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Clinical Protocol CA017076

A Phase 1/2 Study to Evaluate the Pharmacokinetics, Pharmacodynamics, Safety, and Tolerability of BMS-986205 Alone and in Combination with Nivolumab in Chinese Patients with Advanced Malignant Solid Tumors

Revised Protocol 01

Study Director/Medical Monitor

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

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 01	10-Oct-2018	• Incorporated changes to align this protocol with the current standards of the BMS-986205 and nivolumab programs and enhance subject safety across the protocol • Information about Reticulocyte counts and haptoglobin monitoring at baseline and reflex when methemoglobin is elevated over ULN was added • Exclusion criteria was updated to exclude participants with prior exposure to anti-PD-1, anti-PDL-1 therapy was updated • Information on the serotonin syndrome as a possible class effect of IDO1 inhibitors and additional exclusion criteria and dose discontinuation criteria to reflect this possibility • Information about smoking and CYP1A2 was added to other restrictions and precautions and other sections • Administrative changes, minor clarifications, typographical corrections, and updates for consistency were made • Updated notes and provided clarification in the procedure outline and across the protocol
Original Protocol	26-Feb-2018	Not applicable

OVERALL RATIONALE FOR REVISED PROTOCOL 01:

The primary reasons for these changes below were to align this protocol with the current standards of the BMS-986205 and nivolumab programs and enhance subject safety.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-1: Screening Procedural Outline (CA017076)	Updated notes to clarify that Vital signs must be obtained at the screening visit and prior to randomization or first dose must be obtained prior to performing any screening procedures	Updated text for clarity
Table 2-1: Screening Procedural Outline (CA017076)	Updated notes to clarify that G6PD Deficiency Testing will not be done locally	Updated text for clarity
Table 2-1: Screening Procedural Outline (CA017076)	Updated frequency and notes to clarify that methemoglobin levels to be assessed on arterial or venous blood sample	Updated text for clarity
Table 2-1: Screening Procedural Outline (CA017076)	Updated notes to clarify that Reticulocyte counts and haptoglobin will be done at baseline and reflex when methemoglobin is elevated over ULN)	Updated text for clarity
Table 2-2: On-Treatment: BMS-986205 Monotherapy (One 14-Day Cycle) Procedure Outline (CA017076)	Updated notes to delete "For Day 2, only collect predose if elevated either 2 or 4 hours postdose evaluation on Day 1. Predose on Day 4 (± 1 day)".	Updated text for clarity
Table 2-2: On-Treatment: BMS-986205 Monotherapy (One 14-Day Cycle) Procedure Outline (CA017076)	Updated notes about CBC with Differential and Platelets to clarify that additional samples to be collected as clinically indicated	Updated text for clarity

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-4: Follow-Up Procedure Outline (CA017076)	Updated notes about CBC with Differential and Platelets to clarify that additional samples to be collected as clinically indicated	Updated text for clarity
[redacted]		
5.1 Overall Design	Deleted the statement "Participants who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity".	Updated text for clarity
5.1 Overall Design	Clarified that treatment may continue from Cycle 0 (2 weeks) until 50 weeks disease progression, or withdrawal of consent.	Updated text for clarity
5.1 Overall Design Screening	Removed text "If a participant surpasses the 28-day window during the screening phase due to a study-related procedure (eg, waiting time for a study-related laboratory value), the participant must be re-consented but does not need	Updated for consistency purposes

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
	to be assigned a new identification number. In this situation, the least amount of repeat procedures from the initial screening to qualify the participant, while maintaining safety and eligibility under the discretion of the BMS medical monitor and investigator, may be done to reduce any undue burden of procedures in this subject population".	
6.1 Inclusion Criteria 2f	Exclusion criteria was modified to exclude "Participants with prior exposure to therapy with any agent specifically targeting checkpoint pathway inhibition other than PD-1 or PD-L1 (such as anti-PD-1, anti-PDL-1)"	New requirement based on evolving data
6.1 Inclusion Criteria 3f	Modified the exclusion criteria to include "in addition, male subjects must be willing to refrain from sperm donation during this time".	Updated text for clarity
6.2 Exclusion Criteria 2b	Added the exclusion criteria "Participants must not have a prior history of serotonin syndrome"	New requirement based on evolving data
6.2 Exclusion Criteria 3b	Added that "Participants with prior exposure to anti PD-1 or anti-PDL1 therapy must be excluded"	New requirement based on evolving data
6.2 Exclusion Criteria 3c	Updated that participants must not use any strong	New requirement based on evolving data

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
	inhibitors of CYP1A2 in addition to CYP3A4	
7.1.1 BMS-986205 Administration	Clarified that BMS-986205 100 mg oral daily dose must be administered with a meal at approximately the same time each day. .	Updated text for clarity
7.4.4 Guidelines for Permanent Discontinuation of BMS-986205 and Nivolumab	Added that "Any occurrence of serotonin syndrome should result in discontinuation of BMS-986205 only." Deleted "any event requiring more than 1 dose reduction of BMS-986205".	New requirement based on evolving data
7.4.4 Guidelines for Permanent Discontinuation of BMS-986205 and Nivolumab	Clarified that for participants who delay BMS-986205 but continue nivolumab, any dose delay of BMS 986205 lasting >10 weeks will result in the discontinuation of BMS-986205, but not nivolumab treatment.	Updated text for clarity
7.4.7 Treatment of Methemoglobinemia Associated with BMS-986205	Added a new section	Added to align with the program level safety updates
7.7.1 Prohibited and/or Restricted Treatments	Updated Prohibited and/or Restricted Treatments to include strong inhibitors of CYP1A2 and strong inducers of CYP1A2	New requirement based on evolving data
7.7.2 Other Restrictions and Precautions	Restricted therapies are not prohibited but are not recommended; Investigators should consider possible benefit/risk implications of enrolling and treating participants in whom the	Added to align with the program level updates

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
	following are clearly medically indicated. Added the following text:about smoking restriction: Concurrent smoking (tobacco, marijuana, etc.) may induce CYP1A2 and decrease the systemic exposure of BMS-986205. Caution is warranted when consuming marijuana by means other than smoking as it may lead to increased exposure of BMS-986205 through interaction with metabolic enzymes.	
8 Discontinuation Criteria	Added text about serotonin syndrome	New requirement based on evolving data
[redacted]		
9.2.6 Pregnancy	Updated section to clarify that "If the Investigator determines a possible favorable benefit-risk ratio that warrants continuation"	Added to align with the program level updates
Table 9.5.2-1: Pharmacokinetic, Anti-Drug Antibody (ADA) for BMS-986205 and Nivolumab	Removed C0D1 predose row and changed frequency of metabolite urine sample collection	Updated based on evolving data
Table 9.5.2-1: Pharmacokinetic, Anti-Drug Antibody (ADA) for BMS-986205 and Nivolumab	Updated follow-up information	Updated based on evolving data
Appendix 8	Updated list added	Updated to a newer version
[redacted]		

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
All	Minor formatting and typographical corrections	Minor, therefore have not been summarized

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1 SYNOPSIS

Protocol Title: A Phase 1/2 Study to Evaluate the Pharmacokinetics, Pharmacodynamics, Safety, and Tolerability of BMS-986205 Alone and in Combination with Nivolumab in Chinese Patients with Advanced Malignant Solid Tumors

Study Phase: 1/2

[redacted]

Study Population:

The study population includes adult Chinese participants with advanced malignant solid tumors.

Key Inclusion Criteria:

- Participants must have histologic or cytological confirmation of a malignancy (solid tumor) that is advanced (metastatic and/or unresectable) with measureable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.
- Participants must have received, and then progressed or been intolerant to at least one standard treatment regimen in the advanced or metastatic setting, if such a therapy exists. Participants who refuse or are ineligible for standard therapy will be allowed to enroll provided refusal/ineligibility is documented.
- Participants must have an Eastern Cooperative Oncology Group performance status of ≤ 1.
- Participants must present with at least one lesion with measurable disease as defined by RECIST v1.1 for solid tumors for response assessment. Participants with lesions in a previously irradiated field as the sole site of measurable disease will be permitted to enroll provided the lesion(s) have demonstrated clear progression and can be measured accurately.
- Participants with prior exposure to therapy with any agent specifically targeting checkpoint pathway inhibition other than PD-1 or PD-L1 (such as anti-PDL-2, anti-lymphocyte activation gene 3 [LAG-3], and anti-cytotoxic T lymphocyte-associated antigen 4 [CTLA] antibody) are permitted after a washout period of any time greater than 4 weeks from the last treatment. Participants with prior therapy with any agent specifically targeting T-cell costimulation pathways such as anti-glucocorticoid-induced tumor necrosis factor receptor (TNFR) family related gene antibody, anti-CD137, anti-OX40 antibody, are permitted after a washout period of any time greater than 4 weeks from the last treatment.

- Participants who experienced prior Grade 1 to 2 checkpoint therapy-related immune-mediated adverse events (AEs) must have confirmed recovery from these events at the time of study entry, other than endocrinopathies treated with supplementation, as documented by resolution of all related clinical symptoms, abnormal findings on physical examination, and/or associated laboratory abnormalities. Where applicable, these participants must also have completed steroid tapers for treatment of these AEs by a minimum of 14 days prior to commencing treatment with study drug.
- Eligibility of participants with prior ≥ Grade 3 checkpoint therapy-related immune AEs, will be considered on a case-by-case basis after discussion with the Medical Monitor (eg, asymptomatic isolated Grade 3 lipase elevations without clinical or radiological features of pancreatitis will be permitted to enroll).

- Prior palliative radiotherapy must have been completed at least 2 weeks prior to first dose of study drug. Participants with symptomatic tumor lesions at baseline that may require palliative radiotherapy within 4 weeks of first dose of study drug are strongly encouraged to receive palliative radiotherapy prior to enrollment.
- Women must not be pregnant or breastfeeding.

Key Exclusion Criteria:

- Participants with known or suspected central nervous system (CNS) metastases, untreated CNS metastases, or with the CNS as the only site of disease are excluded. However, participants with controlled brain metastases will be allowed to enroll. Controlled brain metastases are defined as no radiographic progression for at least 4 weeks following radiation and/or surgical treatment (or 4 weeks of observation if no intervention is clinically indicated), and off of steroids for at least 2 weeks, and no new or progressive neurological signs and symptoms. Please note: Squamous cell carcinoma of the head and neck (SCCHN) participants with direct extension of tumor through the base of skull will not be excluded, as they are considered distinct from hematogenously spread parenchymal brain metastasis.
- Participants must not have ocular melanoma.
- Participants must not have a prior history of serotonin syndrome.
- Participants must not have a personal or family history or presence of cytochrome b5 reductase deficiency, or other diseases that puts them at risk of methemoglobinemia.
- Participants must not have a history of or current G6PD deficiency (quantitative or qualitative assessments will be checked during screening). Participants must also not have any other congenital or autoimmune hemolytic disorders. If participant has history of transient acquired hemolytic anemia, discuss with Medical Monitor for study eligibility.
- Participants must not have a history or presence of hypersensitivity or idiosyncratic reaction to methylene blue.
- Participants with a prior malignancy are excluded (except non-melanoma skin cancers, and in situ cancers such as the following: bladder, colorectal, cervical/dysplasia, melanoma, or breast). Participants with other second malignancies diagnosed more than 2 years ago who

have received therapy with curative intent with no evidence of disease during the interval who are considered by the investigator to present a low risk for recurrence will be eligible.

- Participants must not have other active malignancy requiring concurrent intervention.
- Participants must not have prior organ allograft or allogeneic bone marrow transplantation.
- Participants must not have any anti-cancer therapy (eg, chemotherapy, biologics, vaccines, or hormonal treatment) including investigational drugs within 4 weeks prior to the first dose of study drug administration, except for non-cytotoxic therapies, for which at least 4 weeks or 5 half-lives (whichever is shorter) must have elapsed between last dose and first treatment with any study drugs; if 5 half-lives is shorter than 4 weeks, agreement with the Medical Monitor must be obtained.
- Participants with prior exposure to anti PD-1 or anti-PDL1 therapy must be excluded.
- Participants must not have had prior therapy with an IDO inhibitor.
- Participants must not have active, known, or suspected autoimmune disease. Participants with vitiligo, type 1 diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, euthyroid participants with a history of Grave's disease (participants with suspected autoimmune thyroid disorders must be negative for thyroglobulin and thyroid peroxidase antibodies and thyroid stimulating immunoglobulin prior to first dose of study drug), psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

Objectives and Endpoints:

Objectives	Endpoints
• The primary objective of this study is to characterize the pharmacokinetics (PK) and assess the safety and tolerability of BMS-986205 administered alone and in combination with nivolumab in Chinese participants with advanced malignant tumors.	• PK parameters, incidence of AEs, serious adverse events (SAEs), AEs leading to discontinuation, deaths, and laboratory abnormalities
The secondary objectives of this study are: • To characterize the pharmacodynamic activity of BMS-986205 administered alone and in combination with nivolumab. • To characterize the immunogenicity of nivolumab when administered in combination with BMS-986205. • To investigate the preliminary anti-tumor activity of BMS-986205 administered in combination with nivolumab in advanced malignant tumors.	• Incidence of anti-drug antibodies (ADA) to nivolumab; measurement of serum kynurenine and tryptophan levels • Overall response rate (ORR), best overall response (BOR) and duration of response (DOR) as assessed per RECIST v1.1 by investigator

Overall Design:

This is a Phase 1/2, open-label study of BMS-986205 administered as a monotherapy and in combination with nivolumab in participants with advanced malignant solid tumors.

Treatment will start with a 2-week monotherapy lead-in (Cycle 0) whereby BMS-986205 100 mg oral daily dose must be administered with a meal at approximately the same time each day. Participants will then proceed to receive the combination of nivolumab and BMS-986205. Nivolumab will be administered at a dose of 480 mg intravenously (IV) every 4 weeks (Q4W).

Number of Participants:

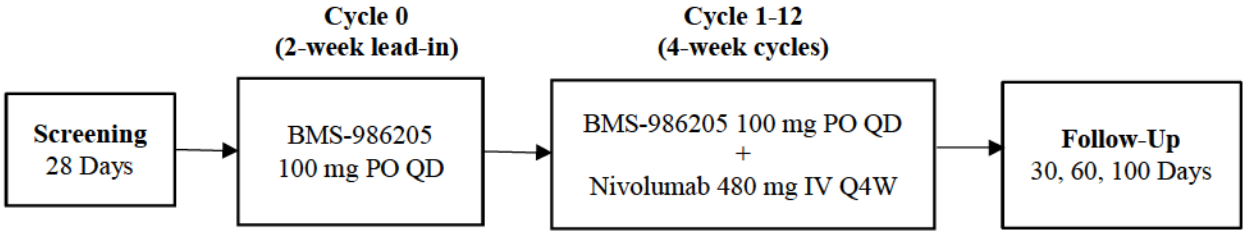
A sample size of 12 PK evaluable subjects is proposed for this study.

Treatment Arms and Duration:

Study Treatments for CA017076		
Medication	**Potency**	**IP/Non-IP**
BMS-986205	50 or 100 mg	IP
Nivolumab Solution for Injection	10 mg/ml (100-mg/vial)	IP

The study design schematic is presented below:

Study Design Schematic



Participants will complete up to 3 phases of the study: Screening, Treatment, and Clinical/Safety Follow-up, as described below.

Screening: The screening phase will last for up to 28 days. Screening begins by establishing the participant's initial eligibility and signing the informed consent form (ICF).

Treatment: The treatment phase consists of the 2-week monotherapy lead-in (Cycle 0) and up to twelve 4-week combination therapy cycles for a total study treatment period up to 50 weeks. Dosing regimens for each phase are as follows:

- Lead-in: single oral daily dose of BMS-986205 for two weeks

- Combination Therapy: single oral daily dose of BMS-986205 and one dose of nivolumab administered intravenously Q4W on Day 1 of each treatment cycle up to 12 cycles.

Clinical/Safety Follow-Up: Upon completion or termination of therapy, all participants will enter the Clinical/Safety Follow-Up period. Participants must be followed for at least 100 days after the last dose of study therapy or 30 days if participant only received BMS-986205.

Dose Modifications:

The sponsor will carefully review the totality of the safety data observed among the 12 Chinese patients treated with nivolumab and BMS-986205. If such review suggests that the risk profile of the treatment regimen deviates significantly from that observed among non-Chinese patients treated with this same regimen, then consideration will be given to studying a lower dose of BMS-986205 in combination with nivolumab or enrolling additional Chinese patients to confirm the safety of the protocol defined treatment regimen.

2 SCHEDULE OF ACTIVITIES

Study assessments and procedures are presented in Table 2-1, Table 2-2, Table 2-3, Table 2-4and in limited instances, scheduled events can occur outside of the indicated timeframes after consultation with the BMS medical monitor/designee on a case by case basis.

In the event that multiple procedures are required at a single time point, the following is a list of procedures from highest priority to low: 1) pharmacokinetic (PK) sampling, 2) electrocardiogram (ECG), and 3) clinical labs.

Table 2-1: Screening Procedural Outline (CA017076)

Procedure	D -28 to D -1	D -14 to D -1	Notes
Eligibility Assessments			
Informed Consent	X		A participant is considered enrolled only when a protocol specific informed consent is signed.
Inclusion/Exclusion Criteria	X		See Section 6.
Medical History	X		Include any toxicities or allergies related to previous treatments as well as any history of cytochrome b5 reductase deficiency or G6PD deficiency, if known.
Prior Systemic Therapies	X		Includes all prior cancer treatment regimens.
Tobacco History/Status	X		
Safety Assessments			
Physical Examination (PE)	X		If the screening PE is performed within 24 hours prior to dosing on Day 1, then a single exam may count as both the screening and predose evaluation.
Physical Measurements	X		Includes height and weight.
ECOG Performance Status	X		ECOG Performance Status (Appendix 6). Performance Status must be obtained at the screening visit and prior to randomization or first dose
Vital Signs	X		Includes body temperature, respiratory rate, and seated blood pressure and heart rate. Blood pressure and heart rate should be measured after the participant has been resting quietly for at least 5 minutes. Consider alternate position(s) for vital sign collection. Vital signs must be obtained at the screening visit and prior to randomization or first dose
Oxygen Saturation	X		Pulse oximetry collected at rest.
Electrocardiograms (ECGs)	X		12-lead ECGs should be recorded after the participant has been supine for at least 5 minutes.
Concomitant Medication Use	X	X	Collect during the 2 weeks prior to Cycle 0 Day 1.
Laboratory Tests			

Table 2-1: Screening Procedural Outline (CA017076)

Procedure	D -28 to D -1	D -14 to D -1	Notes
Chemistry (Excluding Liver Function Test LFTs))		X	Includes assessments for sodium, potassium, chloride, total serum calcium, magnesium, bicarbonate/carbon dioxide, phosphorus, blood urea nitrogen (BUN), creatinine, creatinine clearance, C-reactive protein, fasting glucose, total protein, albumin, amylase, lipase, uric acid, ferritin, and lactase dehydrogenase (LDH).
G6PD Deficiency Testing	X		
Methemoglobin		X	Methemoglobin levels to be assessed on arterial or venous blood sample
Reticulocyte counts and haptoglobin		X	At baseline and reflex when methemoglobin is elevated over upper limit of normal [ULN]). Additional samples as clinically indicated.
CBC with Differential and Platelets		X	Includes hemoglobin, hematocrit, platelet count, and total leukocyte count including differential.
LFT Assessments		X	Includes aspartate aminotransferase (AST) and alanine aminotransferase (ALT), total bilirubin, direct bilirubin (only if total bilirubin is elevated), alkaline phosphatase, and gamma-glutamyl transferase (GGT) (only when alkaline phosphatase increases to ≥ Grade 2).
PT/aPTT/INR		X	
Urinalysis		X	Refer to Table 9.4.1-1
Thyroid Function Tests		X	TSH with free thyroxine (T4) and triiodothyronine (T3)
Serology	X		Refer to Table 9.4.1-1
Pregnancy Test		X	Women of childbearing potential (WOCBP) only at screening and within 24 hours prior to dosing.
Follicle Stimulating Hormone (FSH)	X		If needed to document postmenopausal status as defined in Appendix 4.
Adverse Event Reporting			
Monitor for Serious Adverse Events	X	X	All serious adverse events (SAEs) must be collected from the date of subject's written consent until 100 days post discontinuation of nivolumab (or 30 days if participant only received BMS-986205), or participant's participation in the study if the last scheduled visit occurs

Table 2-1: Screening Procedural Outline (CA017076)

Procedure	D -28 to D -1	D -14 to D -1	Notes
			at a later time. SAEs reported in the BMS EDC tool should be approved within 5 business days of entry.
Baseline Efficacy Assessments			
Diagnostic Imaging	X		Computed tomography (CT) with contrast is the preferred modality (Magnetic resonance imaging [MRI] if CT is not feasible). Assessment should include the chest/abdomen/pelvis at a minimum; and should include other anatomic regions as indicated by individual participant disease histories.
Brain Imaging	X		Brain imaging (CT/MRI) is only required for participants with known history or symptoms of brain metastases and have not had brain imagining within 30 days of anticipated first study drug administration.
Bone Scan	X		As clinically indicated (eg, participants with history of symptoms of bone metastases), but bone scans will not be considered a modality for assessment for measurable disease.

Table 2-2: On-Treatment: BMS-986205 Monotherapy (One 14-Day Cycle) Procedure Outline (CA017076)

Procedure	Cycle 0 D1	Cycle 0 D2	Cycle 0 D8	Cycle 0 D14	Notes
Admit to Clinical Facility	X			X	For the purpose of PK sample collection, participants will be admitted to the clinical facility prior to dosing on C0D1 and C0D14. Participants will remain at the clinical facility until after the dosing on the following day. Participants who are continuing treatment in Cycle 1 after completion of C0D14 will remain at the clinical facility until after dosing on C1D2.
Complete Physical Examination (PE)	X[a]				Predose.
Symptom-Directed PE		X	X	X	Predose.
Vital Signs and Oxygen Saturations	X		X	X	Includes temperature, seated blood pressure, and heart rate. Blood pressure and heart rate should be measured after the subject has been seated quietly for at least 5 minutes.
12-lead ECG	X			X	Collect single ECGs on C0D1 and C0D14 at -1 hour pre-dose and 2 and 4 hours postdose. ECGs should be performed after the subject has been resting supine for at least 5 minutes and should be completed prior to any PK/PD sample blood collections when assessments occur at the same time points.
Laboratory Tests[b]					
Chemistry (Excluding LFTs)	X[a]		X	X	Predose; includes assessments for sodium, potassium, chloride, total serum calcium, magnesium, bicarbonate/carbon dioxide, phosphorus, BUN, creatinine, c-reactive protein, glucose, total protein, albumin, amylase, lipase, and LDH.
Methemoglobin	X		X	X	Pre-dose on Day 1, 8 and 14; if elevated, see Section 7.4.6. Additional samples as clinically indicated.
Reticulocyte counts, haptoglobin and LDH	X		X	X	Reflex when methemoglobin is elevated over ULN. Additional samples as clinically indicated.
CBC with Differential and Platelets	X[a]		X	X	Collect predose. additional samples to be collected as clinically indicated Predose on Day 4 (± 1 day).

