Official Title of Study:

A Phase 1/2 Study of BMS-986408 Alone and in Combination with Nivolumab or with Nivolumab and Ipilimumab in Participants with Advanced Solid Tumors

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CLINICAL PROTOCOL CA099003

A Phase 1/2 Study of BMS-986408 Alone and in Combination with Nivolumab or with Nivolumab and Ipilimumab in Participants with Advanced Solid Tumors

Brief Title:

A Phase 1/2 Study of BMS-986408 with and without Nivolumab or Nivolumab and Ipilimumab in Participants with Solid Tumors

Protocol Amendment 04

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EudraCT/EU Trial Number: 2022-500823-61-00

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Protocol Amendment 04	11-Dec-2023	The following key changes were made to this amendment: • Added [redacted] monotherapy cohort (Group B2). • Added a pH sub-study (Group G). • Added a dose expansion cohort of BMS-986408 in combination with nivolumab (Group D2). • Added dose escalation (Group F) and dose expansion (Group F2) cohorts to evaluate BMS-986408 in combination with nivolumab and platinum-doublet chemotherapy in non-small cell lung cancer.
Protocol Amendment 03	21-Apr-2023	The following key changes were made in this amendment: • Added clarifications around [redacted] exclusionary criteria. • Updated [redacted] exclusionary criteria. • Added guidance regarding [redacted] management. Updated the duration of contraception for males and females.
Protocol Amendment 02	02-Dec-2022	The following key changes were made to this amendment: • Removed SARS-CoV-2 serology requirements. • Added clarification regarding BMS-986408 [redacted] • Added an exploratory biomarker for Groups C, D, and E. • Added [redacted] for BMS-986408 when administered [redacted]. • [redacted]
Administrative Letter 01	03-Jun-2022	• Change in clinical scientist.
Protocol Amendment 01	25-Mar-2022	Dose-limiting toxicity criteria, discontinuation criteria for subjects with elevations in liver function laboratory values, and exclusion criteria for subjects with renal impairment or QT prolongation were modified [redacted]
Original Protocol	18-Nov-2021	Not applicable

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 04:

This protocol was amended to evaluate alternative dosing strategies, formulations, and combinations, and clinical efficacy in expansion cohorts. It includes the addition of the following groups:

- Part 1, Group B2: An optional monotherapy [redacted] cohort [redacted] to evaluate alternative dosing strategies [redacted]
- Part 2, Group G: This cohort will assess the effect of proton pump inhibitor (PPI) use (pH effect) [redacted] BMS-986408. [redacted] After [redacted] participants will be treated with daily dosing of BMS-986408 in combination with nivolumab every 4 weeks (Q4W).
- Part 3, Group D2: Dose expansion of BMS-986408 in combination with nivolumab Q4W in non-small cell lung cancer (NSCLC), melanoma, renal cell carcinoma (RCC), and microsatellite stable (MSS) colorectal cancer (CRC). [redacted]
- Part 2, Group F and Part 3, Group F2: Dose escalation (Part 2, Group F) and dose expansion (Part 3, Group F2) to evaluate BMS-986408 daily in combination with nivolumab and platinum-doublet chemotherapy (PDCT) every 3 weeks (Q3W) in NSCLC without prior systemic anti-cancer given as primary therapy in the advanced or metastatic setting. [redacted]

Other changes include adding safety data from the first 25 treated participants, which aligns with the investigator's brochure (IB). The preclinical sections were updated to align with the IB and provide rationale for the new combination of BMS-986408 with nivolumab plus PDCT. [redacted]. Biopsy samples will now be accepted if collected within the prior 3 months (previously 1 month). The inclusion criteria were updated [redacted] The text was updated throughout the protocol to include the additional cohorts and edited to remove redundant language.

