • Remove text related to possible favorable benefit-risk ratio discussion. • Add reference to Section 9.2.6 Pregnancy.	Modified in-the-case-of-pregnancy instructions to clarify expectations for reporting pregnancy.

Summary of Key Changes for Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 8.1.1 Relatlimab, Nivolumab, BMS-986205, and Ipilimumab Dose Discontinuation	Added bullet: "For BMS-986205 treated participants: any occurrence of [redacted]	Updated scenarios for discontinuing study treatment to include [redacted]
[redacted]		
Section 9.2.6 Pregnancy	Modified second paragraph related to treatment continuation and pregnancy to: • Remove redundant text related to timing of notifying BMS Medical Monitor/designee of pregnancy. • Add text for circumstances in which continuation of study treatment may be discussed.	Updated text related to treatment continuation and pregnancy to clarify the circumstances for continuation of study treatment in the case of pregnancy.
Section 9.3 Overdose	Updated parenthetical text in bullet 2) to "(at least [redacted]."	Updated text to clarify that participants should be monitored for AEs/serious adverse events for at least [redacted]
[redacted]		

Summary of Key Changes for Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 10.3 Statistical Analyses	Added statement: "A description of the participant population will be included in the statistical output reported, including subgroup of age, gender, and race."	Statement added to meet compliance requirements.
Section 10.3.1 Efficacy Analyses	Added sentence: "Efficacy analyses may be performed on selected subgroups, [redacted]"	Clarified that efficacy analysis may be performed on selected subgroups.
Appendix 2 Study Governance Considerations	Modified Good Clinical Practice section in Appendix 2 to: • Add bullet to clarify that the study will also be conducted in accordance with ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines Good Clinical Practice. • Align with revised definition of serious breach to Regulation No 536/2014 of the European Parliament and of the Council.	Modified text to align with statement in the informed consent form and TransCelerate Common Protocol Template.

Summary of Key Changes for Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Appendix 3 Adverse Events and Serious Adverse Events Definitions and Procedures for Recording, Evaluating, and Follow-up and Reporting	Added the following new sections: • Events Meeting the AE Definition. • Events Not Meeting the AE Definition. • Definition of Serious Adverse Event (SAE). Modified the following sections: • SAEs (text related to pregnancy and drug-induced liver injury). • Evaluating AEs and SAEs (updated and rearranged bulleted information). • Reporting of SAEs to Sponsor or Designee (updated and rearranged bulleted information related to pregnancy and paper report forms).	Modifications made to information related to AEs and SAEs to align with the TransCelerate Common Protocol Template, regulatory definition EMA GVP Module VI (EMA/873138/2011) and ICH E2A, and clarify the instructions for reporting pregnancy.
Appendix 4 Women of Childbearing Potential Definitions and Methods of Contraception	Modified Appendix 4 as follows: • Added several methods to list of Unacceptable Methods of Contraception • Added text to contraception guidance for male participates to clarify: o Condom type. o That condom use is required for any sexual activity with WOCBP.	Further clarified unacceptable methods of contraception and requirement of condom use for all males who are sexually active with WOCBP.
[redacted]		
Appendix 13 Statistical Methodology	Modified Section 2 of Appendix 13 as follows: • Updated data tables and descriptive text for Section 2.1 Parameters for Dose Finding. • Added Section 2.2 Dose-Escalation Process in Part 1A and Simulations.	Updated statistical methodology information related to dose-finding parameters and dose-escalation to align with most recent study data available and updated treatment/dose-administration scheme for Part 1A.
All	Minor formatting and typographical corrections.	Corrections for clarity and consistency within the document were minor, and therefore have not been summarized.

Overall Rationale for the Revised Protocol 01, [redacted]

The protocol was revised to address questions and clarifications requested by the [redacted]

Summary of Key Changes for Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 2 Schedule of Activities On-treatment Procedural Outline	[redacted]	[redacted]
Section 6.1 Inclusion Criteria		
Section 6.1 Inclusion Criteria		Inclusion criteria was updated to ensure that patients received appropriate prior therapy.
Section 6.1 Inclusion Criteria		Inclusion criteria was updated to ensure that patients received appropriate prior therapy.
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Section 6.1 Inclusion Criteria		Inclusion criteria was updated to ensure that patients received appropriate prior therapy.
Section 6.2 Exclusion Criteria	Revised exclusion criteria 3 l) to include testing requirements for active or unknown HIV infection	To provide clarification that HIV positive participants are excluded
Section 6.2 Exclusion Criteria	[redacted]	Added for participant safety
Section 7.2 Method of Treatment Assignment	Added language to clarify the way in which all participants in Part 1 will be assigned to either Cohort 1A or 1B [redacted]	Further clarify how subjects will be allocated to cohorts that are open at the same time
Section 7.4.3 BMS-986205 Dose Modifications	Added the following additional criteria for discontinuation: Grade 3 nausea, vomiting or diarrhea related to study treatment that lasts more than 48 hours	Added for participant safety

Summary of Key Changes for Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 7.4.8 Dose Delay Due to Toxicity	Section 7.4.8 was deleted and combined into Section 7.4.5; redundancies were removed	To reduce redundant information in two sections
[redacted]		
All	Minor formatting and typographical corrections	Minor, therefore have not been summarized