Table 2-2: On-Treatment: BMS-986205 Monotherapy (One 14-Day Cycle) Procedure Outline (CA017076)

Procedure	Cycle 0 D1	Cycle 0 D2	Cycle 0 D8	Cycle 0 D14	Notes
LFT Assessments	X[a]		X	X	Collect predose. Includes AST, ALT, total bilirubin, direct bilirubin (only if total bilirubin is elevated), alkaline phosphatase, and GGT (only when alkaline phosphatase is increased to ≥ Grade 2).
Pregnancy Test (WOCBP)	X				Serum or urine pregnancy test must be performed (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG) within 24 hours prior to administration of study drug. If pregnancy test is positive, hold all study drugs and perform confirmatory testing. If pregnancy is confirmed, permanently discontinue all study drugs and immediately notify sponsor per Section 9.2.5.
Concomitant Medication Assessments	X				Review prior to dosing.
Monitor for Nonserious Adverse Events	X				Nonserious AEs will be collected starting with the first dose of study drug and through 100 days after completion of study drugs (or 30 days if subject only received BMS-986205).
Monitor for Serious Adverse Events	X				All SAEs must be collected from the date of participant's written consent until 100 days post last dose of study drugs (or 30 days if participant only received BMS-986205) or participant's participation in the study if the last scheduled visit occurs at a later time. SAEs reported in the BMS EDC tool should be approved within 5 business days of entry.
Pharmacokinetic (PK) Assessments	X				See Section 9.5.1 and. Table 9.5.2-1. Performed in all subjects.
[redacted]					
Urine for p-Chloroaniline	X	X			See Section 9.5.1. Urine (0 to 24 hours) collection start after first dose. An approximately 50 mL aliquot of each urine collection (0 to 8 hours, 8 to 24 hours) will be frozen for shipment.

Table 2-2: On-Treatment: BMS-986205 Monotherapy (One 14-Day Cycle) Procedure Outline (CA017076)

Procedure	Cycle 0 D1	Cycle 0 D2	Cycle 0 D8	Cycle 0 D14	Notes
Study Drug Administration					
Dispense BMS-986205	X				BMS-986205 should be dispensed to participants at Day 1 of Cycle 0.
BMS-986205 Administration	Daily				BMS-986205 administration must be performed daily. BMS-986205 must be administered with a meal at approximately the same time each day. Dosing and associated meal should occur at the site on days when serial PK is collected.
Pill Diary	Daily				Pill diary should be provided to participants at Day 1 of Cycle 0. Pill diary must be completed with each administered daily dose of BMS-986205. Review pill diary during each visit for compliance of daily administration of BMS-986205. Collect pill diary at the completion of each cycle.

[a] C0D1 physical exam and laboratory tests do not need to be repeated if completed within the last 3 days (for all laboratory tests).

[b] Subjects who meet discontinuation criteria during or after Cycle 0 will have complete blood count (CBC) with differential, platelets, methemoglobin levels, and chemistry with LFTs done at the EOT and during the follow-up visit at 7 days.

Table 2-3: On-Treatment: BMS-986205 + Nivolumab (Multiple 4-Week Cycles) Procedure Outline (CA017076)

Procedure	Cycle 1 (4 weeks)				Cycle 2-12 (4-week cycles)			End of Treatment[a,b,c]	Notes
	D1	D8	D15 (±2 days)	D22 (±2 days)	D1	D15 (±2 days)	D22-28		
Admit to Clinical Facility	X								For the purpose of PK sample collection, participants will be admitted to the clinical facility prior to dosing on C1D1. Participants will remain at the clinical facility until after the dosing on the following day. See Table 9.5.2-1.
Safety Assessments									
Complete Physical Examination (PE)	X				X				Predose.
Symptom-Directed PE			X			X		X	Predose.
Vital Signs (VS) and Oxygen Saturations	X	X	X	X	X	X		X	Predose. Includes 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. For nivolumab, VS should be obtained prior to the infusion and then every 30 min (± 10 min) until 1 hour following completion of the infusion, except on C1D1 when VS will be obtained until 4 hours following completion of the infusion. If any vital sign is abnormal (based upon clinician assessment) at the final time point of each visit, the participant must be observed further for a period of time, as clinically indicated.

Table 2-3: On-Treatment: BMS-986205 + Nivolumab (Multiple 4-Week Cycles) Procedure Outline (CA017076)

Procedure	Cycle 1 (4 weeks)				Cycle 2-12 (4-week cycles)			End of Treatment[a,b,c]	Notes
	D1	D8	D15 (±2 days)	D22 (±2 days)	D1	D15 (±2 days)	D22-28		
12-lead ECG	X				X				12-lead ECGs should be recorded after the subject has been supine for at least 5 minutes. ECGs must be collected predose on Day 1 of each cycle.
Laboratory Tests	Laboratory tests must be performed within 3 days and results reviewed prior to dosing of nivolumab at Day 1 of each cycle, unless otherwise specified. All laboratory testing will be done weekly for Cycle 1 only, unless otherwise specified.								
Chemistry (Excluding LFTs)	X	X	X	X	X	X		X	Predose; includes assessments for sodium, potassium, chloride, total serum calcium, magnesium, phosphorus, BUN, creatinine, c-reactive protein, glucose, total protein, albumin, amylase, lipase, and LDH.
Methemoglobin	X	X	X	X	X			X	Collect predose. Starting with C2D1, collect every cycle and as clinically indicated.. Methemoglobin levels to be assessed on arterial or venous blood sample.
Reticulocyte counts, haptoglobin and LDH	X	X	X	X	X			X	Reflex when methemoglobin is elevated over ULN. Additional samples as clinically indicated.
CBC with Differential and Platelets	X	X	X	X	X	X		X	Predose.

Table 2-3: On-Treatment: BMS-986205 + Nivolumab (Multiple 4-Week Cycles) Procedure Outline (CA017076)

Procedure	Cycle 1 (4 weeks)				Cycle 2-12 (4-week cycles)			End of Treatment[a,b,c]	Notes
	D1	D8	D15 (±2 days)	D22 (±2 days)	D1	D15 (±2 days)	D22-28		
LFT Assessments	X	X	X	X	X	X		X	Predose; includes AST, ALT, total bilirubin, direct bilirubin (only if total bilirubin is elevated), alkaline phosphatase, and GGT (only when alkaline phosphatase is increased to ≥ Grade 2).
Thyroid Function Tests					X See notes (every 2 cycles)			X	Collect every 2 cycles, predose, beginning with C3D1 and at the end of treatment. To include TSH with reflex testing to free T3 and free T4 if TSH abnormal. Results should be examined by the investigator or appropriate designee within 48 hours of dose administration.
Pregnancy Test (WOCBP)	X				X			X	Serum or urine pregnancy test must be performed (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG) within 24 hours prior to administration of nivolumab. If pregnancy test is positive, hold all study drugs and perform confirmatory testing. If pregnancy is confirmed, permanently discontinue all study drug and immediately notify sponsor per Section 9.2.5.

Table 2-3: On-Treatment: BMS-986205 + Nivolumab (Multiple 4-Week Cycles) Procedure Outline (CA017076)

Procedure	Cycle 1 (4 weeks)				Cycle 2-12 (4-week cycles)			End of Treatment[a,b,c]	Notes
	D1	D8	D15 (±2 days)	D22 (±2 days)	D1	D15 (±2 days)	D22-28		
Adverse Event Reporting and Concomitant Medication Assessments									
Concomitant Medication Assessments	X	X	X	X	X	X	X	X	Review prior to dosing.
Monitor for Nonserious Adverse Events	X								Nonserious AEs will be collected starting with the first dose of study drug and through 100 days post last dose of study drugs.
Monitor for Serious Adverse Events	X								All SAEs must be collected from the date of subject's written consent until 100 days postdiscontinuation of nivolumab or subject's participation in the study if the last scheduled visit occurs at a later time. SAEs reported in BMS EDC should be approved within 5 business days of entry.
Sample Collection									
PK/ADA Assessments	X								Performed in all subjects. See Section **9.5.2.**
Pharmacodynamic Assessments	X								Performed in all subjects. See Section 9.6.

Table 2-3: On-Treatment: BMS-986205 + Nivolumab (Multiple 4-Week Cycles) Procedure Outline (CA017076)

Procedure	Cycle 1 (4 weeks)				Cycle 2-12 (4-week cycles)			End of Treatment[a,b,c]	Notes
	D1	D8	D15 (±2 days)	D22 (±2 days)	D1	D15 (±2 days)	D22-28		
Efficacy Assessments									
Diagnostic Imaging					X			X	To be collected at the end of Cycle 2 and then every 8 weeks (± 1 week), by methods used at baseline. See Section 9.1 and Section 9.4.2. Same modality/scanner should be used for all assessments. Assessed by RECIST v1.1; see Appendix 5. Assessment must be performed prior to initiating the next cycle of treatment.
Brain Imaging	X								As clinically indicated; see Section 9.1 and Section 9.4.2.
Bone Scan Imaging	X								As clinically indicated; see Section 9.1 and Section 9.4.2.
Study Drug Administration									
Dispense BMS-986205	X				X				BMS-986205 should be dispensed to participants at Day 1 of each cycle.
BMS-986205 Administration	X	Daily							BMS-986205 administration must be performed daily. BMS-986205 must be administered with a meal at approximately the same time each day. Dosing and associated meal should occur at the site on days when serial PK is collected.
Nivolumab Administration	X				X				Nivolumab should be administered at Day 1 of each cycle.

Table 2-3: On-Treatment: BMS-986205 + Nivolumab (Multiple 4-Week Cycles) Procedure Outline (CA017076)

Procedure	Cycle 1 (4 weeks)				Cycle 2-12 (4-week cycles)			End of Treatment[a,b,c]	Notes
	D1	D8	D15 (±2 days)	D22 (±2 days)	D1	D15 (±2 days)	D22-28		
Pill Diary	X	Daily						X	Pill diary should be provided to participants at Day 1 of each cycle. Pill diary must be completed with each administered daily dose of BMS-986205. 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.

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

[b] For subjects who complete all scheduled cycles of therapy, the EOT visit will be the same as the last scheduled and completed on-treatment visit (eg, Cycle 2 Day 22) and the start of the Week 1 Clinical/Safety Follow-Up visit.

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

Table 2-4: Follow-Up Procedure Outline (CA017076)

Procedure	Clinical Safety Follow-Up[a]			Notes
	FU 1 30 days (± 10 days)	FU 2 60 days (± 10 days)	FU 3 100 days (± 10 days)	
Safety Assessments				
Symptom-Directed Physical Examination	X	X	X	
Vital Signs	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.
Laboratory Tests				
Chemistry (Excluding LFTs)	X	X	X	Includes assessments for sodium, potassium, chloride, total serum calcium, magnesium, bicarbonate/carbon dioxide, phosphorus, BUN, creatinine, glucose, total protein, albumin, amylase, lipase, and LDH.
Methemoglobin	X	X	X	Only to be drawn if above ULN at last assessment; not required during follow up.
Reticulocyte count, LDH, and haptoglobin	X	X	X	Reflex when methemoglobin is elevated over ULN. Additional samples as clinically indicated.
CBC with Differential and Platelets	X	X	X	Additional samples as clinically indicated.
LFT Assessment	X	X	X	For participants with LFT abnormalities following the last dose of study drug, consider collecting weekly until normalized. Includes AST, ALT, total bilirubin, direct bilirubin (only if total bilirubin is elevated), alkaline phosphatase, and GGT (only when alkaline phosphatase is increased to ≥ Grade 2).

Table 2-4: Follow-Up Procedure Outline (CA017076)

Procedure	Clinical Safety Follow-Up[a]			Notes
	FU 1 30 days (± 10 days)	FU 2 60 days (± 10 days)	FU 3 100 days (± 10 days)	
Thyroid Function Tests	X	X	X	To include TSH with reflex testing (free T3 and free T4).
Pregnancy Test	X	X	X	For WOCBP; serum or urine pregnancy test may be performed (clinic urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG). If positive, perform confirmatory testing. If pregnancy is confirmed, immediately notify sponsor per Section 9.2.5.
Adverse Event Reporting and Concomitant Medication Assessments				
Monitor for Nonserious Adverse Events	X	X	X	Nonserious AEs will be collected starting with the first dose of study drug and through 100 days post last dose of study drugs (or 30 days if participant only received BMS-986205).
Monitor for Serious Adverse Events	X	X	X	All SAEs must be collected from the date of participant's written consent until 100 post last dose of study drugs (or 30 days if participant only received BMS-986205) or participant's participation in the study if the last scheduled visit occurs at a later time. SAEs reported in the BMS EDC should be approved within 5 business days of entry.
Concomitant Medication Assessments	X	X	X	
Sample Collection				
PK/ADA Assessments	X	X		See Section 9.5.2.
Efficacy Assessments				

Table 2-4: Follow-Up Procedure Outline (CA017076)

Procedure	Clinical Safety Follow-Up[a]			Notes
	FU 1 30 days (± 10 days)	FU 2 60 days (± 10 days)	FU 3 100 days (± 10 days)	
Tumor/Response Assessments			X[b]	Diagnostic imaging by method used at baseline, an unconfirmed PR or CR must be confirmed at least 4 weeks after initial assessments.
New Subsequent Anti-Cancer Therapies	X	X	X	Any new anti-cancer therapies (including surgery and radiotherapy) will be recorded.

[a] Follow-up visits at Days 30, 60, and 100 (± 10 days) should occur after the last dose of study drugs (or at Day 30 if participant only received BMS-986205) or should coincide with the date of discontinuation ± 10 days if date of discontinuation is greater than 30 days after the last dose to monitor for adverse events.

[b] Only participants who have not discontinued study treatment for progressive disease.

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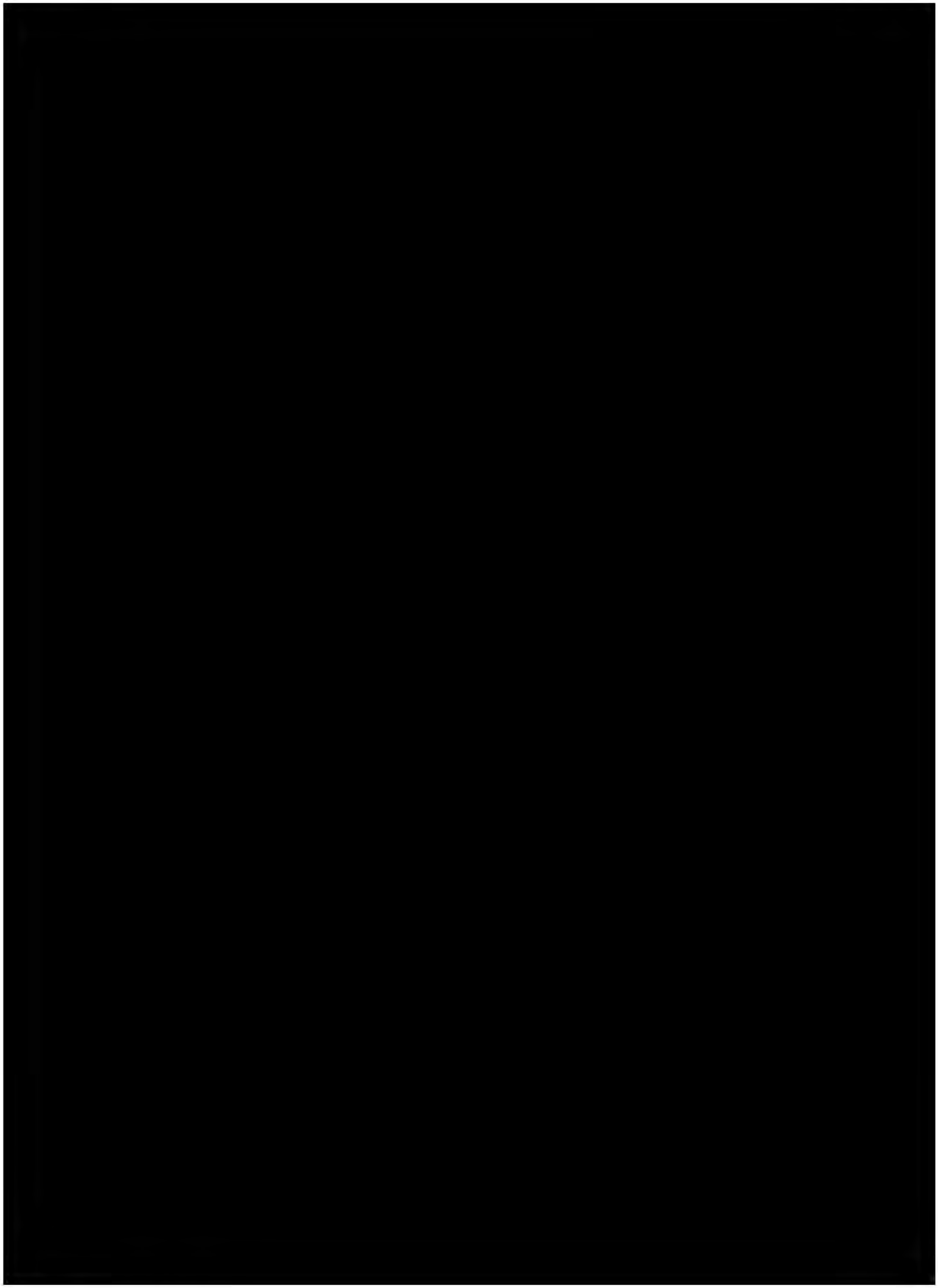