Additional details of the changes are described in the table below.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 1: Protocol Summary	Updated to reflect changes made in the body of the protocol. Transitioned the summary to a table format.	To align with protocol updates. Simplification.
Table 2-1: Screening Procedural Outline (CA099003) Table 2-3: On Treatment Procedural Outline (Parts 2 and 3, Groups D, D2, E, F, F2, and G) Section 3: Introduction Section 3.3: Benefit/Risk Assessment Section 3.3.1: Risk Assessment Section 3.3.2: Benefit Assessment Section 3.3.3: Overall Benefit/Risk Conclusion	Added the assessment of tumor programmed death ligand 1 (PD-L1) status at screening, study treatments, and biopsy requirements (mandatory screening and on-treatment tumor biopsies for Group F and optional for Group F2, if tissue is available for PD-L1 confirmatory testing). Added footnote "e" to Table 2-3. Revised these sections to include rationale and benefit/risk assessment of BMS-986408 in combination with nivolumab and PDCT.	Updated throughout protocol to include the dose escalation (Part 2, Group F) and dose expansion (Part 3, Group F2) cohorts evaluating BMS-986408 in combination with nivolumab and PDCT in participants with NSCLC. This included updating the schedule of activities, rationale, benefits/risks, objectives/endpoints, study design, sample sizes, eligibility criteria, contraception requirements, prohibited medications, and dose-limiting toxicity (DLT), PK, and biomarker assessments.
Table 4-1: Objectives and Endpoints Section 5.1: Overall Design [redacted] Section 5.1.2: Part 2 Combination Therapy Cohorts Section 5.1.2.2: BMS-986408 in Combination with Nivolumab and PDCT (Group F) Section 5.1.3: Part 3 Expansion Cohorts Section 5.1.5: Treatment Period	Updated objectives and endpoints to include BMS-986408 in combination of nivolumab and PDCT. [redacted]	

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.4: Scientific Rationale for Study Design		
Section 5.4.3: Rationale for BMS-986408 in Combination with Nivolumab and PDCT Section 5.5.2: Nivolumab Section 7.1.1: BMS-986408 Dosing Section 7.1.3.1: Paclitaxel and Carboplatin Section 7.1.3.2: Pemetrexed and Cisplatin Section 7.1.3.3: Pemetrexed and Carboplatin Section 7.1.3.4: Optional Continuation Maintenance Section 7.2: Method of Study Intervention Assignment Section 7.4.2: Dose Delays for Chemotherapy Section 7.4.3: Dose Reduction for Chemotherapy Table 7.4.3-1: Dose Reduction for Chemotherapy Section 7.4.3.1: Chemotherapy: Dose Reductions for Hematologic Toxicity Table 7.4.3.1-1: Dose Modification for Hematologic Toxicity (Based on Nadir Counts) Section 7.4.3.2: Chemotherapy: Dose Reductions for Non-hematologic Toxicities Table 7.4.3.2-1: Dose modification for		

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Non-Hematologic Toxicity		
Section 7.4.4.2: Criteria to Resume Treatment with Chemotherapy		
Section 5.2: Number of Participants Section 10.2: Sample Size Determination	Added the sample size for Groups F and F2.	
Section 6.1: Inclusion Criteria	Added inclusion criterion 2)i) and exclusion criterion 3)k).	
Section 6.2: Exclusion Criteria	Added inclusion criterion 4)a)v)2)b) and modified criteria 4)b)i), 4)b)ii), 4)b)iii), and 4)b)iv) (contraception requirements) for participants receiving chemotherapy.	
Table 7-1: Study Intervention(s) for CA099003 Table 7.1-1: Study Intervention(s) Administered Section 7.1.3: BMS-986408 in Combination with Nivolumab and PDCT	Added study interventions to the tables. Added a new section (Section 7.1.3).	
Section 7.4: Dosage Modification	Added dose modification criteria, which includes adding new sections for dose reduction of chemotherapy and criteria to resume treatment with chemotherapy.	
[redacted]		
Section 7.7.1: Prohibited and/or Restricted Treatments	Added that the investigator must also adhere to the contraindications, precautions, and drug interactions found in the United States Prescribing Information (USPI) or local label for each of the chemotherapy agents.	
Section 9.5: Pharmacokinetics	Added Groups F and F2 to PK assessments.	
Table 9.8-1: Biomarker Sampling Schedule for all Participants	Added Groups F and F2 to biomarker assessments.	

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 9.8.2: Tumor-based Biomarkers		
Table 2-1: Screening Procedural Outline (CA099003) Table 2-3: On Treatment Procedural Outline (Parts 2 and 3, Groups D, D2, E, F, F2, and G) Table 9.4.4-1: Clinical Laboratory Assessments [redacted] Section 5.1.3: Part 3 Expansion Cohorts Section 5.4: Scientific Rationale for Study Design Section 5.5.2: Nivolumab Section 7.2: Method of Study Intervention Assignment	Added Group D2 to the tables. Added optional screening and on-treatment biopsies as well as clinical assessments. [redacted]	Updated throughout protocol to add the dose expansion cohorts for BMS-986408 [redacted] in combination with nivolumab Q4W (Part 3, Group D2) in NSCLC, RCC, melanoma, and MSS CRC. This included updating the schedule of activities, study design, sample sizes, eligibility criteria, and PK and [redacted]
Section 5.2: Number of Participants Section 10.2: Sample Size Determination	Added the sample size for Group D2.	
Section 6.1: Inclusion Criteria	Added new eligibility criteria, including inclusion criterion 2)h) and related subcriteria.	
Table 7-1: Study Intervention(s) for CA099003 Table 7.1-1: Study Intervention(s) Administered Section 7.1.1: BMS-986408 Dosing	Added study interventions.	
Section 9.5: Pharmacokinetics	Added Group D2 to PK assessments.	
Table 9.8-1: Biomarker Sampling Schedule for all Participants Section 9.8.2: Tumor-based Biomarkers	Added Group D2 to biomarker assessments.	