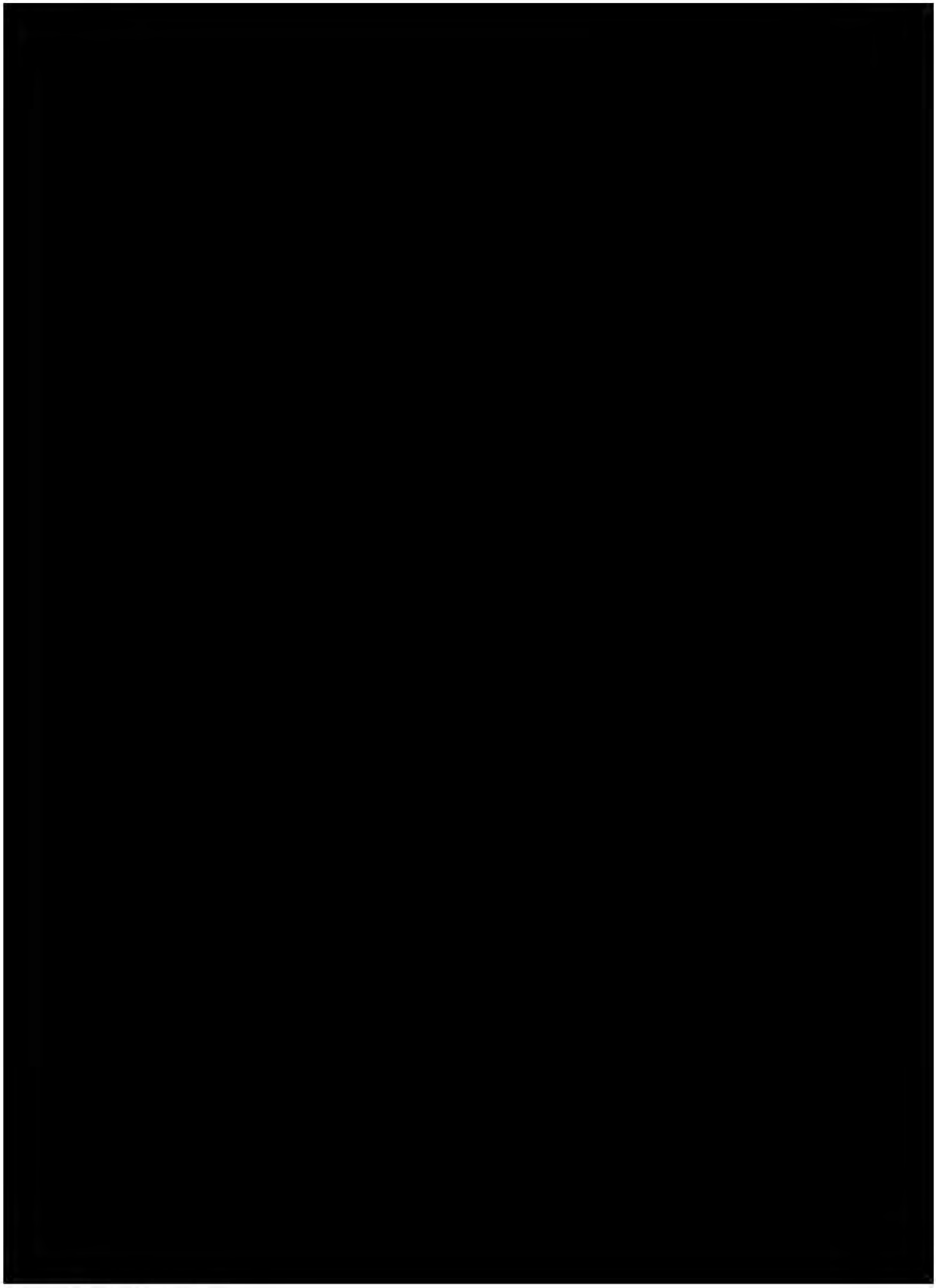

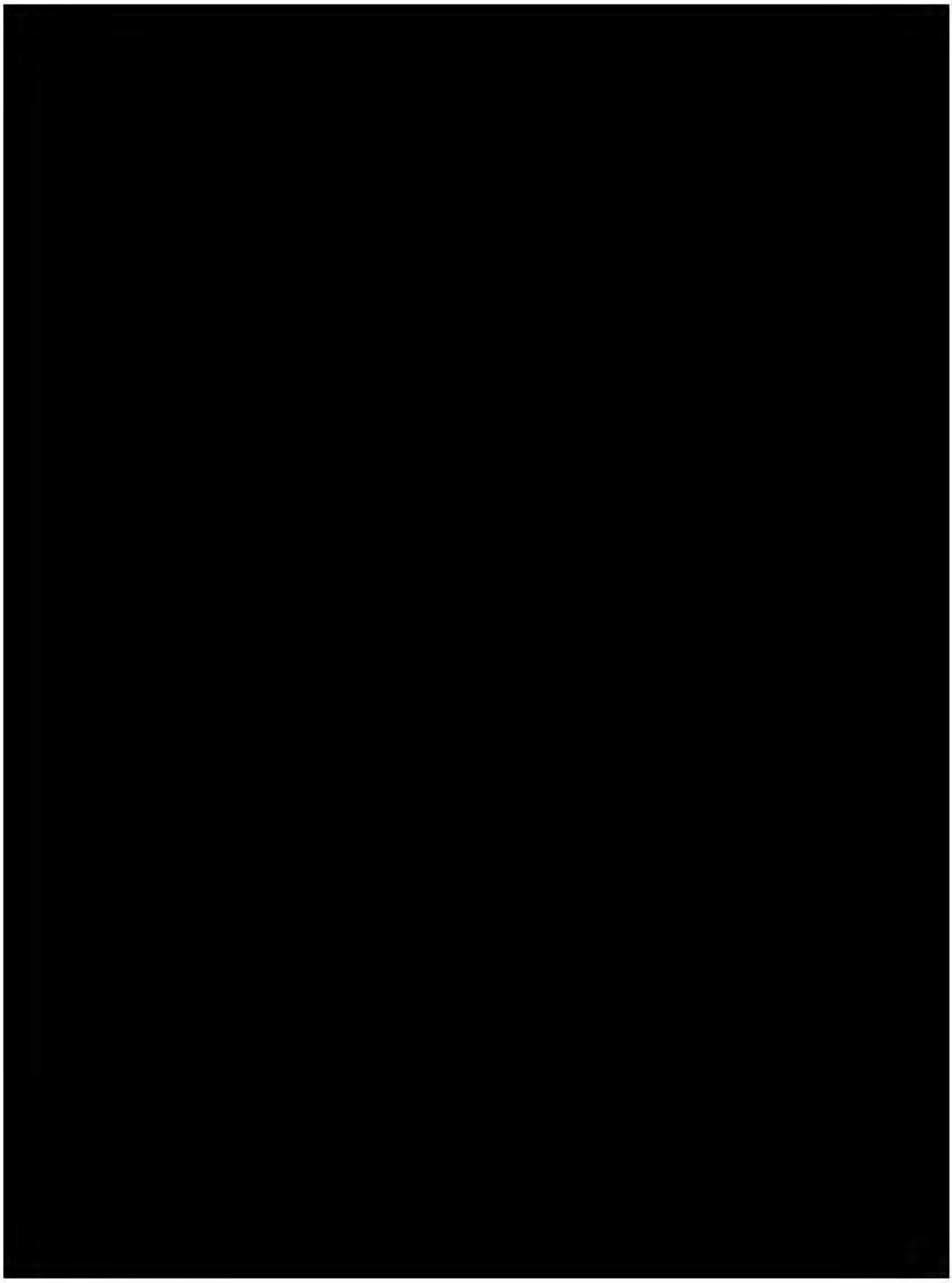

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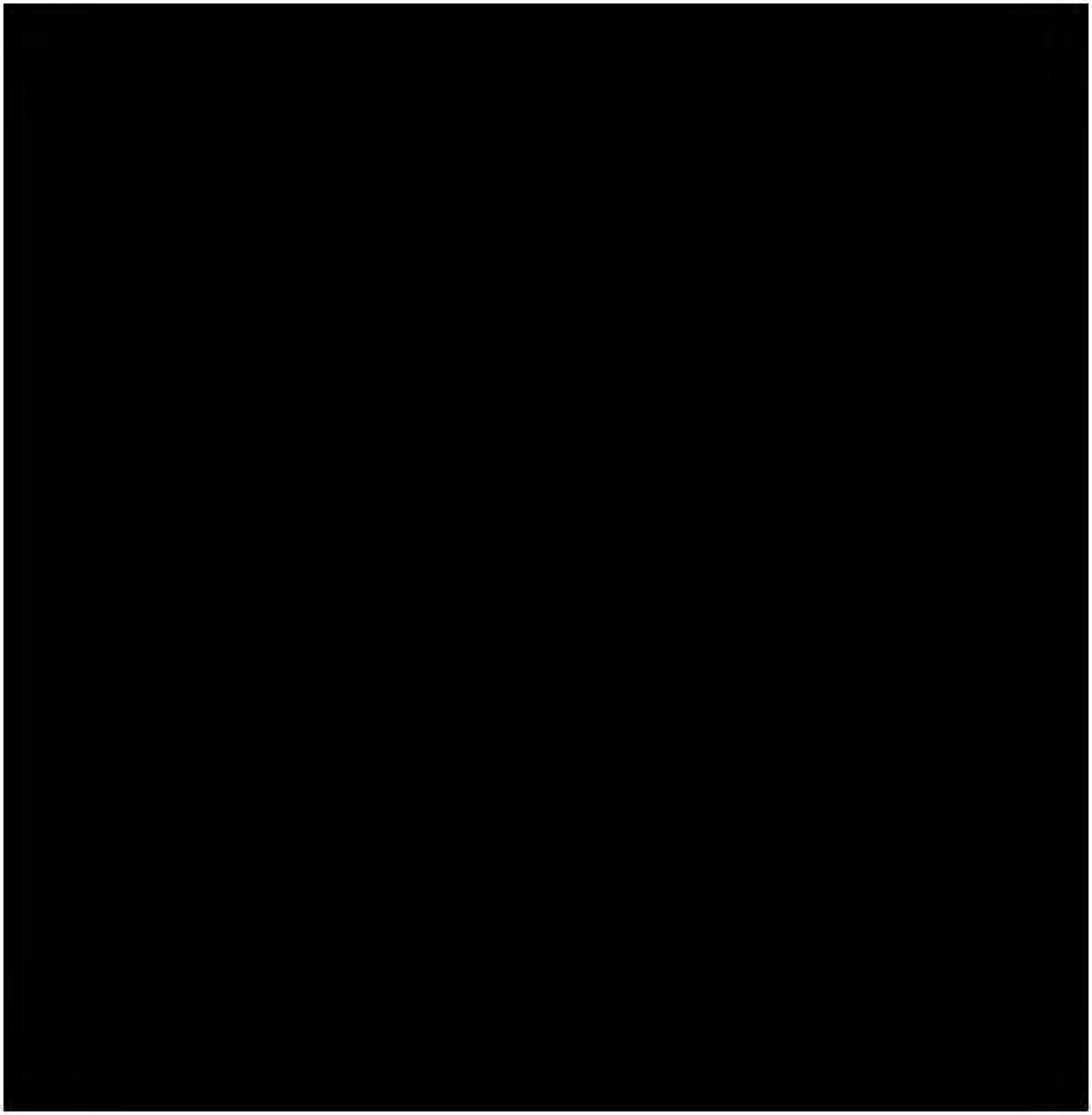

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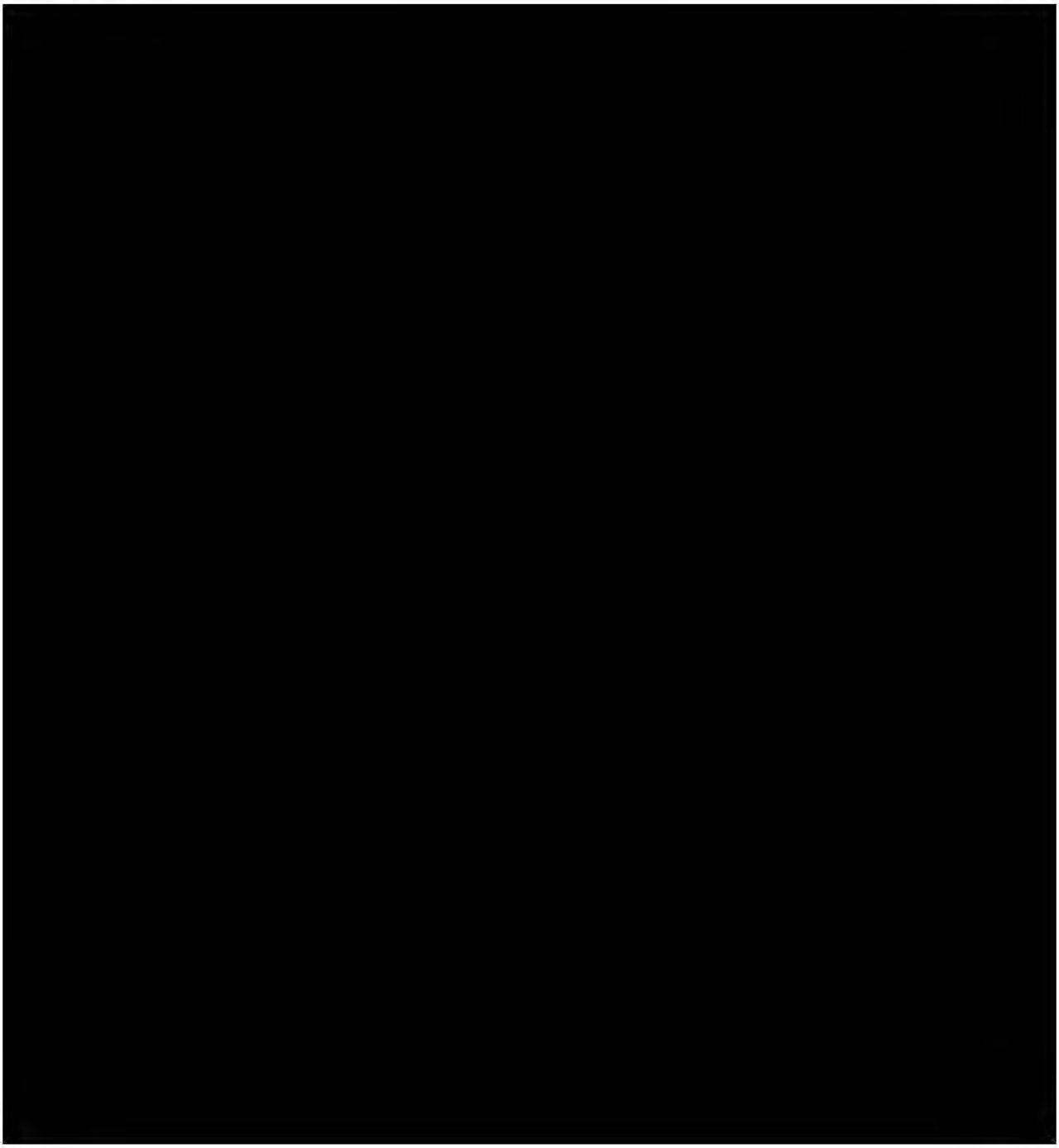

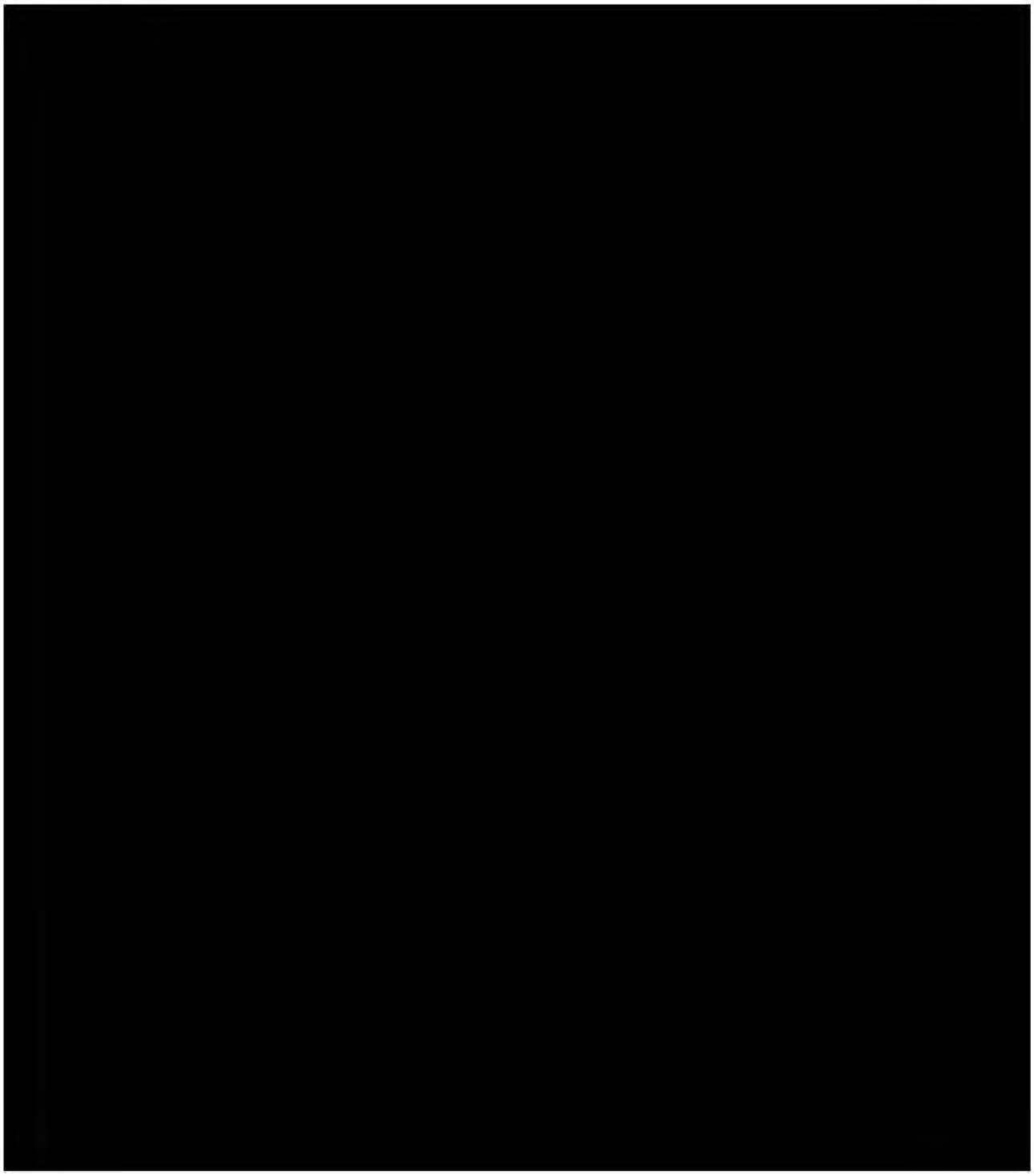

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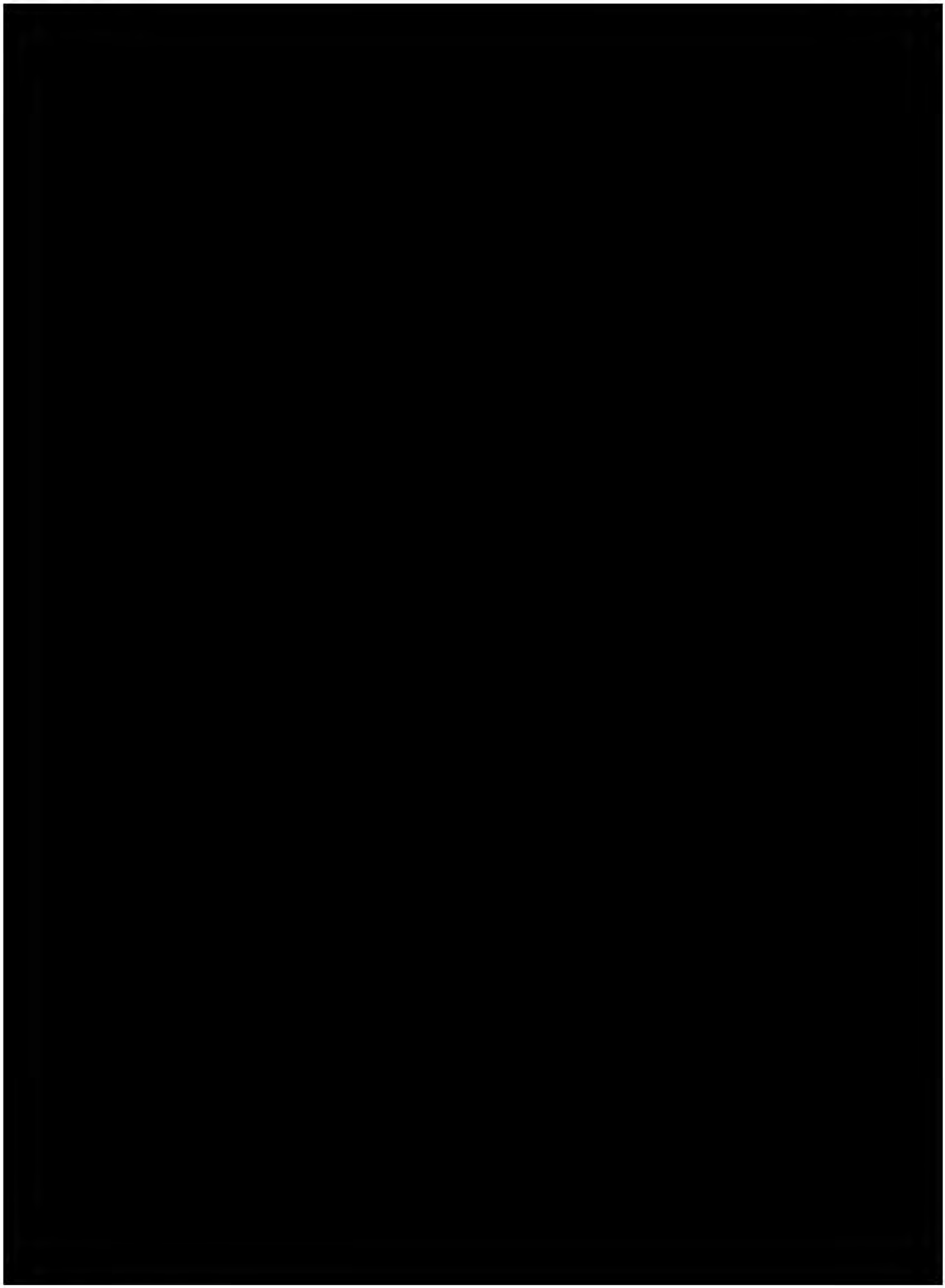

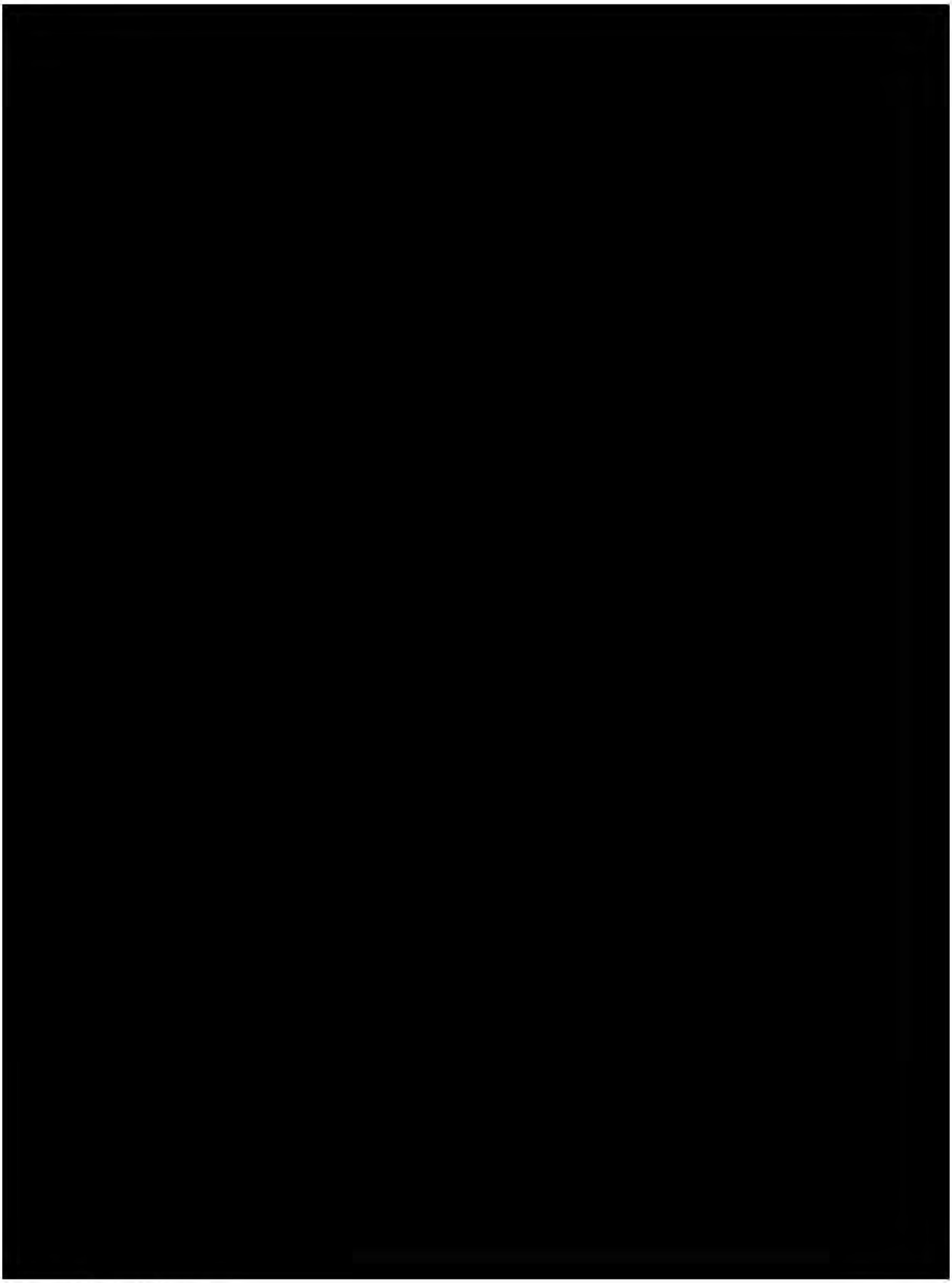

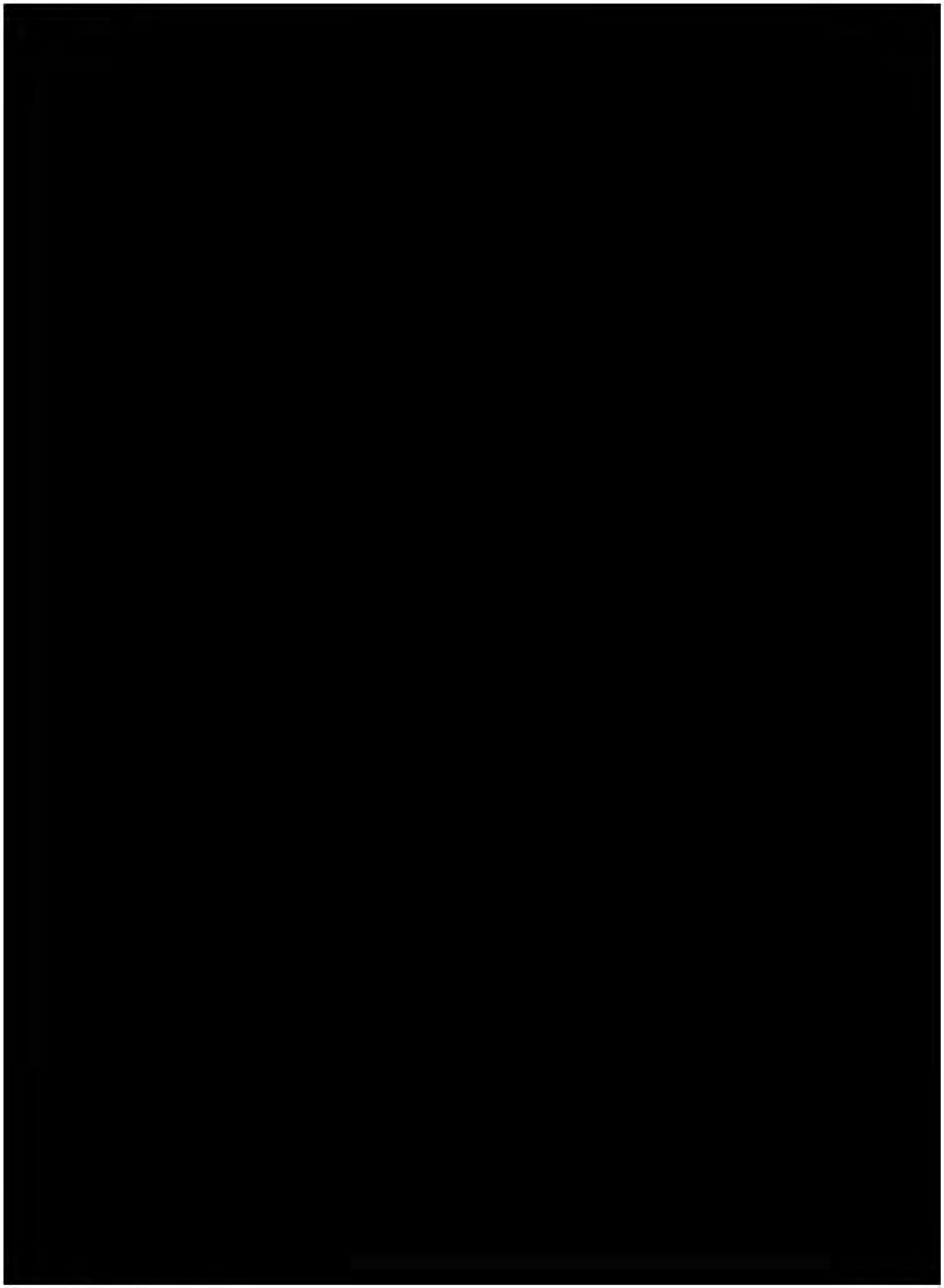

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4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
• The primary objective of this study is to characterize the PK and assess the safety and tolerability of BMS-986205 administered alone and in combination with nivolumab in Chinese participants with advanced malignant tumors.	• PK parameters Incidence of AEs, SAEs, AEs leading to discontinuation, deaths, and laboratory abnormalities
The secondary objectives of this study are: • To characterize the pharmacodynamic activity of BMS-986205 administered alone and in combination with nivolumab. • To characterize the immunogenicity of nivolumab when administered in combination with BMS-986205. • To investigate the preliminary anti-tumor activity of BMS-986205 administered in combination with nivolumab in advanced malignant tumors.	• Incidence of anti-drug antibodies (ADA) to nivolumab; measurement of serum kynurenine and tryptophan levels • ORR, best overall response (BOR) and duration of response (DOR) as assessed per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 by investigator

5 STUDY DESIGN

5.1 Overall Design

This is a Phase 1/2, open-label study of BMS-986205 administered as a monotherapy and in combination with nivolumab in participants with advanced malignant solid tumors.

Treatment will start with a 2-week monotherapy lead-in (Cycle 0) whereby

BMS-986205 100 mg oral daily dose must be administered with a meal at approximately the same time each day.

Participants will then proceed to receive the combination of nivolumab and BMS-986205. Nivolumab will be administered at a dose of 480 mg IV Q4W.

Cycle 0

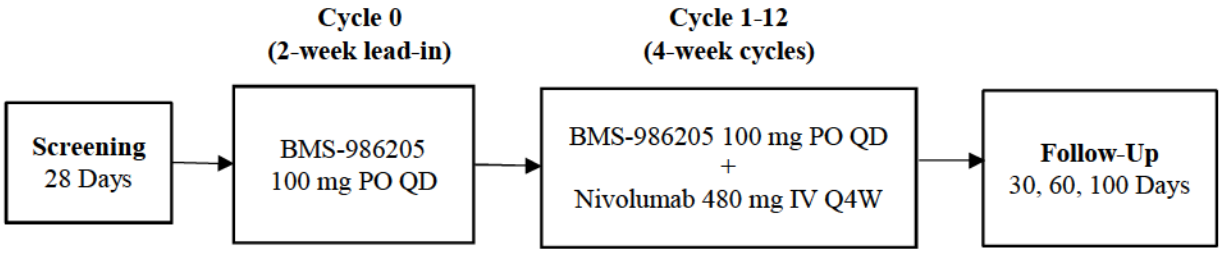
Participants will start with Cycle 0, which is a 2-week BMS-986205 monotherapy lead-in, with a 100-mg oral daily dose. Participants who have received at least 75% of doses in Cycle 0 will be eligible to proceed to receive the combination of nivolumab and BMS-986205 (Cycle 1).

The following AEs will prohibit a participant from proceeding to combination with nivolumab (Cycle 1):

- Grade 2 or higher immune-related AEs (irAEs) considered related to BMS-986205 (eg, immune-mediated pneumonitis, colitis, hepatitis, nephritis, and renal dysfunction) with the exception of immune-mediated hypothyroidism and hyperthyroidism
- Grade 2 AST and ALT elevations that do not resolve to Grade 1 or baseline within 1 week
- ≥ Grade 3 elevation of AST, ALT, or total bilirubin that persists for ≥ 7 days
- Grade 2 AST or ALT elevation with symptomatic liver inflammation (eg, right upper quadrant tenderness, jaundice, pruritus)
- AST or ALT > 3× upper limit of normal (ULN) and concurrent total bilirubin > 2× ULN without initial findings of cholestasis (elevated serum alkaline phosphatase, eg, findings consistent with Hy's law or FDA definition of potential drug-induced liver injury [DILI])
- Grade 2 or greater episcleritis, uveitis, or iritis
- Any other Grade 2 eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks OR requires systemic treatment
- Grade 3 or greater uveitis, pneumonitis, bronchospasm, neurologic toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
- Any Grade 3 or greater non-dermatologic, non-hepatic, non-hematologic toxicity with the following specific EXCEPTIONS:
  - Grade 3 or Grade 4 electrolyte abnormalities that are not complicated by associated clinical adverse experiences, last less than 48 hours and either resolve spontaneously or respond to conventional medical intervention
  - Grade 3 nausea, vomiting, or diarrhea that lasts less than 48 hours, and either resolves spontaneously or responds to conventional medical intervention
  - Isolated Grade 3 elevation of amylase or lipase not associated with clinical or radiographic evidence of pancreatitis
  - Isolated Grade 3 fever not associated with hemodynamic compromise (eg, hypotension, clinical or laboratory evidence of impaired end-organ perfusion)
  - Grade 3 endocrinopathy that is well-controlled by hormone replacement
  - Grade 3 tumor flare (defined as pain, irritation, or rash that localizes to site of known or suspected tumor)
  - Grade 3 fatigue
- Grade 3 rash if no improvement (ie, resolution to ≤ Grade 1) after a 1- to 2-week dose delay.
- Grade 4 rash of any duration
- Methemoglobin levels ≥ 15% and study-drug related
- Grade 4 neutropenia ≥ 5 days in duration and study-drug related
- Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding (study-drug related), or any requirement for platelet transfusion (study-drug related)
- Grade ≥ 3 febrile neutropenia for 48 hours, study-drug related
- Grade ≥ 3 hemolysis (ie, requiring transfusion or medical intervention such as steroids), study-drug related
- Grade 4 anemia not explained by underlying disease (study-drug related)

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

Figure 5.1-1: Study Design Schematic



Treatment may continue from Cycle 0 (2 weeks) until 50 weeks (or up to a total maximum of 98 weeks if applicable), disease progression, or withdrawal of consent.

In addition, cohort may be expanded in this study to gather additional safety, tolerability, PK, pharmacodynamics, and preliminary efficacy information regarding BMS-986205 in combination with nivolumab in certain tumor type(s).

Participants will complete up to 3 phases of the study: Screening, Treatment, and Clinical/Safety Follow-up, as described below.

Screening

The screening phase will last for up to 28 days. Screening begins by establishing the participant's initial eligibility and signing the informed consent form (ICF).

Treatment

The treatment phase consists of the 2-week monotherapy lead-in (Cycle 0) and up to twelve 4-week combination therapy cycles. The 2-week lead-in treatment consists of a single oral daily dose of BMS-986205. The combination therapy cycles are comprised of an oral daily dose of BMS-986205 and one dose of nivolumab administered intravenously Q4W on Day 1 of each treatment cycle up to 12 cycles. Total study treatment period is up to 50 weeks.

Following every two combination therapy treatment cycles (8 weeks) starting with Cycle 1, the decision to treat a participant with additional cycles of study therapy will be based on radiological tumor assessments (initial evaluation performed at baseline, end of Cycle 2, and every 8 weeks). Assessments of PR and CR must be confirmed at least 4 weeks following initial assessment. Tumor progression or response endpoints will be assessed using RECIST v1.1 criteria for solid tumors (Appendix 5).

Treatment beyond progression may be allowed in select participants with initial RECIST v1.1 disease progression (PD) after discussion and agreement with the BMS medical monitor (with proper documentation in the Trial Master File) that the benefit/risk assessment favors continued administration of study therapy (eg, participants are continuing to experience clinical benefit as assessed by the investigator, tolerating treatment, and meeting other criteria specified in Section 8.1.2).

Participants with a response of stable disease (SD), PR, or CR at the end of a given cycle will continue to the next treatment cycle. Participants will generally be allowed to continue study therapy until the first occurrence of either: 1) completion of the maximum number of 12 cycles; 2) PD; 3) clinical deterioration suggesting that no further benefit from treatment is likely; 4) intolerability to therapy; or 5) the participant meets criteria for discontinuation of study therapy as outlined in Section 7.4.4. Individual participants with confirmed CR will be given the option to discontinue study therapy on a case-by-case basis after specific consultation and agreement between the investigator and BMS medical monitor in settings where benefit/risk justify discontinuation of study therapy.

In all parts of this study, all participants will be treated for 48 weeks of BMS-986205 in combination with nivolumab unless criteria for study drug discontinuation are met earlier (Section 7.4.4). All participants completing approximately 48 weeks of combination study therapy with ongoing disease control (CR, PR, or SD) may be eligible for an additional 48 weeks of study therapy at the originally assigned dose regimen beyond the initial 48 weeks, on a case-by-case basis, after careful evaluation and discussion with the BMS medical monitor to determine whether the benefit/risk ratio supports administration of further study drug. Subjects whose last assessment of the initial 48-week period shows PD will also be eligible to continue to additional cycles if they are still deriving clinical benefit, as per the guidance of treatment beyond progression (Section 8.1.2). Upon completion of 48 weeks of combination treatment (or up to a maximum of 96 weeks if applicable), all subjects will enter the Clinical/Safety Follow-Up period.

Clinical/Safety Follow-Up

Upon completion of 48 weeks of combination treatment (or up to a maximum of 96 weeks if applicable), all participants will enter the Clinical/Safety Follow-Up period after the decision is made to discontinue the participant from treatment (eg, at end of treatment [EOT]).

For participants who complete all scheduled cycles of therapy, the EOT visit will be the same as the last scheduled and completed on-treatment visit, and the start of the Week 1 Clinical/Safety Follow-Up visit. For participants who do not complete all scheduled cycles of therapy, the EOT visit will be the most recent on-treatment visit (with all available safety and response data) and does not need to be repeated, and will be considered the start of the Week 1 Clinical/Safety Follow-Up visit.

Participants who discontinue the treatment phase will enter the Clinical/Safety Follow-Up period. Participants must be followed for at least 100 days after the last dose of study therapy or 30 days if participant only received BMS-986205. Follow-up visits should occur at Days 30, 60, and 100 (± 10 days) after the last dose of study therapy or should coincide with the date of discontinuation (± 10 days) if date of discontinuation is greater than 30 days after the last dose of study therapy to monitor for AEs. All participants will be required to complete one (if participant only received BMS-986205) or three Clinical/Safety Follow-Up visits regardless of whether they start a new anti-cancer therapy, except those participants who withdraw consent for study participation.

5.1.1 Data Monitoring Committee and Other External Committees

Not applicable.

5.2 Number of Participants

A sample size of 12 PK evaluable subjects is proposed for this study. Based on preliminary PK results from Study CA017003 cohorts 25 to 200 mg, assuming the inter-subject coefficient of variation (CV) for AUC24 is 42%, a sample size of 12 PK evaluable subjects will be sufficient for the point estimates of the mean PK parameter to fall within 80% to 125% of the true value, with 91% confidence level. Assuming the inter-subject CV for Cmax is 29%, a sample size of 12 PK evaluable subjects will be sufficient for the point estimates of the mean PK parameter to fall within 80% to 125% of the true value, with 98% confidence level. Twelve subjects will provide 90% probability of observing at least 1 occurrence of a specific AE that would occur with an 18% incidence in the population. If a participant discontinues before or at Cycle 1 Day 1, an additional patient will be enrolled to ensure 12 PK evaluable participants are to be enrolled in this study.

5.3 End of Study Definition

The start of the trial is defined as first visit for first participant screened. End of trial is defined as the last visit or scheduled procedure shown in the Schedule of Activities 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.

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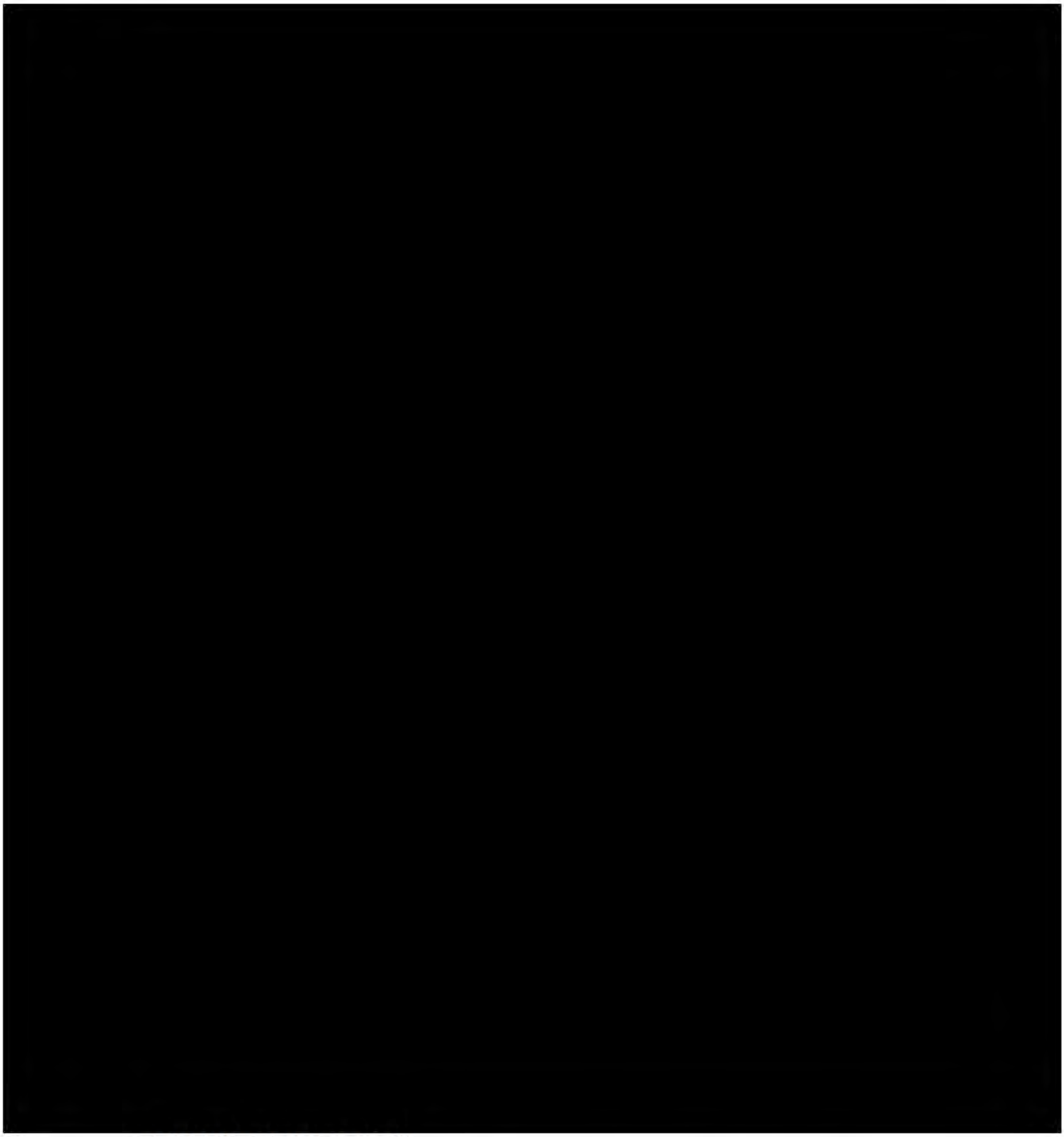


6 STUDY POPULATION

For entry into the study (prior to C0D1), the following criteria MUST be met.

6.1 Inclusion Criteria

1) Signed Written Informed Consent

a) The participant must sign and date an IRB/IEC-approved ICF prior to the performance of any study related procedures that are not considered part of standard of care.

2) Type of Participant and Target Disease Characteristics

a) Participants must have histologic or cytological confirmation of a malignancy (solid tumor) that is advanced (metastatic and/or unresectable) with measureable disease per RECIST v1.1 (see Appendix 5).

b) Participants must have received, and then progressed or been intolerant to at least one standard treatment regimen in the advanced or metastatic setting, if such a therapy exists. Participants who refuse or are ineligible for standard therapy will be allowed to enroll provided refusal/ineligibility is documented.

c) Participants must have an Eastern Cooperative Oncology Group performance status of ≤ 1.

d) Participants must be able to swallow pills or capsules.

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

f) Participants with prior exposure to therapy with any agent specifically targeting checkpoint pathway inhibition other than PD-1 or PD-L1 (such as; anti-PDL-2, anti-lymphocyte activation gene 3 [LAG-3], and anti CTLA-4 antibody) are permitted after a washout period of any time greater than 4 weeks from the last treatment. Participants with prior therapy with any agent specifically targeting T-cell costimulation pathways such as anti-glucocorticoid-induced tumor necrosis factor receptor (TNFR) family related gene antibody, anti-CD137, anti-OX40 antibody, are permitted after a washout period of any time greater than 4 weeks from the last treatment.

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

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

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

h) Participants must have blood methemoglobin levels within the ULN.

i) Participants must have adequate marrow function for participants with solid tumor histologies as defined by the following:

   – White blood cells (WBC) ≥ 2000/μL (stable off any growth factor within 4 weeks of first study drug administration)

- Neutrophils ≥ 1500/μL (stable off any growth factor within 4 weeks of first study drug administration)
- Platelets ≥ 100× 10^3/μL (transfusion to achieve this level is not permitted within 2 weeks of first study drug administration)
- Hemoglobin ≥ 8.5 g/dL (transfusion to achieve this level is not permitted within 2 weeks of first study drug administration)

j) Participants must have adequate other organ function as defined by the following:

i) ALT and AST ≤ 3× institutional ULN

ii) Total bilirubin ≤ 1.5× institutional ULN (except participants with Gilbert's Syndrome who must have normal direct bilirubin)

iii) Normal thyroid function, subclinical hypothyroidism (thyroid-stimulating hormone [TSH] < 10 mIU/mL) or have controlled hypothyroidism on appropriate thyroid supplementation

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

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

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

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

l) Life expectancy ≥ 3 months.

3) Age and Reproductive Status

a) Participants must be male and female, age ≥ 18 years at the time of informed consent.

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

c) Women must not be pregnant or breastfeeding.

d) WOCBP must agree to follow instructions for method(s) of contraception (Appendix 4) for the duration of treatment with study treatment(s) plus 5 months (approximately 23 weeks) post-treatment completion.

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception (Appendix 4) for the duration of treatment with study treatment(s) plus an additional 7 months (approximately 31 weeks) post-treatment completion. In addition, male participants must be willing to refrain from sperm donation during this time.

f) Males who are sexually active with WOCBP must agree to use a condom (see Appendix 4) for the duration of treatment with study treatment plus 7 months after the last dose of the study treatment (ie, 90 days [duration of sperm turnover] plus the time required for nivolumab to undergo approximately 5 half-lives). In addition, male subjects must be willing to refrain from sperm donation during this time. This criteria applies to azoospermic males as well.

g) WOCBP who are continuously not heterosexually active are also exempt from contraceptive requirements, but 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 (Appendix 4) that have a failure rate of < 1% when used consistently and correctly. It is important to note that contraceptive methods that rely on hormones are not considered highly effective for subjects receiving BMS-986205.