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-1: Screening Procedural Outline (CA099003) Table 2-3: On Treatment Procedural Outline (Parts 2 and 3, Groups D, D2, E, F, F2, and G) Table 9.4.4-1: Clinical Laboratory Assessments	Added Cycle 0 to the scheduled activities and study treatments (rabeprazole and [redacted] BMS-986408). Added screening and on-treatment tumor biopsies as well as clinical assessments. Added footnotes "c" and "f" to Table 2-3.	Updated throughout the protocol to include the PK group to assess the pH effect of [redacted] BMS-986408 (Part 2, Group G). This included updates to the schedule of activities, objectives/endpoints, study design, sample size, study population, study interventions, and PK and biomarker assessments.
Table 4-1: Objectives and Endpoints	Added the exploratory objective [redacted] Added the exploratory objective [redacted]	
Section 5.1.2: Part 2 Combination Therapy Cohorts [redacted]	[redacted]	
Section 5.1.2.3: pH Effect PK Sub-study [redacted] (Group G) [redacted]		
Section 5.5.2: Nivolumab		
Section 7.2: Method of Study Intervention Assignment		
Section 5.2: Number of Participants	Added sample size for Group G.	
Section 10.2: Sample Size Determination		
Section 6.1: Inclusion Criteria	Added eligibility criteria, including inclusion criterion 2)h) and related subcriteria.	

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 7-1: Study Intervention(s) for CA099003 Table 7.1-1: Study Intervention(s) Administered Section 7.1.1: BMS-986408 Dosing Section 7.7.1: Prohibited and/or Restricted Treatments	Added study interventions.	
Section 9.5: Pharmacokinetics Table 9.5-3: Pharmacokinetic and Immunogenicity Sampling Schedule for Part 2, Groups D (Combination Cohort with Nivolumab), F (Combination Cohort with Nivolumab and Chemotherapy), and G (Starting C1D1), and Part 3 Combination Expansion Table 9.5-5: Pharmacokinetic Sampling Schedule for Part 2, Group G (Cycle 0 pH Effect)	Added Group G to PK assessments.	
Section 9.8.2: Tumor-based Biomarkers	Added Group G to biomarker assessments.	
Table 2-2: On Treatment Procedural Outline (Part 1, Groups A, B, B2, and C) [redacted] Section 5.1.1: Part 1 Monotherapy Cohorts Section 5.1.5: Treatment Period	Added [redacted]. Added screening and on-treatment tumor biopsies. [redacted]	Updated throughout the protocol to include an optional monotherapy cohort (Group B2) [redacted]. This included updating the schedule of activities, study design, sample sizes, study population, eligibility criteria, study intervention, DLT, and PK and biomarker assessments.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.2: Number of Participants Section 10.2: Sample Size Determination	Added the sample size for Group B2.	
Section 6.1: Inclusion Criteria	Added eligibility criteria. Modified inclusion criterion 2)a) to apply to Group B2.	
Table 7-1: Study Intervention(s) for CA099003 Table 7.1-1: Study Intervention(s) Administered Section 7.1.1: BMS-986408 Dosing	Added study interventions. [redacted] [redacted].	
Section 9.5: Pharmacokinetics Table 9.5-2: Pharmacokinetic and Immunogenicity Sampling Schedule for Part 1 Groups A, B, B2, and C Table 9.5-5: Pharmacokinetic Sampling Schedule for Part 2, Group G (Cycle 0 pH Effect)	Added Group B2 to PK assessments. Included Table 9.5-5 for the sampling schedule [redacted] followed by the Table 9.5-3 schedule starting at C1D1.	
Table 9.8-1: Biomarker Sampling Schedule for all Participants Section 9.8.2: Tumor-based Biomarkers	Added Group B2 to biomarker assessments.	
Table 2-1: Screening Procedural Outline (CA099003)	Edited a note to the row “Brain Imaging.”	To clarify that MRI of the brain without and with contrast is required for all NSCLC and melanoma participants in Part 3, Groups D2 and F2.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-4: Follow-up Procedural Outline (CA099003)	The safety follow-up period was revised from "last dose of study treatment" to "end of treatment (EOT)." Updated the note in the row "Concomitant Medication Use."	To align with the study design. To clarify the minimum period in which the use of concomitant medication should be recorded.
Section 3.2.1.2: BMS-986408 Nonclinical Pharmacology [redacted] Section 3.2.1.4: BMS-986408 Nonclinical Toxicology Section 3.2.1.5: BMS-986408 Clinical Activity	[redacted] Added Section 3.2.1.5 and preliminary clinical data from CA099003.	Updated to align with the IB. Removed preclinical data that can be found in IB. Added clinical data to align with the IB.
Table 2-4: Follow-up Procedural Outline (CA099003) Section 9.2.3: Follow-up of AEs and SAEs Section 3.3: Benefit/Risk Assessment Section 9.2.1: Time Period and Frequency for Collecting AE and SAE Information	Removed text related to serious adverse events (SAEs) and adverse events (AEs) associated with confirmed or suspected severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections. Removed language related to acute SARS-CoV-2 infections and vaccines. Relocated text related to AEs associated with SARS-CoV-2 infection.	Updated information and language regarding SARS-CoV-2.
Section 5.1.2: Part 2 Combination Therapy Cohorts Section 5.1.2.3: pH Effect PK Sub-study [redacted] Section 5.1.3: Part 3 Expansion Cohorts Table 7-1: Study Intervention(s) for CA099003	Updated all parts of the study to allow [redacted] Added BMS-986408 [redacted] the list of study interventions.	[redacted] may be assessed in the protocol.
Section 5.1.6: Follow-up Period	Changed the survival follow-up period start from the date of discontinuation of study treatment to the EOT visit.	Updated to align with the Schedule of Activities (Section 2).