6.2 Exclusion Criteria

1) Target Disease Exceptions

a) Participants with known or suspected CNS metastases, untreated CNS metastases, or with the CNS as the only site of disease are excluded. However, participants with controlled brain metastases will be allowed to enroll. Controlled brain metastases are defined as no radiographic progression for at least 4 weeks following radiation and/or surgical treatment (or 4 weeks of observation if no intervention is clinically indicated), and off of steroids for at least 2 weeks, and no new or progressive neurological signs and symptoms. Please note: SCCHN participants with direct extension of tumor through the base of skull will not be excluded, as they are considered distinct from hematogenously spread parenchymal brain metastasis.

b) Participants must not have ocular melanoma.

2) Medical History and Concurrent Disease

a) Participants must not have a personal or family history or presence of cytochrome b5 reductase deficiency, or other diseases that puts them at risk of methemoglobinemia.

b) Participants must not have a prior history of serotonin syndrome.

c) Participants must not have a history of or current G6PD deficiency (quantitative or qualitative assessments will be checked during screening). Participants must also not have any other congenital or autoimmune hemolytic disorders. If participant has history of transient acquired hemolytic anemia, discuss with medical monitor for study eligibility.

d) Participants must not have a history or presence of hypersensitivity or idiosyncratic reaction to methylene blue.

e) Participants with a prior malignancy are excluded (except non-melanoma skin cancers, and in situ cancers such as the following: bladder, colorectal, cervical/dysplasia, melanoma, or breast). Participants with other second malignancies diagnosed more than 2 years ago who have received therapy with curative intent with no evidence of disease during the interval who are considered by the investigator to present a low risk for recurrence will be eligible.

f) Participants must not have other active malignancy requiring concurrent intervention.

g) Participants must not have prior organ allograft or allogeneic bone marrow transplantation.

h) Participants must not have any anti-cancer therapy (eg, chemotherapy, biologics, vaccines, or hormonal treatment) including investigational drugs within 4 weeks prior to the first dose of study drug administration, except for non-cytotoxic therapies, for which at least

4 weeks or 5 half-lives (whichever is shorter) must have elapsed between last dose and first treatment with any study drugs; if 5 half-lives is shorter than 4 weeks, agreement with the Medical Monitor must be obtained.

i) Participants must not have had prior therapy with an IDO inhibitor.

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

k) Participants must not have a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration.

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

l) Participants must not require daily supplemental oxygen.

m) Participants must not have uncontrolled or significant cardiovascular disease including, but not limited to, any of the following:
   i) Myocardial infarction or stroke/transient ischemic attack within the past 6 months.
   ii) Uncontrolled angina within the past 3 months.
   iii) Any history of clinically significant arrhythmias (such as ventricular tachycardia, ventricular fibrillation, or Torsades de pointes).
   iv) QT interval corrected for heart rate using Fridericia's formula (QTcF) prolongation ≥ 480 msec.
   v) History of other clinically significant heart disease (eg, cardiomyopathy, congestive heart failure with New York Heart Association functional classification III-IV, pericarditis, significant pericardial effusion, or myocarditis).
   vi) Cardiovascular disease-related requirement for daily supplemental oxygen therapy.

n) Participants must not have a history of any chronic hepatitis as evidenced by:
   i) Positive test for hepatitis B surface antigen.
   ii) Positive test for qualitative hepatitis C viral load (by polymerase chain reaction [PCR]).

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

o) Participants must not have a history of other preexisting liver disease (eg, nonalcoholic fatty liver disease [NAFLD]).

p) Participants must not have significant gastrointestinal disease, or other conditions known to interfere significantly with the absorption of oral medication. Contact BMS medical monitor/designee if needed.

q) Participants must not have active interstitial lung disease/pneumonitis or with a history of interstitial lung disease/pneumonitis requiring steroids.

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

s) Participants must not have a known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).

Note: Testing for HIV must be performed at site.

t) Participants must not show evidence or history of active or latent tuberculosis infection including PPD recently converted to positive; chest x-ray with evidence of infectious infiltrate; and recent unexplained changes in fever/chill patterns.

u) Participants must not have had any major surgery within 4 weeks of study-drug administration. Participants must have recovered from the effects of major surgery or significant traumatic injury at least 14 days before the first dose of study drug.

v) All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have resolved to Grade 1 (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v5.0) or baseline before administration of study drug. Participants with toxicities attributed to prior anti-cancer therapy that are not expected to resolve and result in long lasting sequelae, such as neuropathy after platinum based therapy, are permitted to enroll.

w) Participants must not have a history of life-threatening toxicity related to prior immune therapy (eg, anti-CTLA-4 or anti-PD-1/PDL-1 treatment or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways).

x) Participants must not have a known or underlying medical condition that, in the opinion of the investigator or sponsor, could make the administration of study drug hazardous to the participants, or could adversely affect the ability of the participant to comply with or tolerate the study.

3) Prior/Concomitant Therapy

a) Participants must be able to comply with restrictions and prohibited treatments as listed in Section 7.7, Concomitant Therapy.

b) Participants with prior exposure to anti PD-1 or anti-PDL1 therapy must be excluded.

c) Participants must not use any strong inhibitors of CYP3A4 and/or CYP1A2 or strong inducers of CYP3A4 and/or CYP1A2 (see Appendix 8).

d) Participants must not use non-oncology vaccines containing live virus for prevention of infectious diseases within 12 weeks prior to study drug. The use of inactivated seasonal influenza vaccines will be permitted on study without restriction.

e) Participants must not use packed red blood cells or have a platelet transfusion within 2 weeks prior to the first dose of study drug.

f) Prior Traditional Chinese Medicines (TCMs) are not prohibited; however, prior TCMs with anti-cancer claims should be stopped for at least 14 days prior to dosing. Prior use of TCMs is not considered prior-line of therapy.

4) Physical and Laboratory Test Findings

a) Participants must not exhibit any of the following on a 12-lead ECG prior to study drug administration, confirmed by repeat:

i) QRS ≥ 120 msec, except right bundle branch block

ii) QTcF ≥ 480 msec, except right bundle branch block

5) Allergies and Adverse Drug Reaction

a) Participants must not have a history of allergy to any of the study treatment components.

b) Participants must not have a history of any significant drug allergy (such as anaphylaxis or hepatotoxicity) to prior anticancer immune-modulating therapies (for example, checkpoint inhibitors and T cell costimulatory antibodies).

6) Other Exclusion Criteria

a) Prisoners or participants who are involuntarily incarcerated are excluded from the study. (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 BMS approval is required.)

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

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.

6.4 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 serious AEs.

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 pre-treatment failure (ie, participant has not been treated). If re-enrolled, the participant must be re-consented. Retesting of laboratory parameters and/or other assessments within any single screening period will be permitted (in addition to any parameters that require a confirmatory value). The most current result prior to treatment is the value by which study inclusion will be assessed, as it represents the participant's most current, clinical state.

Laboratory parameters and/or assessments that are included in Table 2-1 may be repeated in an effort to find all possible well-qualified participants. Consultation with the medical monitor 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 treatment allocation.

Study treatment includes Investigational [Medicinal] Product (IP/IMP) and can consist of the following:

- BMS-986205
- Nivolumab

Product description and storage information are described in Table 7-1. Preparation, administration, and storage instructions will be provided separately. An IP, also known as IMP 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 IP. Not applicable for this study.

Table 7-1: Study Treatments for CA017076

Product Description / Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
BMS-986205	100 mg	IP	Open Label	Tablet	Refer to the label on container and/or pharmacy manual
BMS-986205	50 mg	IP	Open Label	Tablet	Refer to the label on container and/or pharmacy manual
Nivolumab Solution for Injection	10 mg/mL (100-mg/vial)	IP	Open Label	Vial	Refer to the label on container and/or pharmacy manual

7.1 Treatments Administered

The selection and timing of dose for each participant is shown in Table 7.1-1:

Table 7.1-1: Selection and Timing of Dose

Study Treatment	Unit dose strength(s)/Dosage level(s)	Dosage formulation Frequency of Administration	Route of Administration
BMS-986205	100 mg/tablet	1 tablet/daily	Oral
Nivolumab	480 mg	Solution for injection/ every 4 weeks	IV

7.1.1 BMS-986205 Administration

A bottle of BMS-986205 should be dispensed to participants at Day 1 of each cycle.

BMS-986205 is administered as a tablet. The tablet must be administered by mouth, swallowed whole, and not be crushed, chewed, dissolved, or altered in any way. BMS-986205 100 mg oral daily dose must be administered with a meal at approximately the same time each day. On the morning of Cycle 0 Days 1 and 14, and Cycle 1 Day 1 when serial PK samples are collected, after fasting for at least 10 hours, each participant will receive a single oral dose of BMS-986205 within approximately 5 minutes of completing a meal. At the time of dosing, approximately 240 mL of water will be administered to the participant along with BMS-986205. The time of BMS-986205 administration will be called "0" hour.

7.1.2 Nivolumab Administration

During combination therapy, infusion of nivolumab should start approximately 30 minutes following BMS-986205. Nivolumab should be infused over 30 minutes. Further details regarding preparation and administration will be provided separately in site/pharmacy materials. Restrictions related to food and fluid intake are described in Section 7.7.2.

7.2 Method of Treatment Assignment

Enrolled participants, including those not dosed, will be assigned sequential participant numbers starting with 00001 (eg, 00001, 00002, 00003.... 00010). Those enrolled participants meeting inclusion and exclusion criteria will be eligible to be dosed.

[redacted]

7.4 Dosage Modification

The sponsor will carefully review the totality of the safety data observed among the 12 Chinese patients treated with nivolumab and BMS-986205. If such review suggests that the risk profile of the treatment regimen deviates significantly from that observed among non-Chinese patients treated with this same regimen, then consideration will be given to studying a lower dose of

BMS-986205 in combination with nivolumab or enrolling additional Chinese patients to confirm the safety of the protocol defined treatment regimen.

7.4.1 Guidelines For Dose Modification

A dose reduction of BMS-986205 is defined as a change from a 100 mg QD tablet to a 50 mg QD tablet.

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

- Grade 3 fatigue, nausea, vomiting, or anemia related to study treatment
- Methemoglobin ≥ 15%
- Clinically significant elevations in methemoglobin (generally 10%, with a normal hemoglobin level[42]) with any associated Grade 3 AE (hypoxia, dyspnea, confusion, etc.) attributable to sustained elevations of methemoglobin and not attributable to another etiology
- QTcF > 500 msec confirmed by at least 1 repeat ECG and at least 60 msec above baseline (see Appendix 9)

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 after consultation with the BMS Medical Monitor and should be well documented. 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 delay (Section 7.4.2).

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

Only one dose reduction is permitted. The participant must discontinue study treatments if a subsequent dose reduction of BMS-986205 is required (see Section 7.4.4).

There will be no dose escalations or reductions of nivolumab allowed. For Q4W dosing cycles, participants may be dosed within a ± 3 day window. For this dosing cycle, participants may be dosed no less than 25 days and no more than 31 days between doses. In extenuating circumstances in which the participant cannot make the dosing schedule within the 3-day window, the BMS medical monitor/designee should be contacted.

Premedications are not recommended for the first dose of nivolumab.

7.4.2 Dose Delay due to Toxicity

BMS-986205 and nivolumab administration should be delayed for the following:

- Grade 2 non-skin, drug-related AE, with the exception of fatigue, nausea, vomiting, and anemia
- Grade 2 drug-related creatinine, AST, ALT, and/or total bilirubin abnormalities
- Grade 3 drug-related skin AE
- Grade 3 drug-related fatigue, nausea, vomiting, diarrhea, and anemia
- Grade 3 drug-related laboratory abnormality, with the following exceptions:

  - Grade 3 lymphopenia or asymptomatic amylase or lipase elevations do not require dose delay
  - Grade ≥3 AST, ALT, total bilirubin will require dose discontinuation (see Section 7.4.4)
- Any AE, laboratory abnormality, or intercurrent illness that, in the judgment of the investigator, warrants delaying the dose of study medication (should consult the BMS medical monitor and should be well documented)

In addition, **only BMS-986205** should be delayed for the following:

- Methemoglobin ≥ 15%
- Clinically significant elevations in methemoglobin (generally 10% with a normal hemoglobin level[42]) with any associated Grade 3 AE (hypoxia, dyspnea, confusion, etc.) attributable to sustained elevations of methemoglobin and not attributable to another etiology
- QTcF > 500 msec confirmed by at least 1 repeat ECG and at least 60 msec above baseline (see Appendix 9).

Participants may continue to receive nivolumab during dose delays of BMS-986205 for elevations of methemoglobin and associated events, as well as QTcF prolongations.

For participants with methemoglobin elevations with associated Grade 3 AEs, if contribution of nivolumab to the associated AE cannot be ruled out (eg, a participant with dyspnea in whom pneumonitis has not yet been ruled out), nivolumab dosing should be delayed as well. See Section 7.4.6 for management of methemoglobinemia.

If BMS-986205 dosing is delayed, dose reduction may be necessary, see Section 7.4.1.

If dosing is resumed after a delay, BMS-986205 may be resumed as soon as the criteria to resume treatment are met (see Section 7.4.3). Nivolumab should be resumed as soon as possible after criteria to resume treatment are met but may be resumed later than BMS-986205 given the differences in each drug's administration.

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

The end of cycle tumor assessments (ie, CT/MRI, etc.) will continue as scheduled regardless of any treatment delay incurred.

7.4.3 Criteria to Resume Treatment of BMS-986205 and Nivolumab

Participants may resume treatment with study treatments when the drug-related AE(s) resolve to Grade ≤ 1 or baseline value, with the following exceptions:

- Participants may resume treatment in the presence of Grade 2 fatigue.
- Participants who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- For participants with Grade 2 AST, ALT, and/or total bilirubin abnormalities, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete.

- Participants with combined AST/ALT AND total bilirubin values meeting discontinuation parameters (Section 7.4.4) should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed. Participants with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by BMS medical monitor/designee.

Participants with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the BMS medical monitor/designee. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.

For participants who have BMS-986205 held for elevations of methemoglobin, dosing may resume when the methemoglobin levels have decreased to below the institutional ULN and any associated AEs have resolved to Grade ≤ 1 or baseline value. Dose modification of BMS-986205 should be considered when resuming after a delay (see Section 7.4.1).

7.4.4 Guidelines for Permanent Discontinuation of BMS-986205 and Nivolumab

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

- Any occurrence of serotonin syndrome should result in discontinuation of BMS-986205 only.
- Any Grade 2 drug-related uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the time frame permitted for dose delays OR requires systemic treatment
- Any Grade 3 non-skin, drug-related AE lasting > 7 days or that recurs, with the following exceptions for laboratory abnormalities, drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, hypersensitivity reactions, infusion reactions, and endocrinopathies:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, neurological toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation.
  - Grade 3 drug-related endocrinopathies, adequately controlled with only physiologic hormone replacement do not require discontinuation. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia lasting 7 days or associated with bleeding requires discontinuation
    - Grade ≥ 3 drug-related AST, ALT, or total bilirubin requires discontinuation*
    - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN
    * In most cases of Grade 3 AST or ALT elevation, 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.
- Any Grade 4 drug-related AE or laboratory abnormality (including but not limited to creatinine, AST, ALT, or total bilirubin), except for the following events which do not require discontinuation:

  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia or leukopenia or asymptomatic amylase or lipase
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 48 hours of their onset
  - Grade 4 drug-related endocrinopathy AEs, such as, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS medical monitor/designee.
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the participant with continued BMS-986205 and nivolumab dosing
- Any event that leads to delay in dose administration > 10 weeks from the previous dose requires discontinuation, with the following exceptions:
  - Dose administration delays to allow for prolonged steroid tapers to manage drug-related AEs are allowed.
  - Dose administration delays lasting > 10 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS medical monitor/designee.

Prior to re-initiating treatment in a participant with a dose delay lasting > 10 weeks, the BMS medical monitor/designee must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue Q4W or more frequently if clinically indicated during such dosing delays.

- For participants who delay BMS-986205 but continue nivolumab, any dose delay of BMS-986205 lasting >10 weeks will result in the discontinuation of BMS-986205, but not nivolumab treatment.

All participants who discontinue IP 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 (eg, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

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

7.4.5 Management Algorithms for Immuno-Oncology Agents

Immuno-oncology (IO) agents are associated with AEs that can differ in severity and duration from AEs caused by other therapeutic classes. Nivolumab and BMS-986205 are considered IO agents in this protocol. Early recognition and management of AEs associated with IO agents may

mitigate severe toxicity. Management algorithms have been developed from extensive experience with nivolumab to assist investigators in assessing and managing the following groups of AEs:

- gastrointestinal
- renal
- pulmonary
- hepatic
- endocrinopathies
- skin
- neurological

The clinical nature of AEs noted with BMS-986205 will determine the role of the above algorithms for use in toxicities related to its use in this study. The algorithms recommended for utilization in this protocol are included in Appendix 7.

7.4.6 *Management of Treatment-Related Hematological Adverse Events and Detection of Methemoglobinemia*

[redacted] Symptoms of methemoglobinemia are related to the lack of oxygen delivery to tissues and are proportional to the fraction of methemoglobin, as described below for participants with normal hemoglobin levels.

Symptoms associated with elevations of methemoglobin are as follows:

- 0% to 10% - Usually asymptomatic
- 10% to 20% - Cyanosis without other symptoms
- 20% to 50% - Headache, dyspnea, lightheadedness (possibly syncope), weakness, confusion, palpitations, chest pain
- 50% to 70% - Coma, seizures, arrhythmias; acidosis
- > 70% - Usually death

Note that participants with anemia may experience symptoms at lower methemoglobin percentages than listed above, depending on the degree of anemia.

Increasing levels of methemoglobin may confound the results of standard pulse oximeters, with values of around 85% reported consistently as methemoglobin levels increase, regardless of the true oxygen saturation.

When methemoglobinemia is suspected, part of the diagnostic work-up includes evaluation for other disorders that can present with a similar clinical picture, including cardiac and pulmonary disease. A fresh peripheral blood sample (either venous or arterial) should be sent for evaluation of methemoglobin levels; methemoglobin levels may vary with storage of blood.

For management of methemoglobinemia, see Section 7.4.6. Testing is done at screening and as clinically indicated.

7.4.7 Treatment of Methemoglobinemia Associated with BMS-986205

The following management recommendations are intended as guidelines for the Investigator and may be modified based on institutional practices or local standard of care, as appropriate. See Section 7.4.6 for guidance on detection of methemoglobinemia.

Initial care includes supportive measures and the administration of supplemental oxygen. In mild cases, recovery often occurs simply by interrupting the administration of the offending medication. Concomitant medication lists should be reviewed for medications other than the study treatment that can cause methemoglobinemia (see Appendix 10).

Further treatment of methemoglobinemia is generally indicated when the methemoglobin level is above 20% or is associated with symptoms.

Intravenous methylene blue is the first-line antidotal agent and works by restoring the oxygen carrying capacity of hemoglobin by reduction of methemoglobin from its oxidized state. It is given as a 1% solution at a dose of 1 to 2 mg/kg. Most participants require only 1 dose, and symptoms should resolve within 1 hour. Methylene blue may confound the interpretation of methemoglobin levels detected by co-oximetry; alternative methods should be used after treatment with methylene blue if methemoglobin level monitoring is required. Methylene blue should be used with caution in participants with concurrent use of serotonergic psychiatric medications, as this could increase the risk of serotonin syndrome.

Exchange transfusion and hyperbaric oxygen treatment are second-line options for participants with severe methemoglobinemia whose condition does not respond to methylene blue or who cannot be treated with methylene blue. Participant transfer should occur when life-threatening methemoglobinemia that is refractory to treatment occurs in a facility that cannot provide the appropriate critical care.

7.5 Preparation/Handling/Storage/Accountability

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

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

Refer to the current IBs for BMS-986205 and nivolumab for complete storage, handling, and dispensing information.

7.5.1 Retained Samples for Bioavailability/Bioequivalence

Not applicable.

7.6 Treatment Compliance

At scheduled PK sample collection as well as laboratory evaluation days, BMS-986205 and associated meal will be administered to the participant in the clinical facility. At all other times throughout the study, BMS-986205 will be administered on an out-participant basis, except when participants are seen in the clinical facility for administration of nivolumab, assessment of AEs, and laboratory evaluation. Trained medical personnel will dispense BMS-986205 to the participants. Treatment compliance will be monitored by drug accountability, as well as by recording BMS-986205 administration in the participant pill diary, medical record, and CRF. Participants should bring all drug containers for BMS-986205 to each study visit for drug reconciliation.

7.6.1 Treatment of Drug-Related Infusion Reactions

Because nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the BMS medical monitor and reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE v5.0 guidelines.

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

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

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

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

- Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the participant with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen 325 to 1000 mg (acetaminophen); monitor participant until resolution of symptoms.
- Bronchodilator or corticosteroid therapy may also be administered as appropriate.
- The infusion may be restarted at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor participant closely.
- The amount of study drug infused must be recorded on the CRF.

- If symptoms recur, then no further nivolumab, as the case may be, will be administered at that visit.
- The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional nivolumab administrations. If necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent) may be used.

Late-occurring symptoms:

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

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

Immediately discontinue study drug infusion. Begin an IV infusion of normal saline and treat the participant as follows: recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Participant should be monitored until the investigator is comfortable that the symptoms will not recur. Study drug will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor participant until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids).

7.7 Concomitant Therapy

7.7.1 Prohibited and/or Restricted Treatments

Prohibited and/or restricted medications taken prior to study drug administration in the study are described below:

- Prior exposure to BMS-986205 or other IDO inhibitor.
- Concurrent administration of any anti-cancer therapies (investigational or approved) with the exception of participants in the follow up of the study.
- Concomitant use of strong inhibitors of CYP3A4 and/or CYP1A2 or strong inducers of CYP3A4 and/or CYP1A2 (see Appendix 8).
- Immunosuppressive agents (except as stated in Section 7.7.3), unless they are utilized to treat an AE.
- Palliative radiotherapy is permitted only under certain conditions as described in Section 6.1.

- Use of any medicinal herbal preparations within 2 weeks of the first dose of study drug and during study treatment unless prescribed by a treating physician.
- Avoid co-administration of TCMs with nivolumab and BMS-986205, unless with sponsor approval. TCMs with anti-cancer claims should be stopped for at least 14 days prior to dosing.

Medications taken within 2 weeks prior to study drug administration must be recorded on the CRF.

Any concomitant therapies must be recorded on the CRF.

7.7.2 Other Restrictions and Precautions

Restricted therapies are not prohibited but are not recommended; Investigators should consider possible benefit/risk implications of enrolling and treating participants in whom the following are clearly medically indicated:

- Grapefruit and Seville oranges and their juices can inhibit CYP3A4 and should not be consumed while on study.
- Concurrent use of moderate inhibitors or inducers of CYP3A4 and/or CYP1A2 may affect the systemic exposure of BMS-986205. The BMS medical monitor should be consulted prior to use. See Appendix 8 for a list of CYP3A4 and/or CYP1A2 modulators.
- Concurrent smoking (tobacco, marijuana, etc.) may induce CYP1A2 and decrease the systemic exposure of BMS-986205.
- Caution is warranted when consuming marijuana by means other than smoking as it may lead to increased exposure of BMS-986205 through interaction with metabolic enzymes.
- Caution is warranted when administering BMS-986205 to participants taking drugs that are highly dependent on CYP3A4 or CYP2B6 for metabolism. See Appendix 8 for a list of sensitive CYP3A4 and CYP2B6 substrates.
- Caution is warranted when administering BMS-986205 to participants taking drugs that may be associated with QT prolongation. See Appendix 9 for a list of common medications associated with QT prolongation.
- Caution is warranted when administering BMS-986205 to participants taking drugs that are subject to extensive intestinal efflux by P-gp/BCRP. See Appendix 10 for a list of common P-gp/BCRP substrates.
- In vitro solubility data indicate that BMS-986205 has decreased solubility with increasing pH. Until further data are available, participants should try to avoid taking proton pump inhibitors. H2 antagonists and short-acting antacid agents, such as Maalox® or TUMS®, may be taken, but it is recommended that these not be taken 4 hours before or 4 hours after dosing of BMS-986205.
- Caution is warranted when using other agents known to cause methemoglobinemia (see Appendix 11). Dapsone, topical anesthetics, and antimalarial drugs are the most likely agents and thus these drugs should only be used after discussion with the Study Director/Medical Monitor.

The development of serotonin syndrome has been associated with exposure to another investigational agent that inhibits the IDO1 enzyme. No case of serotonin syndrome has been observed with administration of BMS-986205. Given the possibility of a class effect, there is a theoretical risk that BMS-986205 could cause an increase in serotonin levels in the brain that might trigger serotonin syndrome when administered in combination with serotonergic agents or

tryptophan supplements. Use caution and monitor for symptoms of serotonin syndrome in participants receiving concurrent serotonergic psychiatric medications and/or tryptophan supplements.

7.7.3 Permitted Therapy

- Participants are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Treatment with a short course of steroids (< 5 days) up to 7 days prior to initiating study drug is permitted. A brief course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of nonautoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.
- Inhaled or intranasal corticosteroids (with minimal systemic absorption may be continued if the participant is on a stable dose) are permitted in the absence of active autoimmune disease. Nonabsorbed intra-articular steroid injections will be permitted.
- Immunosuppressive agents and the use of systemic corticosteroids are permitted in the context of treating AEs. Participants receiving corticosteroids for treatment of drug-related AEs must be at < 10 mg/day prednisone or equivalent prior to re-initiation of study drug. Participants may continue to receive HRT.
- Participants receiving RANK-L inhibitors or bisphosphonates are permitted as clinically indicated but should be avoided, if possible, prior to completion of Cycle 1.

7.7.3.1 Palliative Local Therapy

Palliative and supportive care for disease-related symptoms may be offered to all participants on the trial. 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 during radiation as the potential for overlapping toxicities with radiotherapy and BMS-986205, or combination of BMS-986205 and nivolumab is currently not known. Anecdotal data suggest that radiotherapy administered to participants while receiving nivolumab therapy is tolerable. However, because concurrent radiotherapy and immunotherapies in cancer have not been formally evaluated, in cases where palliative radiotherapy is required for a tumor lesion, then BMS-986205 alone or BMS-986205 in combination with nivolumab 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 end of the study, BMS will not continue to provide BMS supplied study treatment to participants/investigators unless BMS chooses to extend the study. The investigator should ensure that the participant receives appropriate standard of care to treat the condition under study.

8 DISCONTINUATION CRITERIA

8.1 Discontinuation from Study Treatment

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

- Participant's request to stop study treatment. Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information
- Any clinical AE, laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant
- Termination of the study by BMS
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Inability to comply with protocol
- Discretion of the investigator
- Pregnancy
- Completion of study required procedures
- Documented and confirmed disease progression as defined by RECIST v1.1 (see Appendix 5) unless participant meets criteria for treatment beyond progression (Section 8.1.2)
- 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
- Protocol-defined reasons for discontinuation (see Section 7.4.4 and Section 8.2)

In the case of pregnancy, the investigator must notify within 24 hours of awareness of the pregnancy, the BMS medical monitor/designee of this event. In the event a female participant becomes pregnant during this clinical trial, the study treatment must be discontinued immediately. In most cases, the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). Please call the BMS medical monitor within 24 hours of awareness of the pregnancy. Refer to Section 9.2.6.

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 Poststudy Treatment Study Follow-up

In this study, safety and tolerability of BMS-986205 administrated as monotherapy and in combination with nivolumab is a key endpoint of the study. Poststudy follow-up is of critical importance and is essential to preserving participant safety and the integrity of the study. Participants who discontinue study treatment must continue to be followed for collection of outcome for at least 100 days after the last dose of study therapy.

8.1.2 Treatment Beyond Progression

A subset of participants with solid tumors treated with immunotherapy may derive clinical benefit despite initial evidence of PD. Participants will be permitted to continue on treatment beyond initial RECIST v1.1 (see Appendix 5) defined PD, as long as they meet the following criteria:

- Investigator-assessed clinical benefit, and not having rapid disease progression;
- Continue to meet all other study protocol eligibility criteria;
- Tolerance of study drug;
- Stable performance status;
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases);
- Participant provides written informed consent prior to receiving any additional nivolumab and/or BMS-986205 treatment, using an ICF describing any reasonably foreseeable risks or discomforts, or other alternative treatment options.

The assessment of clinical benefit should take into account whether the participant is clinically deteriorating and unlikely to receive further benefit from continued treatment. All decisions to continue treatment beyond initial progression must be discussed with the BMS medical monitor and an assessment of the benefit/risk of continuing with study drug must be documented in the study records. Participants will be re-consented to explain the rationale for this ongoing treatment.

8.1.3 Discontinuation due to Further Progression (Confirmed Progression)

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

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

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

New lesions are considered measurable at the time of initial progression if the longest diameter is at least 10 mm.

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

8.1.4 Assessment Schedule for Participants with Post Progression Treatment

Participants should continue to receive monitoring according to the on-treatment assessments in Section 9.1. Radiographic assessment by CT (preferred) or MRI described in Section 9.1 is required when participants continue post progression treatment. For participants who discontinue post progression treatment with study drug, no additional radiographic assessments will be required.

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

9 STUDY ASSESSMENTS AND PROCEDURES

- Study assessments, procedures, and timing are presented in Table 2-1, Table 2-2, Table 2-3, and Table 2-4 .
- 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 dosing. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Schedule of Activities.

9.1 Efficacy Assessments

Disease assessment with CT and/or MRI as appropriate will be performed at baseline, end of Cycle 2 and every 8 weeks during study treatment until disease progression, at the completion of follow-up, or until participants withdraw from the study. Assessment of tumor response will be reported by the investigator for appropriate populations of participants as defined by RECIST v1.1 (see Appendix 5). At the sponsor's discretion, scans and measurements may be collected centrally to be reviewed by independent radiologists using RECIST v1.1, or other criteria at a later date, or at any time during the study.

Changes in tumor measurements and tumor responses will be assessed by the investigator using RECIST criteria. Investigators will also report the number and size of new lesions that appear while on study. The tumor assessment time points will be reported on the CRF based on investigators' assessment using RECIST criteria. Please refer to Appendix 5 for specifics of RECIST v1.1 criteria to be utilized in this study.

Body Imaging

CT with contrast is the preferred modality (MRI if CT is not feasible). Assessment should include the chest/abdomen/pelvis at a minimum; and other known/suspected sites of disease should be performed. These assessments will be performed at the end of Cycle 2 and then every 8 weeks (± 1 week) during study treatment until disease progression, at the completion of follow-up, or until participants withdraw from the study.

Disease assessments at other time points may be performed as clinically indicated.

Brain Imaging

Brain imaging is only required at screening for subjects with known history or symptoms of brain metastases and who have not had brain imaging within 30 days of anticipated first study drug administration). After screening, brain imaging is required only as clinically indicated.

Bone Scan

Bone scans may be performed as clinically indicated at baseline (eg, subjects with history of symptoms of bone metastases), but bone scans will not be considered a modality for assessment for measurable disease. After baseline, bone scans are required only as clinically indicated.

Imaging Modalities

For all subjects, the following imaging assessments should be performed at study-specified schedule: CT of the chest, CT or MRI of the abdomen, pelvis, and other known sites of disease.

- CT scans should be acquired with slice thickness of 5 mm or less with no intervening gap (continuous).
- Should a participant have a contraindication for CT IV contrast, a non-contrast CT of the chest and a contrast enhanced MRI of the abdomen and pelvis and other sites of disease may be obtained. MRIs should be acquired with slice thickness of 5 mm or less with no gap (continuous).
- Should a participant have contraindication for both MRI and CT intravenous contrasts, a non-contrast CT of the chest and a non-contrast MRI of the abdomen, pelvis, and other known/suspected sites of disease should be obtained.
- Positron emission tomography (PET) alone will not be considered for the disease assessment. Complementary CT and/or MRI or biopsy must be performed in such cases.
- Note: Use of CT component of a PET/CT scanner: Combined modality scanning, such as with fluorodeoxyglucose (FDG)-PET/CT, is increasingly used in clinical care and is a modality/technology that is in rapid evolution; therefore, the recommendations outlined here may change rather quickly with time. At present, low-dose or attenuation correction CT portions of a combined FDG-PET/CT are of limited use in anatomically-based efficacy assessments, and it is, therefore, suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for anatomically-based RECIST v1.1 measurements (Appendix 5). However, if a site can document that the CT performed as part of a FDG-PET/CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the FDG-PET/CT can be used for RECIST v1.1 measurements. Note, however, that the FDG-PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

9.2 Adverse Events

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

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

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

Contacts for SAE reporting specified in Appendix 3.

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

The collection of nonserious AE information should begin at initiation of study treatment until the time points specified in the Schedule of Activities (Section 2). Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the participants.

Sections 5.6.1 and 5.6.2 in the IB represent the Reference Safety Information to determine expectedness of SAEs for expedited reporting. Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 100 days of discontinuation of dosing and for 30 days post discontinuation of study drug for subjects not receiving combination therapy. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

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.
- All SAEs will be recorded and reported to sponsor or designee within 24 hours, as indicated in Appendix 3.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of this being available.

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

Adverse events 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 AE 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.

9.2.3 Follow-up of AEs and SAEs

- Nonserious 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 nonserious AEs that cause interruption or discontinuation of study treatment and for those present at the end of study treatment as appropriate.
- All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic). Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

All SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, 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 by the investigator to the sponsor of SAEs 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 Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

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

[redacted]

[redacted]

9.2.6 Pregnancy

If, following initiation of the IP, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half-lives + 30 days after nivolumab administration (for a total of 23 weeks post-treatment completion), the investigator must notify the BMS medical monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to the BMS designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Section 9.2.1.

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 nonserious 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 would be used by the reporting investigator (eg, anemia versus 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 drug-induced liver injury (DILI) event. All occurrences

of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 9.2.1 for reporting details).

Potential DILI is defined as:

1) Aminotransferase (AT) (ALT or AST) elevation > 3x ULN

AND

2) Total bilirubin > 2x 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 nonserious AE or serious AE, 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. All occurrences of overdose must be reported as an SAE (see Section 9.2.1).

9.4 Safety Assessment

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

AEs will be assessed continuously during the study and for 100 days after the last dose of nivolumab. AEs will be evaluated according to the NCI CTCAE v5.0 and should be followed per requirements in Section 9.2.1 and Section 9.2.2. AEs will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA) and reviewed for potential significance and importance. Participants should be followed until all treatment-related AEs have recovered to baseline or are deemed irreversible by the investigator.

9.4.1 Clinical Safety Laboratory Assessments

Investigators must document their review of each laboratory safety report.

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

Results of clinical laboratory tests performed on Day -1 must be available prior to dosing. Table 9.4.1-1 lists the clinical laboratory tests that will be performed.

Table 9.4.1-1: Clinical Laboratory Assessments

Hematology	
Hemoglobin Hematocrit Total leukocyte count, including differential Platelet count Methemoglobin Reticulocyte counts and haptoglobin (at baseline and reflex when methemoglobin is elevated over ULN) PT/aPTT/INR G6PD, quantitative or qualitative - screening only	
Serum Chemistry	
Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Total bilirubin Direct bilirubin (only if total bilirubin is elevated) Alkaline phosphatase GGT only when alkaline phosphatase is abnormal Lactate dehydrogenase (LDH) Creatinine Blood urea nitrogen (BUN) Amylase Lipase C-reactive protein	Total protein Albumin Sodium Potassium Chloride Total serum calcium Phosphorus Magnesium Bicarbonate/carbon dioxide Uric acid - screening only Glucose - Fasting at screening only Creatinine clearance (CrCl) - screening only Ferritin - screening only
Urinalysis (at screening)	
Protein Glucose Blood Leukocyte esterase Specific gravity pH Microscopic examination of sediment will be done if blood, protein, or leukocyte esterase is positive on dipstick.	
Other	
24 hour urine collection for testing of p-chloroaniline	
Serology	
Serum for hepatitis C antibody (if Hepatitis C antibody is positive reflex to hepatitis C RNA), hepatitis B surface antigen, HIV-1, HIV-2 antibody.	

Table 9.4.1-1: Clinical Laboratory Assessments

Other Analyses
Pregnancy test (WOCBP only)
TSH with free T3 and free T4 at screening and TSH with reflex to free T3 and free T4 as applicable on treatment phase
FSH (if needed to document postmenopausal status as defined in Appendix 4)

Results of all laboratory tests required by this protocol must be provided to BMS, either recorded on the laboratory pages of the CRF or by another mechanism as agreed upon between the investigator and BMS (eg, provided electronically). If the units of a test result differ from those printed on the CRF, the recorded laboratory values must specify the correct units. Any abnormal laboratory test result considered clinically significant by the investigator must be recorded on the appropriate AE page of the CRF (see Section 9.2.4).

9.4.2 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 as per standard medical/clinical judgment.

9.5 Pharmacokinetics and Immunogenicity

Pharmacokinetics of BMS-986205 [redacted] will be derived from plasma concentration versus time and urinary excretion data. Individual participant PK parameter values will be derived by noncompartmental methods by a validated PK analysis program. Actual times will be used for the analyses.

9.5.1 Pharmacokinetic Assessment following Monotherapy of BMS-986205

The PK parameters to be assessed for BMS-986205 following multiple dose administration in Cycle 0 during the dose escalation phase may include but not limited to:

Cmax	Maximum observed plasma concentration
Tmax	Time of maximum observed plasma concentration
Ctrough	Trough observed plasma concentration
AUC(TAU)	Area under the concentration-time curve in one dosing interval
CLT/F	Apparent total body clearance
Vss/F	Apparent volume of distribution at steady-state
AI	Accumulation index, calculated based on ratio of AUC(TAU) and Cmax at steady state to after the first dose
T-HALF (eff, AUC)	Effective elimination half-life that explains the degree of AUC accumulation observed
%UR24	Percent urinary recovery over 24 hours

[redacted]

9.5.2 Pharmacokinetic Assessment following Combination Therapy of BMS-986205 and Nivolumab

Plasma samples for BMS-986205 will be collected for all participants receiving combination treatment of BMS-986205 and nivolumab. PK will be assessed for BMS-986205 when in combination of nivolumab (Cycle 1 Day 1).

Serum samples for nivolumab PK and immunogenicity assessments will be collected for all participants receiving combination treatment of BMS-986205 and nivolumab. End-of-infusion (Ceoi) and trough (Ctrough) concentrations will be tabulated using summary statistics. These data may also be pooled with other datasets for population PK analysis, which will be presented in a separate report.

Detailed sampling schedules to be followed for the assessment of PK and immunogenicity for all analytes in the study are provided in Table 9.5.2-1. All time points are relative to the start of BMS-986205 dosing. Predose samples should be taken within 30 minutes before the start of BMS-986205 administration. Nivolumab end-of-infusion samples should be taken just prior to the end of infusion (preferably within 2 minutes).

Further details of sample collection, processing, and shipment will be provided in the laboratory procedures manual. On-treatment PK samples are intended to be drawn relative to actual dosing days; if a dose occurs on a different day within the cycle due to delays or minor schedule adjustments, PK samples should be adjusted accordingly.

Table 9.5.2-1: Pharmacokinetic, Anti-Drug Antibody (ADA) for BMS-986205 and Nivolumab

Study Day of Sample Collection	Event	Time (Relative To BMS-986205 Dose) Hour: Min	BMS-986205 [redacted] Plasma Sample	BMS-986205 [redacted] Urine Sample	Nivolumab Serum Sample	Nivolumab ADA Sample
Cycle 0						
C0D1		1:00	X	X 0-8 h		
		2:00	X			
		3:00	X			
		4:00	X			
		6:00	X			
		8:00	X			
C0D2	predose	0:00	X	X 8-24 h		
C0D8	predose	0:00	X			
C0D14	predose	0:00	X			
		1:00	X			
		2:00	X			
		3:00	X			
		4:00	X			
		6:00	X			
		8:00	X			
C0D15[a]	predose		X			
Cycle 1						
C1D1	predose[b]	0:00	X		X	X
	EOI[c]	1:00	X		X	
		2:00	X			
		3:00	X			
		4:00	X			
		6:00	X			
		8:00	X			
C1D2	predose		X			

Table 9.5.2-1: Pharmacokinetic, Anti-Drug Antibody (ADA) for BMS-986205 and Nivolumab

Study Day of Sample Collection	Event	Time (Relative To BMS-986205 Dose) Hour: Min	BMS-986205 [redacted] Plasma Sample	BMS-986205 [redacted] Urine Sample	Nivolumab Serum Sample	Nivolumab ADA Sample
Cycle 3						
C3D1	predose	0:00	X		X	X
	EOI	1:00	X		X	
		2:30 – 4:00	X			
Cycle 5 +						
Every 4 Cycles from C5D1	predose	0:00	X		X	X
	EOI	1:00	X		X	
EOT and FU						
EOT			X		X	X
FU-1			X		X	X
FU-2			X		X	X

[a] This sample should be taken 24 hours after the previous BMS-986205 dose on Cycle 0 Day 14 if Cycle 1 Day 1 does not occur on the next day of Cycle 0 Day 14.

[b] This sample should be taken 24 hours after the previous BMS-986205 dose on Cycle 0 Day 14 if Cycle 1 Day 1 occurs on the next day of Cycle 0 Day 14.

[c] EOI samples should be taken immediately prior to stopping the nivolumab infusion (preferably within 2 minutes prior to the end of infusion). If the end of infusion is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.

The plasma and urine samples of BMS-986205 [redacted] will be analyzed by validated [redacted] liquid chromatography-mass spectrometry (LC-MS) assays as applicable, and serum samples of nivolumab and anti-nivolumab antibody will be analyzed by validated immunoassays. In addition, plasma samples will be archived for potential additional metabolite analysis, if the need arises and to the extent possible. Treatment assignments will be released to the bioanalytical laboratory in order to minimize unnecessary analysis of samples.

9.6 Pharmacodynamics

Pharmacodynamic analysis will be performed on serum by measuring kynurenine and tryptophan levels pre and postdose of BMS-986205 and nivolumab [redacted]. Serum will be collected at the time points specified in Table 9.6-1. [redacted]

Table 9.6-1: Pharmacodynamic Serum Collection to Measure Kynurenine and Tryptophan Levels Pre- and Postdose of BMS-986205 and Nivolumab

Study Day of Sample Collected	Events	Serum Sample
C1D1	Predose	X
C1D1	Postdose (at 6 hours)	X
C1D2	Predose	X
Disease Progression	- -	X

[redacted]

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

The sample size for this study is not based on statistical power, but based on consideration of the precision of the estimate of geometric means of Cmax and AUC of BMS-986205. [redacted]

[redacted]

10.2 Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
All Enrolled Participants	All participants who sign informed consent.
All Treated Participants	All enrolled participants who take at least one dose of study treatment.
Pharmacokinetic Population	The PK data set includes all available concentration-time data from the participants who received any BMS-986205 or nivolumab.
Evaluable Pharmacokinetic Population	Participants who have adequate PK profiles and have no protocol deviations considered to affect the PK assessments. All available derived PK parameter values will be included in the PK data set and reported, but only participants with evaluable PK will be included in the summary statistics.
Immunogenicity	The immunogenicity data set consists of all available immunogenicity data from the participants who receive nivolumab and have a baseline and at least one post-treatment immunogenicity measurement.

10.3 Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock and will describe the selection of participants to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. Below is a summary of planned statistical analyses of the primary and secondary endpoints.

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

10.3.1 Efficacy Analyses

Endpoint	Statistical Analysis Methods
ORR	ORR is defined as the total number of participants whose BOR is either a CR or PR divided by the total number of participants in the population of interest. To describe the anti-tumor activity of BMS-986205 in combination with nivolumab, ORR will be calculated. ORR and corresponding 2-sided exact 95% CI by the Clopper and Pearson method will be provided by treatment, and/or dose level and tumor type (if appropriate).
BOR, DOR	BOR: defined as the best response designation over the study as a whole, recorded between the dates of first dose until the last tumor assessment prior to subsequent therapy. CR or PR determinations included in the BOR assessment must be confirmed by a second scan performed no less than 4 weeks after the criteria for response are first met. For those participants who have surgical resection, only presurgical tumor assessments will be considered in the determination of BOR. Listing of tumor measurements will be provided by subject. Individual participant's BOR will be listed based on RECIST v1.1 for solid tumors. DOR, computed for all treated participants with a BOR of CR or PR, is defined as the time between the date of first response and the date of disease progression or death, whichever occurs first. Median DOR and corresponding 2 sided 95% CI may be reported by treatment, and/or dose level and tumor type (if appropriate). DOR will be analyzed using the Kaplan-Meier method.
[redacted]	

10.3.2 Safety Analyses

All safety analyses for treated participants will be performed on the Safety Sample.