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 6.1: Inclusion Criteria	Modified criterion 2)d) to apply to Groups F and G as well and to state "3 months" instead of "1 month" before the start of the screening period.	Biopsy samples will now be accepted if collected within the prior 3 months.
Section 6.2: Exclusion Criteria	Modified exclusion criterion [redacted]	To align with the definition of [redacted]
	Added criterion [redacted]	To list an exclusion criterion pertaining to Part 2, Group F and Part 3, Group F2.
	Modified criterion [redacted]	To clarify that the [redacted]
	Modified criteria [redacted]	To clarify that [redacted]
	Modified criterion [redacted]	Revised to align with the target participant population for enrollment purposes.
	Modified criterion [redacted]	Only [redacted] should be considered an exclusion criterion.
	Added criterion 5)c).	Added to address the addition of chemotherapy.
Table 7-1: Study Intervention(s) for CA099003	Modified the potency of nivolumab from "100 mg or 40 mg" to "100 mg/vial."	Updated to align with the pharmacy manual.
Section 7.4.5: [redacted]	Added guidance in case of suspected or confirmed [redacted]	Included guidance on diagnosis and management of [redacted]
Section 8.1: Discontinuation From Study Intervention	Added instructions for discontinuation from study intervention for all groups in Parts 2 and 3.	To align with the addition of new cohorts in Parts 2 and 3.
Table 9.4.4-1: Clinical Laboratory Assessments	Added [redacted] assessment to the list of analyses required [redacted]	Updated the laboratory assessments based on the addition of [redacted]