Endpoint	Statistical Analysis Methods
The occurrence of non-serious AEs, SAEs, AEs leading to discontinuation or death	All AEs will be listed and summarized by system organ class and preferred term for all treated participants and coded according to the most current version of Medical Dictionary for Regulatory Activities (MedDRA). Listing will presented for deaths.
Clinical laboratory tests, vital sign measurements, ECGs, and physical examinations; and marked abnormalities in clinical laboratory test results	Vital signs, ECGs, and laboratory test results will be listed and summarized by time point. Any significant physical examination findings and marked abnormal clinical laboratory test results will be listed. ECG recordings will be evaluated by the investigator and abnormalities, if present, will be listed.
[redacted]	

10.3.3 Pharmacokinetic Analyses

Endpoint	Statistical Analysis Methods
BMS-986205 Cmax, AUCtau, CLT/F, Vss/F	Summary statistics: geometric means and coefficients of variation
BMS-986205 T-HALF(eff, AUC)	Summary statistics: means and SD
BMS-986205 Tmax	Summary statistics: medians and ranges
BMS-986205 Ctrough	Summary statistics to assess attainment of steady state: geometric means and coefficients of variation; plots vs time by dose
BMS-986205 %UR	List will be presented for %UR. Plots of individual cumulative percent of dose recovered in urine versus end of interval time. Mean plots of cumulative percent of dose recovered in urine versus end of interval time
[redacted]	
Nivolumab end of infusion (Ceoi), Ctrough	Summary statistics

10.3.4 Immunogenicity Analyses

The immunogenicity will be assessed by the frequency of positive ADA to nivolumab. A listing of all available immunogenicity data will be provided by treatment, dose, and immunogenicity status. The frequency of participants with a baseline and/or at least one positive ADA assessment of nivolumab will be summarized.

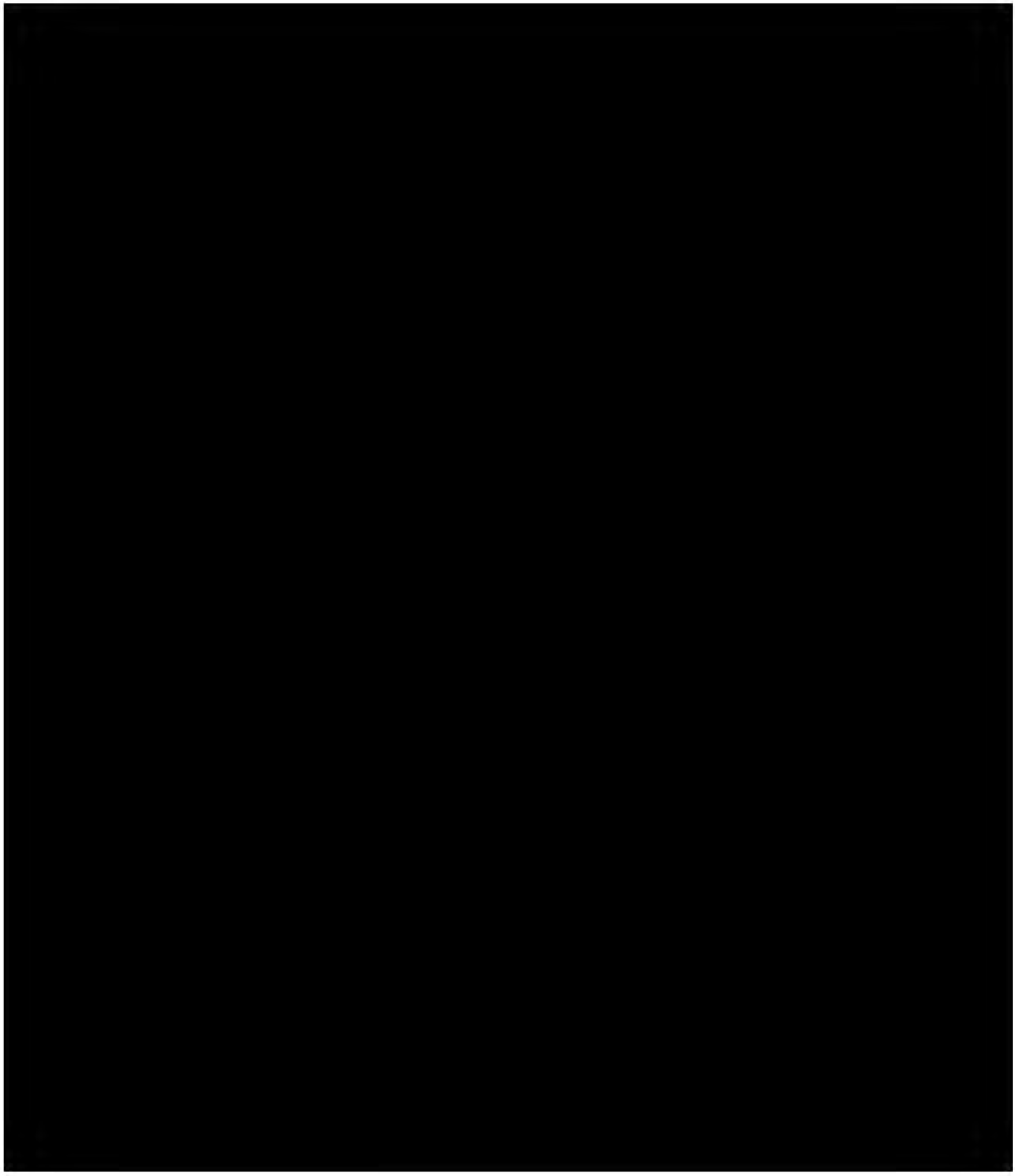
10.3.5 Other Analyses

The population pharmacokinetics analysis and pharmacodynamic analyses will be presented separately from the main clinical study report.

[redacted]

[redacted]

[redacted]



12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
ADA	anti-drug antibodies
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
[redacted]	
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BCRP	breast cancer resistance protein
[redacted]	
BID	twice daily
BOR	best overall response
BUN	blood urea nitrogen
CBC	complete blood count
CI	confidence interval
Cmax	maximum observed concentration
[redacted]	
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CR	complete response
[redacted]	
CrCl	creatinine clearance
CRF	case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA	cytotoxic T lymphocyte-associated antigen 4
CV	coefficient of variation
CV%	geometric mean
[redacted]	

Term	Definition
DILI	drug-induced liver injury
[redacted]	
DOR	duration of response
[redacted]	
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
EMH	extramedullary hematopoiesis
EOT	end of treatment
FDG	fluorodeoxyglucose
FSH	follicle stimulating hormone
FU	follow-up
GGT	gamma-glutamyl transferase
[redacted]	
HIV	human immunodeficiency virus
[redacted]	
IB	Investigator's Brochure
[redacted]	
ICF	informed consent form
IDO1	indoleamine 2,3-dioxygenase 1
[redacted]	
IO	Immuno-oncology
IP	investigational product
irAEs	immune-related AEs
IV	intravenous

Term	Definition
[redacted]	
LAG-3	lymphocyte activation gene 3
LC-MS	liquid chromatography-mass spectrometry
LDH	lactate dehydrogenase
LFTs	liver function tests
[redacted]	
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NAFLD	nonalcoholic fatty liver disease
NCI	National Cancer Institute
[redacted]	
ORR	overall response rate
PCR	polymerase chain reaction
PD	disease progression
PD1	programmed cell death 1
PDL-1	programmed death receptor-ligand 1
PE	physical examination
PET	positron emission tomography
P-gp	P-glycoprotein
PK	pharmacokinetics
PO	orally
PPK	population PK
PR	partial response
PT	prothrombin time
Q2W	every 2 weeks
Q4W	every 4 weeks
QD	once daily
QTcF	Fridericia's-corrected QT interval

Term	Definition
RBC	red blood cell
[redacted]	
RECIST	Response Evaluation Criteria in Solid Tumors
[redacted]	
SAEs	serious adverse events
SCCHN	squamous cell carcinoma of the head and neck
SD	standard deviation (statistics)
SD	stable disease
TCMs	Traditional Chinese Medicines
[redacted]	
T-HALF	terminal phase half-life
Tmax	time of maximum observed plasma concentration
TNFR	tumor necrosis factor receptor
[redacted]	
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
US	United States
VS	vital signs
Vss	volume of distribution at steady state
WBC	white blood cells
WOCBP	women of childbearing potential

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

The term 'Participant' is used in the protocol to refer to a person who has consented to participate in the clinical research study. The term 'Subject' used in the eCRF is intended to refer to a person (Participant) who has consented to participate in the clinical research study.

REGULATORY AND ETHICAL CONSIDERATIONS

GOOD CLINICAL PRACTICE

This study will be conducted in accordance with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical GuidelinesGood Clinical Practice (GCP),
- as defined by the International Council on Harmonisation (ICH)
- in accordance with the ethical principles underlying European Union Directive 2001/20/EC
- United States Code of Federal Regulations, Title 21, Part 50 (21CFR50)
- applicable local requirements.

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

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

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

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

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, participant recruitment materials (eg, advertisements), and any other written information to be provided to subjects. The investigator or BMS should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to subjects and any updates.

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

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

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

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

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

Documentation of approval/favorable opinion signed by the chairperson or designee of the IRB(s)/IEC(s) and if applicable, also by local health authority must be sent to BMS.

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

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

FINANCIAL DISCLOSURE

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

INFORMED CONSENT PROCESS

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

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

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

Investigators must:

- Provide a copy of the consent form and written information about the study in the language in which the participant is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
- Allow time necessary for participant or participant's legally acceptable representative to inquire about the details of the study.
- Obtain an informed consent signed and personally dated by the participant or the participant's legally acceptable representative and by the person who conducted the informed consent discussion.
- Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.

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

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

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

The consent form must also include a statement that BMS and regulatory authorities have direct access to participant records.

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 informed consent form 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 assent.

Subjects unable to give their written consent (e.g., stroke or subjects with or 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 consent form 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 subjects are the most important considerations and should prevail over interests of science and society.

SOURCE DOCUMENTS

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

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

STUDY TREATMENT RECORDS

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

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

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

CASE REPORT FORMS

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

For sites using the Sponsor or designee electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the electronic SAE form and Pregnancy Surveillance form, respectively. If electronic SAE form is not available, a paper SAE form can be used. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by Sponsor or designee.

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

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

The completed CRF, SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form. Subinvestigators in Japan may not be delegated the CRF approval task For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet Sponsor or designee training requirements and must only access the BMS electronic data capture tool using the unique user account provided by Sponsor or designee. User accounts are not to be shared or reassigned to other individuals

MONITORING

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

In addition, the study may be evaluated by 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 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 designee, whichever is longer. The investigator (or head of the study site in Japan) must contact BMS prior to destroying any records associated with the study.

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

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

RETURN OF STUDY TREATMENT

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

If..	Then
Study treatments supplied by BMS (including its vendors	Any unused study treatments supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless study treatments containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics). If study treatments will be returned, the return will be arranged by the responsible Study Monitor.
Study treatments sourced by site, not supplied by BMS (or its vendors) (examples include study treatments sourced from the sites stock or commercial supply, or a specialty pharmacy)	It is the investigator's or designee's responsibility to dispose of all containers according to the institutional guidelines and procedures.

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

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

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

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

CLINICAL STUDY REPORT AND PUBLICATIONS

For this single site protocol, the Principal Investigator for the site will sign the clinical study report.

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

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

ADVERSE EVENTS

Adverse Event Definition:

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study treatment and that does not necessarily have a causal relationship with this treatment.

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

Events Meeting the AE Definition

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

Events NOT Meeting the AE Definition

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

DEFINITION OF SAE

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

SERIOUS ADVERSE EVENTS

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

Pregnancy and potential drug induced liver injury (DILI) must follow the same transmission timing and processes to BMS as used for SAEs (see section 9.2.5 for reporting pregnancies).

Any component of a study endpoint that is considered related to study therapy should be reported as SAE (e.g., death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported).

EVALUATING AES AND SAES

Assessment of Causality

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

Follow-up of AEs and SAEs

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

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

All SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

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

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

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

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

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

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

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

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

One of the highly effective methods of contraception listed below is required during study duration and until the end of relevant systemic exposure, defined as 5 months after the end of study treatment.*

Highly Effective Methods That Are User Independent
• Non-hormonal intrauterine devices (IUDs) such as ParaGard® • Bilateral tubal occlusion
• Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.* • It is not necessary to use any other method of contraception when complete abstinence is elected. • WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2. • Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence

Unacceptable Methods of Contraception*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal) • Progestogen-only hormonal contraception associated with inhibition of ovulation (oral or injectable) • Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • Hormonal methods of contraception including oral contraceptive pills containing a combination of estrogen and progesterone, vaginal ring, injectables, implants and intrauterine hormone-releasing system (IUS) and hormonal IUDs • Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously • Diaphragm with spermicide • Cervical cap with spermicide • Vaginal Sponge with spermicide • Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action • Periodic abstinence (calendar, symptothermal, post-ovulation methods) • Withdrawal (coitus interruptus). • Spermicide only • Lactation amenorrhea method (LAM)

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

CONTRACEPTION GUIDANCE FOR MALE PARTICIPANTS WITH PARTNER(S) OF CHILD BEARING POTENTIAL.

Male participants with female partners of childbearing potential are eligible to participate if they agree to the following during the treatment and until the end of relevant systemic exposure.

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Male participants are required to use a condom for study duration and until end of relevant systemic exposure defined as 7 months after the end of study treatment.
- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 7 months after the end of treatment in the male participant.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 7 months after the end of study treatment.
- Refrain from donating sperm for the duration of the study treatment and until 7 months after the end of study treatment.

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 9.2.5 and the Appendix for Adverse Events and Serious Adverse Events Definitions and procedures for Evaluating, Follow-up and Reporting

APPENDIX 5 RESPONSE EVALUATION CRITERIA IN SOLID TUMORS GUIDELINES (VERSION 1.1) [redacted]

1 EVALUATION OF LESIONS

Solid tumors will be evaluated using Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1) guideline [redacted].[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 2.3.2-1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline. When patients have non-measurable (therefore non-target) disease only, Table 2.3.2-2 is to be used.

Table 2.3.2-1: Time Point Response: Patients With Target (± Non-Target) Disease

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

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

Table 2.3.2-2: Time Point Response: Patients with Non-target Disease Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD

Table 2.3.2-2: Time Point Response: Patients with Non-target Disease Only		
Non-Target Lesions	**New Lesions**	**Overall Response**
Any	Yes	PD
CR = complete response, PD = progressive disease and NE = inevaluable		

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

2.3.3 Best Overall Response

Best response determination of complete or partial response requires confirmation: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point of ≥ 4 weeks (28 days) later. In this circumstance, the best overall response can be interpreted as in Table 2.3.3-1. When SD is believed to be best response, it must meet the protocol specified minimum time from the date of first treatment or randomization date.

For example, if the first scheduled follow-up imaging visit is Week 6 (± 7 days) for a particular protocol, a Best Response of SD can only be made after the subject is on-study for a minimum of 6 weeks (42 days) minus 7 days, for an absolute minimum time on-study of 35 days from the reference start date (reference date is considered Day 1 on study). If the subject is not on-study for at least this amount of time, any tumor assessment indicating stable disease before this time period will have a Best Response of NE unless PD is identified.

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

Table 2.3.3-1: Best Overall Response (Confirmation of CR 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
PR	CR	PR
PR	PR	PR

Table 2.3.3-1: Best Overall Response (Confirmation of CR and PR Required)		
Overall Response First Time Point	**Overall Response Subsequent Time Point**	**Best Overall Response**
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.

[redacted]

APPENDIX 6 ECOG PERFORMANCE STATUS

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

[redacted]

APPENDIX 7 MANAGEMENT ALGORITHMS

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

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

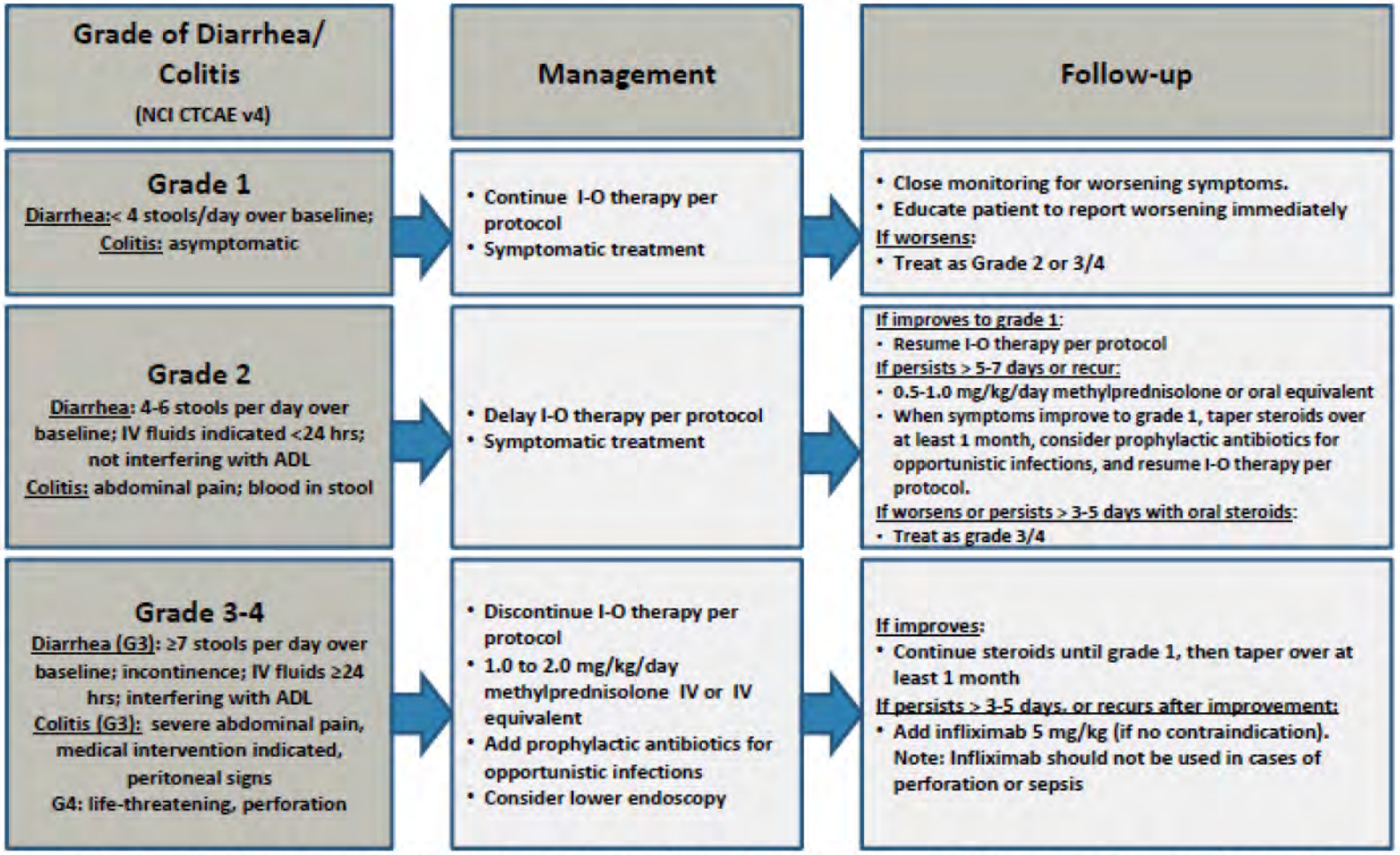
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the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

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

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

GI Adverse Event Management Algorithm

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



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

Updated 05-Jul-2016

Approved v2.0 [redacted]

Renal Adverse Event Management Algorithm

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

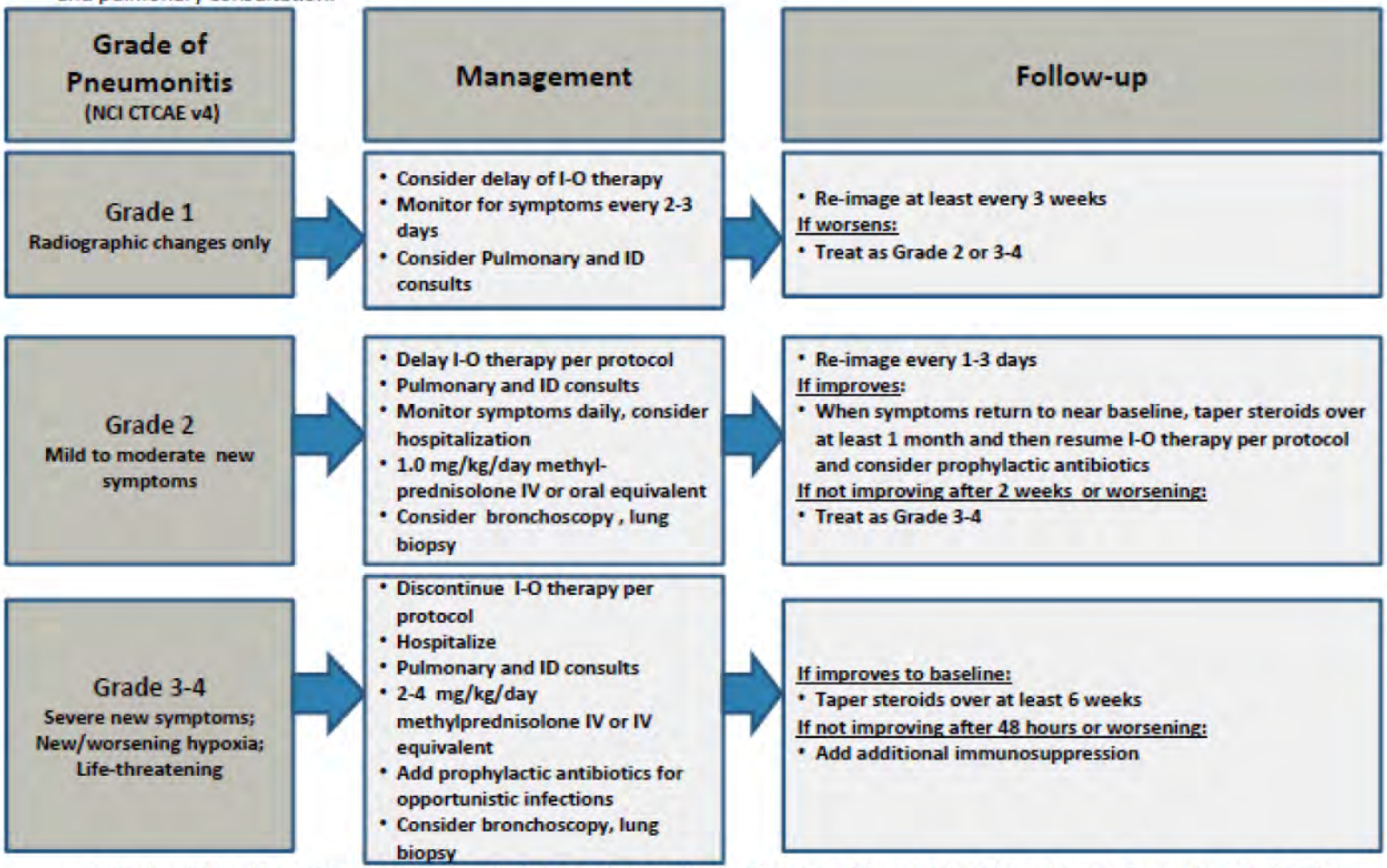
Grade of Creatinine Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 Creatinine > ULN and > than baseline but ≤ 1.5x baseline	• Continue I-O therapy per protocol • Monitor creatinine weekly	<u>If returns to baseline:</u> •Resume routine creatinine monitoring per protocol <u>If worsens:</u> •Treat as Grade 2 or 3/4
Grade 2-3 Creatinine > 1.5x baseline to ≤ 6x ULN	• Delay I-O therapy per protocol • Monitor creatinine every 2-3 days • 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent • Consider renal biopsy with nephrology consult	<u>If returns to Grade 1:</u> •Taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy and routine creatinine monitoring per protocol <u>If elevations persist > 7 days or worsen:</u> •Treat as Grade 4
Grade 4 Creatinine > 6x ULN	• Discontinue I-O therapy per protocol • Monitor creatinine daily • 1.0-2.0 mg/kg/day methylprednisolone IV or IV equivalent • Consult nephrologist • Consider renal biopsy	<u>If returns to Grade 1</u> : Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections

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

Updated 05-Jul-2016

Pulmonary Adverse Event Management Algorithm

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



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

Updated 05-Jul-2016

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.