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 9.5: Pharmacokinetics	Removed "predose (within approximately 2 hours prior to dosing; [redacted] and added "The [redacted] collected from the participant during each time interval should be recorded [redacted]	To update the guidance for [redacted] collection and analyses.
	Added that [redacted] samples will also be collected from all participants treated with [redacted]	Update to align with new groups.
	Modified the text to state that, after the scheduled analysis of PK samples are complete, [redacted].	Clarification.
	Added that BMS-986408 PK parameters will be derived from plasma concentration-time data during combination with nivolumab and chemotherapy.	To clarify that these derivations will also be performed in cohorts with combination with nivolumab and chemotherapy.
	Added "in the plasma" in the paragraph related to concentration analyses.	Clarification.
	In Table 9.5-2, footnote "b," added "and prior to blood collections."	To clarify that all ECGs should be recorded prior to blood collections.
Table 9.5-3: Pharmacokinetic and Immunogenicity Sampling Schedule for Part 2, Groups D (Combination Cohort with Nivolumab), F (Combination Cohort with Nivolumab and Chemotherapy), and G (Starting C1D1), and Part 3 Combination Expansion Table 9.5-4: Pharmacokinetic and Immunogenicity Sampling Schedule for Part 2, Group E (Combination Cohort with Nivolumab and Ipilimumab)	Added a pre-dose plasma sample collection for BMS-986408 PK analyses in C1D1.	Included to establish participant baseline.
	Revised footnote "b."	To clarify that flush is mandatory to ensure delivery of the entire drug dose.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 9.5-3: Pharmacokinetic and Immunogenicity Sampling Schedule for Part 2, Groups D (Combination Cohort with Nivolumab), F (Combination Cohort with Nivolumab and Chemotherapy), and G (Starting C1D1), and Part 3 Combination Expansion	Added footnote "d" to C1D22.	To clarify that this collection is not applicable for Group F.
Former Section 9.8.1.1: [redacted] Former Section 9.8.1.4: [redacted]	Deleted these sections.	Characterization of [redacted] will no longer be performed.
Table 2-1: Screening Procedural Outline (CA099003) Table 2-2: On Treatment Procedural Outline (Part 1, Groups A, B, B2, and C) Table 2-3: On Treatment Procedural Outline (Parts 2 and 3, Groups D, D2, E, F, F2, and G)	Clarified the schedule of activities by consolidating the rows [redacted] for NSCLC and melanoma participants, clarifying targeted physical examination (PE), separating single from triplicate ECGs, and referencing Section 9.10 for details [redacted]	To clarify and/or increase readability.
Section 6.1: Inclusion Criteria	Added criterion 2)b)v). Criterion 2)c) is no longer applicable per Protocol Amendment 04. Former criterion 2)c) is a subcriterion from 2)b). Edited criterion 4)a)v)2)a).	
Section 7.7.1: Prohibited and/or Restricted Treatments	Clarified the use of immunosuppressive doses of systemic corticosteroids.	
Section 9.2: Adverse Events	Added a reference to the electronic case report form instructions.	
Section 9.2.3: Follow-up of AEs and SAEs	Modified the text to limit SAE follow-up to [redacted]	

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 9.4.3: Electrocardiograms	Removed "a single 12-lead ECG will be collected as outlined" and added a reference to Section 2.	
Table 9.4.4-1: Clinical Laboratory Assessments	Added that the assessment of prothrombin time is needed at screening only.	
Table 9.5-2: Pharmacokinetic Sampling Schedule for Part 1, Groups A, B, B2, and C	Removed the baseline sample collections and added a pre-dose collection in C1D1.	
Table 9.8-1: Biomarker Sampling Schedule for all Participants	Former biomarker sampling schedule tables were merged into a single table for all participants in the study. [redacted]	
Section 10.3: Analysis Sets	Updated the description of the biomarker population.	Clarification.
Appendix 2: Study Governance Considerations	Removed requirement to adhere to the European Union (EU) Directive 2001/20/EC.	To align with new EU regulations.
All	Updated references to groups (eg, "Groups D and E" may be updated to "Part 2" to account for the new Groups F and G). Updated the tables and text throughout the protocol to include the new groups and study interventions.	The protocol was updated throughout to align with the addition of new groups
	Minor formatting and typographical corrections.	Minor; therefore, have not been summarized.

TABLE OF CONTENTS

1 PROTOCOL SUMMARY

Protocol Title	A Phase 1/2 Study of BMS-986408 Alone and in Combination with Nivolumab or with Nivolumab and Ipilimumab in Participants with Advanced Solid Tumors	
Brief Title	A Phase 1/2 Study of BMS-986408 with and without Nivolumab or Nivolumab and Ipilimumab in Participants with Solid Tumors	
Background and Rationale	BMS-986408 is a novel small-molecule dual inhibitor [redacted].	
Objectives and Endpoints	**Objectives**	**Endpoints**
	Primary	
	• To characterize the safety and tolerability, and to establish the MTD, maximum administered dose, and/or RP2D(s), and optimal schedule of oral BMS-986408 administered as monotherapy and in combination with nivolumab ± ipilimumab or chemotherapy to participants with advanced cancer.	• Incidence of DLTs, AEs, SAEs, AEs leading to discontinuation, and deaths.
	Secondary	
	• To characterize the PK profile of BMS-986408 following oral administration as monotherapy and in combination with nivolumab ± ipilimumab or chemotherapy to participants with advanced solid tumors.	• Summary measures of BMS-986408 PK parameters in plasma, such as, but not limited to, Cmax, Tmax, and AUC(0-T), from concentration-time data during BMS-986408 monotherapy and in combination with nivolumab ± ipilimumab or chemotherapy.
	• To evaluate the preliminary anti-tumor activity of BMS-986408 as monotherapy and in combination with nivolumab ± ipilimumab or chemotherapy in participants with advanced cancer.	• ORR and DOR per RECIST v1.1.
Overall Design	CA099003 is a Phase 1/2, first-in-human, multi-center, open-label study of oral BMS-986408 administered as a single agent or in combination with nivolumab, nivolumab and ipilimumab, or nivolumab and PDCT in participants with solid tumors. The study is composed of 3 parts, with monotherapy dose escalation evaluated in Part 1 and combination therapy of escalating doses of BMS-986408 with nivolumab, nivolumab and ipilimumab, or nivolumab and PDCT evaluated in Part 2. Part 3 will include expansion cohorts to evaluate the combination of BMS-986408 with nivolumab or nivolumab and PDCT. All participants will complete 3 study periods: screening [redacted] treatment (approximately 104 weeks), and follow-up (up to 2 years following the end of treatment visit). The duration of study participation by individual participants will be approximately 4 years.	

Number of Participants	The approximate total number of participants treated will be 402 for Parts 1, 2, and 3: [redacted]
Study Population	• Males or females ≥ 18 years of age or local age of majority at the time of consent. • Part 1, Groups A, B, and B2: Advanced, unresectable/metastatic, solid malignancy of any histology that is measurable by RECIST v1.1, and have received, be refractory to, ineligible for, or intolerant of existing therapy(ies) known to provide clinical benefit for the condition of the participant. • Part 1, Group C and Part 2, Groups D and E: Advanced, unresectable/metastatic malignancy measurable by RECIST v1.1, with the following histologies: HNSCC, NSCLC, melanoma, or RCC, have previously received therapy containing anti-PD-L1 or anti-CTLA-4 agents, and have received, be refractory to, ineligible for, or intolerant of existing therapy(ies) known to provide clinical benefit for the condition of the participant. • Part 1, Group C and Part 2, Groups D, E, F, and G: Tumor lesions that can be biopsied at acceptable risk (pretreatment and on treatment). • Part 2, Group G and Part 3, Group D2: Measurable disease by RECIST v1.1 and received and then progressed or been intolerant to anti-PD-1 or anti-PD-L1 (anti-PD-1/PD-L1 not required for MSS CRC) in the advanced or metastatic setting as the most recent therapy with the following histologies: NSCLC, melanoma, RCC, or MSS CRC. • Part 2, Group F and Part 3, Group F2: Metastatic Stage IV A/B NSCLC of non-squamous or squamous histology that have not had prior exposure to IO and no prior systemic anti-cancer given as primary therapy for advanced or metastatic NSCLC.
Study Intervention Administration and Duration	For Part 1, Groups A and B2 (if evaluated), participants will take oral BMS-986408 once daily. For Part 1, Group B (if evaluated), participants will take oral BMS-986408 twice daily (approximately once every 12 hours). The planned cohorts in Parts 1, Group C, Part 2, and Part 3 will take BMS-986408 utilizing the schedule described for Groups A, B, or B2. Participants receiving combination with nivolumab (Groups D, D2, E, and G) will receive BMS-986408 daily and nivolumab 480 mg Q4W. Participants receiving ipilimumab (Group E) will receive ipilimumab 1 mg/kg Q8W after nivolumab as above. Participants receiving PDCT (Groups F and F2) will be treated with BMS-986408 in combination with nivolumab 360 mg and PDCT Q3W. For Group G, PK sub-study, participants will receive a single dose of BMS-986408 (1 of 3 formulations). Some participants will be treated with rabeprazole starting 4 days prior to BMS-986408 for a total of 5 days. After the PK sub-study, participants will be treated with BMS-986408 daily in combination with nivolumab 480 mg Q4W.
Statistical Methods	There is no formal research hypothesis for this study to be statistically tested. The dose escalation decisions in Parts 1 and 2 will be guided [redacted].

Data Monitoring or Other Committee	A data monitoring committee will not be used in the study.