Grade of Liver Test Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 AST or ALT > ULN to 3.0 x ULN and/or T. bili > ULN to 1.5 x ULN	• Continue I-O therapy per protocol	• Continue LFT monitoring per protocol If worsens: • Treat as Grade 2 or 3-4
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and/or T. bili > 1.5 to ≤ 3 x ULN	• Delay I-O therapy per protocol • Increase frequency of monitoring to every 3 days	If returns to baseline: •Resume routine monitoring, resume I-O therapy per protocol If elevations persist > 5-7 days or worsen : • 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol
Grade 3-4 AST or ALT > 5 x ULN or T.bili >3 x ULN	• Discontinue I-O therapy* • Increase frequency of monitoring to every 1-2 days • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent** • Add prophylactic antibiotics for opportunistic infections • Consult gastroenterologist	If returns to grade 2: • Taper steroids over at least 1 month If does not improve in >3-5 days, worsens or rebounds: • Add mycophenolate mofetil 1 g BID • If no response within an additional 3-5 days, consider other immunosuppressants per local guidelines

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

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

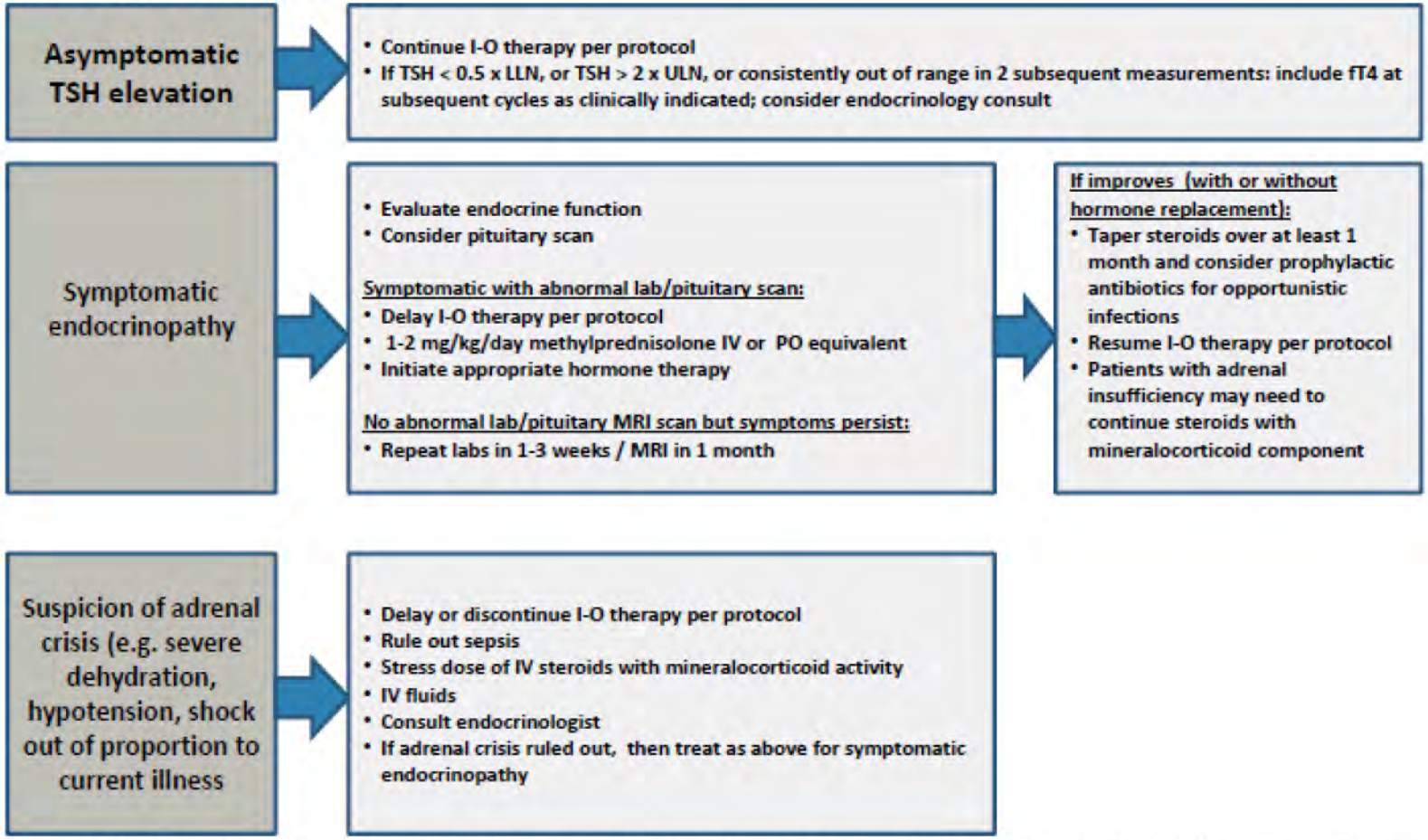
**The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

Updated 05-Jul-2016

Approved v2.0 [redacted]

Endocrinopathy Management Algorithm

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



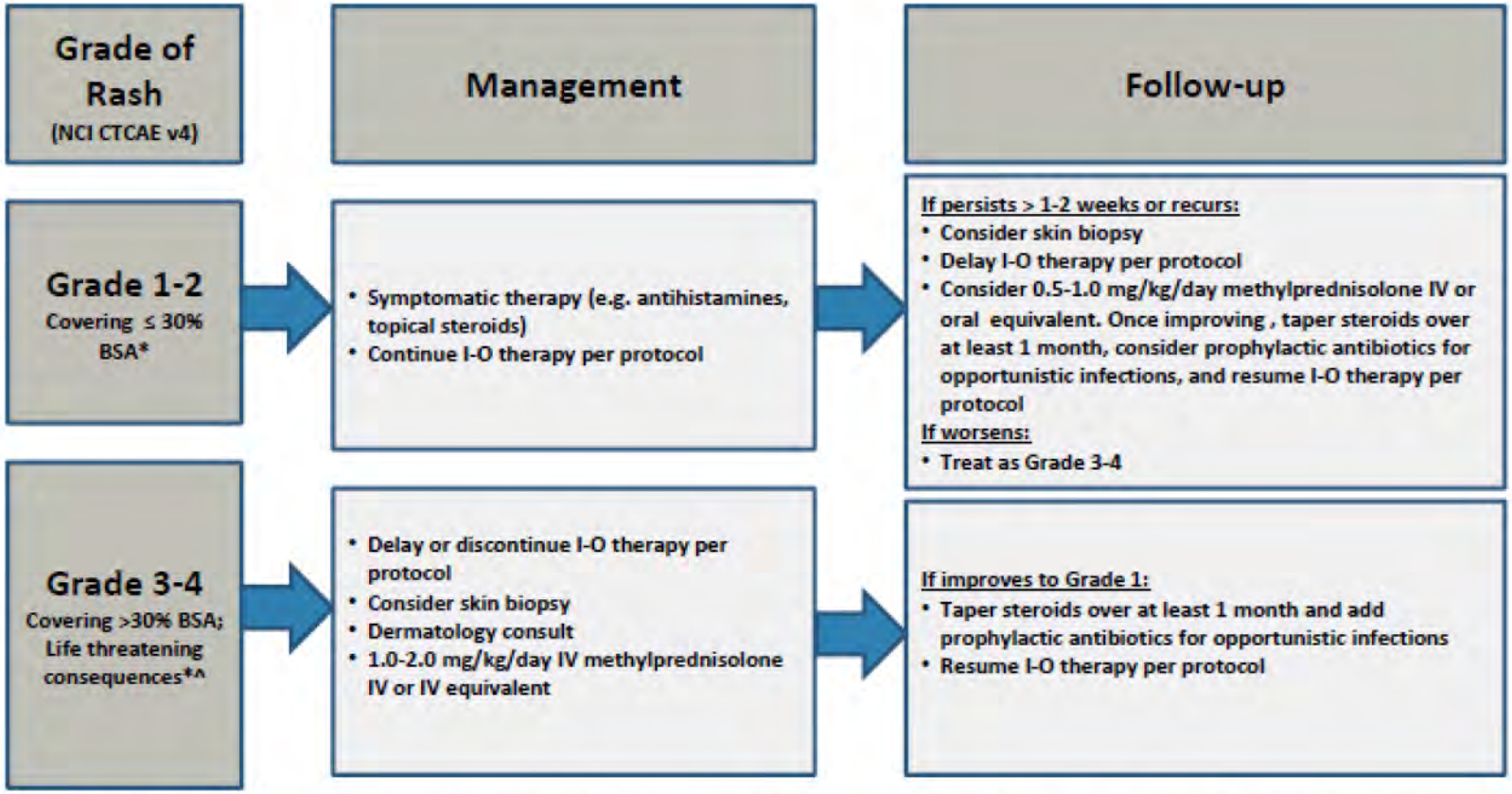
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

Approved v2.0 [redacted]

Skin Adverse Event Management Algorithm

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



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*Refer to NCI CTCAE v4 for term-specific grading criteria.
^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

Updated 05-Jul-2016

Neurological Adverse Event Management Algorithm

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

Grade of Neurological Toxicity (NCI CTCAE v4)	Management	Follow-up
Grade 1 Asymptomatic or mild symptoms; Intervention not indicated	• Continue I-O therapy per protocol	Continue to monitor the patient. If worsens: • Treat as Grade 2 or 3-4
Grade 2 Moderate symptoms; Limiting instrumental ADL	• Delay I-O therapy per protocol • Treat symptoms per local guidelines • Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or PO equivalent	If improves to baseline: •Resume I-O therapy per protocol when improved to baseline If worsens: • Treat as Grade 3-4
Grade 3-4 Severe symptoms; Limiting self-care ADL; Life-threatening	• Discontinue I-O therapy per protocol • Obtain neurology consult • Treat symptoms per local guidelines • 1.0-2.0 mg/kg/day IV methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections	If improves to Grade 2: • Taper steroids over at least 1 month If worsens or atypical presentation: • Consider IVIG or other immunosuppressive therapies per local guidelines

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

Updated 05-Jul-2016

APPENDIX 8 CYP3A4, CYP1A2 AND CYP2B6 GUIDANCE

The lists below are not meant to be all inclusive. Please consult individual drug labels for further information. Additional information is also available at:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

Table 1: Classification of In Vivo Inhibitors of CYP Enzymes

CYP Enzymes	Strong Inhibitors[a] ≥ 5-fold Increase in AUC or > 80% Decrease in CL	Moderate Inhibitors[b] ≥ 2 but < 5-fold Increase in AUC or 50-80% Decrease in CL	Weak Inhibitors[c] ≥ 1.25 but < 2-fold Increase in AUC or 20-50% Decrease in CL
CYP3A	Boceprevir, clarithromycin, conivaptan, grapefruit juice,[d] indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil,[e] nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole	Amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice,[d] imatinib, verapamil	Alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide, cilostazol, cimetidine, cyclosporine, fluoxetine, fluvoxamine, ginkgo,[f] goldenseal,[f] isoniazid, nilotinib, oral contraceptives, ranitidine, ranolazine, tipranavir/ritonavir, zileuton
CYP1A2	ciprofloxacin, enoxacin, fluvoxamine[g], zafirlukast	methoxsalen, mexiletine, oral contraceptives	acyclovir, allopurinol, cimetidine, peginterferon alpha-2a, piperine, zileuton

Please note that this is not an exhaustive list.

[a] A strong inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a substrate for that CYP by equal or more than 5-fold.

[b] A moderate inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 5-fold but equal to or more than 2-fold.

[c] A weak inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 2-fold but equal to or more than 1.25-fold.

[d] The effect of grapefruit juice varies widely among brands and is concentration, dose, and preparation dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (eg, high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (eg, low dose, single strength).

[e] Withdrawn from the United States market because of safety reasons.

[f] Herbal product.

[g] Strong inhibitor of CYP1A2 and CYP2C19, and moderate inhibitor of CYP2D6 and CYP3A

Abbreviations: AUC = area under the concentration-time curve; CYP = cytochrome P450.

Table 2: Classification of In Vivo Inducers of CYP Enzymes

CYP Enzymes	Strong Inducers ≥ 80% Decrease in AUC	Moderate Inducers 50-80% Decrease in AUC	Weak Inducers 20-50% Decrease in AUC
CYP3A	Avasimibe,[a] carbamazepine, phenytoin, rifampin, St. John's wort[b]	Bosentan, efavirenz, etravirine, modafinil, nafcillin	Amprenavir, aprepitant, armodafinil, echinacea,[c] pioglitazone, prednisone, rufinamide
CYP1A2		Phenytoin[d], rifampin[e], ritonavir[f], smoking, teriflunomide	

Please note that this is not an exhaustive list.

[a] Not a marketed drug.

[b] The effect of St. John's wort varies widely and is preparation dependent.

[c] Herbal product.

[d] Strong inducer of CYP3A and moderate inducer of CYP1A2, CYP2C19.

[e] Strong inducer of CYP2C19, CYP3A, and moderate inducer of CYP1A2, CYP2B6, CYP2C8, CYP2C9.

[f] Strong inducer of CYP2C19 and moderate inducer of CYP1A2, CYP2B6, CYP2C9.

Abbreviations: AUC = area under the concentration-time curve; CYP = cytochrome P450.

Table 3: Examples of Sensitive In Vivo CYP Substrates and CYP Substrates with Narrow Therapeutic Range

CYP Enzymes	Sensitive Substrates[a]	Substrates with Narrow Therapeutic Range[b]
CYP3A	Alfentanil, aprepitant, budesonide, buspirone, conivaptan, darifenacin, darunavir, dasatinib, dronedarone, eletriptan, eplerenone, everolimus, felodipine, indinavir, fluticasone, lopinavir, lovastatin, lurasidone, maraviroc, midazolam, nisoldipine, quetiapine, saquinavir, sildenafil, simvastatin, sirolimus, tolvaptan, tipranavir, triazolam, vardenafil	Alfentanil, astemizole,[c] cisapride,[c] cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine[c]
CYP2B6	Bupropion, efavirenz	

Please note that this is not an exhaustive list.

[a] Sensitive CYP substrates refers to drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a known CYP inhibitor.

[b] CYP substrates with narrow therapeutic range refers to drugs whose exposure-response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns (eg, Torsades de Pointes).

[c] Withdrawn from the United States market because of safety reasons.

Abbreviations: AUC = area under the concentration-time curve; CYP = cytochrome P450.

APPENDIX 9 MEDICATIONS ASSOCIATED WITH QT PROLOGATION

The list below is not meant to be all inclusive. Please consult individual drug labels for further information.

quinidine, procainamide, disopyramide,
amiodarone, sotalol, ibutilide, dofetilide,
erythromycins, clarithromycin,
chlorpromazine, haloperidol, mesoridazine, thioridazine, pimozide,
cisapride, bepridil, droperidol, methadone, arsenic, chloroquine, domperidone,
halofantrine, levomethadyl, pentamidine, sparfloxacin, lidoflazine

APPENDIX 10 P-GP AND BCRP GUIDANCE

The list below is not meant to be all inclusive. Please consult individual drug labels for further information. Additional information is also available at:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm

Table 1: Examples of In Vivo Substrates for Selected Transporters

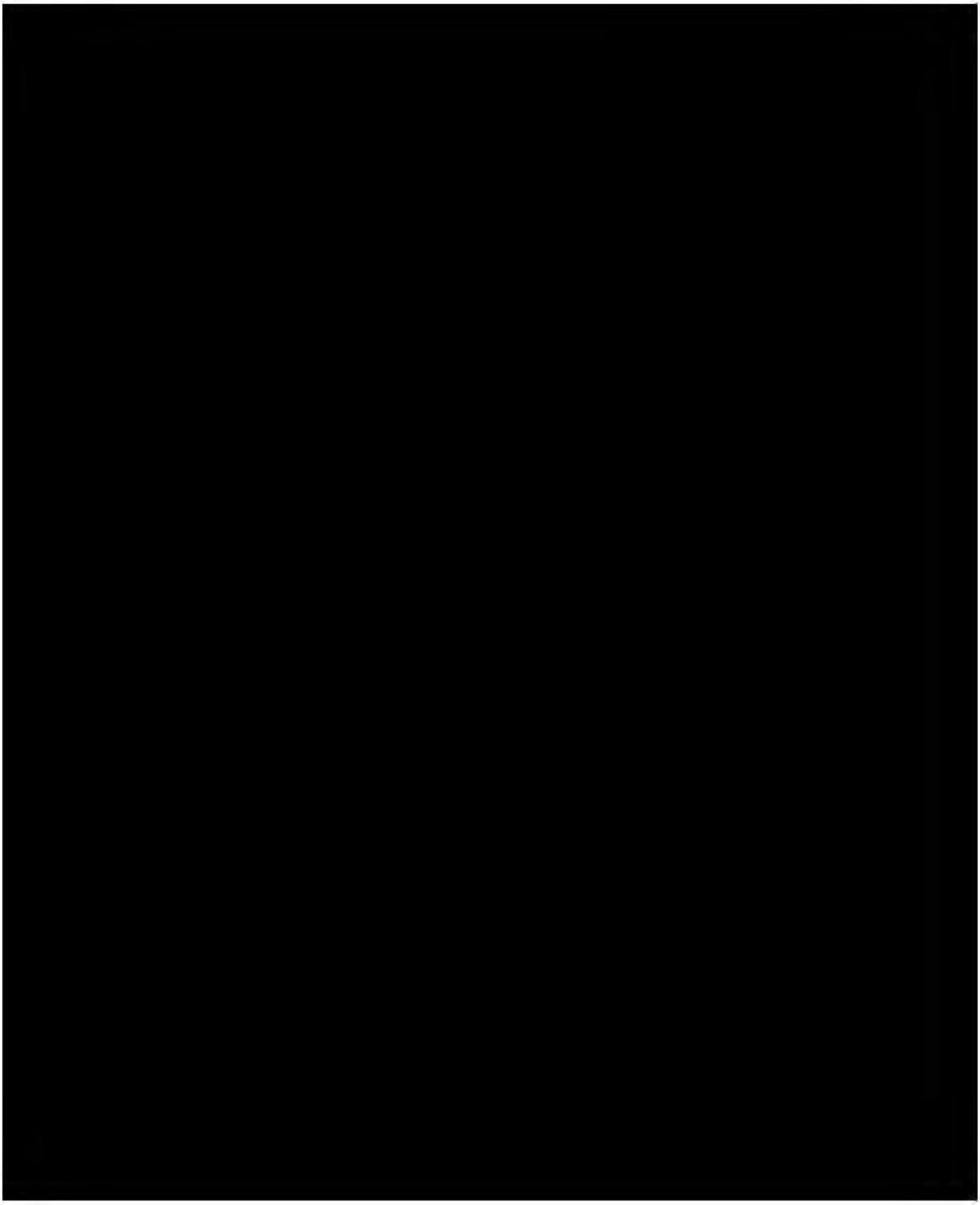
Transporter	Gene	Substrate
P-gp	*ABCB1*	Aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus, fexofenadine, imatinib, lapatinib, maraviroc, nilotinib, posaconazole, ranolazine, saxagliptin, sirolimus, sitagliptin, talinolol, tolvaptan, topotecan
BCRP	*ABCG2*	Methotrexate, mitoxantrone, imatinib, irrinotecan, lapatinib, rosuvastatin, sulfasalazine, topotecan

Please note that this is not an exhaustive list.
Abbreviations: BCRP = breast cancer resistance protein; P-gp = P-glycoprotein.

APPENDIX 11 AGENTS KNOWN TO CAUSE METHEMOGLOBINEMIA

- Acetanilid
- p-Amino salicylic acid
- Aniline, aniline dyes
- Benzene derivatives
- Clofazimine
- Chlorates
- Chloroquine
- Diaminodiphenylsulfone
- Local anesthetic agents
  - Benzocaine
  - Lidocaine
  - Prilocaine
- Menadione
- Metoclopramide
- Methylene blue*
- Naphthoquinone
- Naphthalene
- Nitrites
  - Amyl nitrite
  - Farryl nitrite
  - Sodium nitrite
  - Nitroglycerin
  - Nitric oxide
- Nitrobenzene
- Paraquat
- Phenacetin
- Phenazopyridine
- Primaquine
- Rasburicase
- Resorcinol
- Sulfonamides

While methylene blue is a recognized treatment for methemoglobinemia, it is an agent with oxidant potential (and may worsen the clinical situation) since in individuals with glucose-6-phosphate dehydrogenase deficiency, it induces acute hemolysis that can further decrease oxygen delivery to the tissues. Paradoxically, in high doses, methylene blue can also increase methemoglobinemia.



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