Abbreviations: AE, adverse event; AUC(0-T), area under the concentration-time curve from time 0 to time of last quantifiable concentration; Cmax, maximum concentration; CRC, colorectal cancer; CTLA-4, cytotoxic T lymphocyte-associated protein 4; DGK, diacylglycerol kinase; DLT, dose-limiting toxicity; DOR, duration of response; HNSCC, squamous cell carcinoma of the head and neck; IO, immuno-oncology; ipi, ipilimumab; MSS, microsatellite stable; MTD, maximum tolerated dose; nivo, nivolumab; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD-L1, programmed death ligand 1; PDCT, platinum-doublet chemotherapy; PK, pharmacokinetics; Q3W, every 3 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; RCC, renal cell carcinoma; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended Phase 2 dose; SAE, serious adverse event; Tmax, time of maximum observed concentration; [redacted]

2 SCHEDULE OF ACTIVITIES

Abbreviations used in this protocol are listed in Appendix 1.

Table 2-1: Screening Procedural Outline (CA099003)

Procedure	Screening Visit (Days -28 to -1)	Notes
Eligibility Assessments		
Informed Consent	X	A participant is considered enrolled only when a protocol-specific informed consent form is signed. Must be obtained prior to performing any screening procedures. If a participant is re-enrolled, the participant must be reconsented.
IRT Participant Assignment	X	Register in IRT system to obtain participant number prior to starting any screening procedures. After completing all screening procedures, utilize IRT to either screen fail or obtain treatment assignment information, as applicable. Treatment assignment can occur up to 3 days prior to first dose. See Section 7.2.
Inclusion/Exclusion Criteria	X	Must be confirmed prior to first dose. See Section 6.
Medical History	X	All medical history relevant to disease under study, including tobacco history. Include any clinically significant toxicities or allergies related to previous treatments.
Prior Cancer Therapies	X	Including all prior cancer treatment regimens and medications administered.
Safety Assessments		
Physical Examination (PE)	X	If the screening PE is performed within 72 hours prior to dosing on Day 1, then a single exam may count as both the screening and pre-dose evaluation.
Physical Measurements	X	Includes height, weight, and BMI.
Vital Signs and Oxygen Saturation	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. Obtain oxygen saturation by pulse oximetry at rest.
ECOG Performance Status	X	See Appendix 6.
Concomitant Medication Use	X	Within 14 days prior to dosing on Day 1. Vaccine use must be collected within [redacted] days prior to first dose. See Section 6.2.
Electrocardiogram (ECG)	X	ECGs should be recorded after the participant has been supine for at least 5 minutes. Screening ECG is to be collected as a single reading on the site's local ECG machine.
Laboratory Tests		
Clinical Laboratory Assessments	X	Includes blood and urine samples. See Section 9.4.4.

Table 2-1: Screening Procedural Outline (CA099003)

Procedure	Screening Visit (Days -28 to -1)	Notes
Pregnancy Test (WOCBP only)	X	Serum or urine pregnancy test (minimum sensitivity equivalent units 25 IU/L or equivalent units of hCG) to be done at screening visit and repeated within 24 hours prior to first dose of study treatment. WOCBP must have a negative pregnancy test within 24 hours prior to the start of study therapy and results also must be evaluated prior to study therapy administration. If pregnancy test is taken within 24 hours of dosing (C1D1), a further pregnancy test is not required. An extension up to 72 hours prior to the start of study treatment is permissible in situations where results cannot be obtained within standard 24-hour window.
Follicle-stimulating Hormone	X	Women only, as needed to document postmenopausal status. Refer to Appendix 4.
Serology	X	See Section 9.4.4 for list of laboratory tests to conduct.
HPV Status of Tumor for HNSCC of the Oropharynx	X	Historical HPV status for oropharyngeal cancers should be documented if available, but it is not required. HPV status should have been determined using p16 IHC or HPV PCR, if available.
[redacted]	X	See Section 6.1.
Tumor PD-L1 Expression	X	See Section 6.1.
Biomarker Assessments		
Collection of Fresh Biopsy	X	Biopsies are optional at the discretion of the Investigator and/or Participant for Part 1, Groups A, B, and B2 and Part 3, Groups D2 and F2. Part 1, Group C and Part 2, Groups D, E, F, and G: A fresh pre-treatment biopsy from a single, appropriately accessible lesion (obtained from a core biopsy, excisional biopsy, incisional, or surgical specimen), is required during the screening period or within 3 months before the start of the screening period, with no intervening systemic anti-cancer treatment between time of acquisition and enrollment, must be sent to the central laboratory. Participants must have a lesion that can be biopsied at an acceptable clinical risk as judged by the Investigator to be eligible for the study. Fine needle aspirates and other cytology specimens are not allowed. A repeat biopsy at screening from the same or an alternative site will be required if clinically feasible (at the discretion of the Investigator), and the initial attempt was unsuccessful in obtaining adequate tissue for biomarker analysis. Only 1 repeat attempt may be performed, if clinically feasible. An unsuccessful fresh tumor biopsy at screening will not exclude participants from receiving or continuing study treatment. The biopsy sample should be submitted to central laboratory prior to treatment assignment except if biopsy was attempted but was not completed due to safety concerns. [redacted]

Table 2-1: Screening Procedural Outline (CA099003)

Procedure	Screening Visit (Days -28 to -1)	Notes
		[redacted] Bone lesions are unacceptable sites for biopsy. See Section 9.8 and Table 9.8-1. Instructions for the collection and processing of all samples will be provided in the laboratory manual.
Collection of Archival Tumor Tissue	X	OPTIONAL at the discretion of the Investigator and/or participant for all parts of the study, EXCEPT for participants in Group F2, for whom it is mandatory unless FFPE material is provided. Archived tumor specimens, in the form of blocks or sectioned slides, are optional and can be submitted prior to study treatment administration, if available. Instructions for the collection and processing of all samples will be provided in the laboratory manual. An archival sample cannot be substituted for a required fresh biopsy.
AE Reporting		
Assessment of Signs and Symptoms	X	Within 14 days prior to dosing.
Monitor for non-serious AEs and SAEs	X	Part 1: All non-serious AEs associated with SARS-CoV-2 and SAEs must be collected from the date of participant's written consent until [redacted] post discontinuation of study treatment or participation in the study, if the last scheduled visit occurs at a later time. Parts 2 and 3: All non-serious AEs associated with SARS-CoV-2 and SAEs must be collected from the date of participant's written consent until [redacted] post discontinuation of study treatment or participation in the study, if the last scheduled visit occurs at a later time.

Table 2-1: Screening Procedural Outline (CA099003)

Procedure	Screening Visit (Days -28 to -1)	Notes
Tumor Assessments		
Body Imaging	X	Contrast-enhanced CT of the chest, abdomen, pelvis, and all other known and/or suspected sites of disease, within 28 days prior to first dose. CT/MRI of the neck is required only for HNSCC participants. Refer to Imaging Assessment details in Section 9.1.1.
Brain Imaging	X	MRI of the brain without and with contrast is required for all NSCLC and melanoma participants in Groups D2 and F2 and participants with known or suspected brain metastases, unless participant has completed an imaging study of the brain within 28 days prior to date of first dose. CT of the brain without and with contrast can be performed if MRI is contraindicated. See Section 9.1.1 for further details.

Abbreviations: AE, adverse event; [redacted] BMI, body mass index; [redacted] C, cycle; CT, computed tomography; D, day; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; [redacted]; FFPE, formalin-fixed paraffin-embedded; h, hour; hCG, human chorionic gonadotrophin; HNSCC, squamous cell carcinoma of the head and neck; [redacted] IHC, immunohistochemistry; IRT, interactive response technology; [redacted]; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; [redacted] PCR, polymerase chain reaction; PD-L1, programmed death ligand 1; PE, physical examination; [redacted]; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome-coronavirus 2; WOCBP, women of childbearing potential.

Table 2-2: On Treatment Procedural Outline (Part 1, Groups A, B, B2, and C)

Procedure[a,b]	Cycle 0		Cycle 1						Cycles 2 and 3		Cycle 4+	EOT[d]	Notes 1 Cycle = 4 Weeks Exception: Group B2 (Cycle 0 = 2 Weeks)
	D1	D8	D1	D2	D8	D15	D16	D22	D1	D15	D1		
Visit Window (days)		±2			±2	± 2	± 2	± 2	±2	± 2	± 2		**The C1D15 and C1D16 visits must occur within the visit window stated and must be 24 h apart.**
Safety Assessments													
Physical Examination (PE)	X		X						X		X	X	If the screening PE is performed within 72 hours prior to dosing on Day 1 then a single exam may count as both the screening and pre-dose evaluation. If there are any new or worsening clinically significant changes since the last examination, report changes on the appropriate nonserious or serious AE CRF page.
Targeted PE		X		X	X	X	X	X		X			Symptom directed as clinically indicated.
Vital Signs (including oxygen saturation)	X	X	X	X	X	X	X	X	X	X	X	X	Includes body temperature, respiratory rate, 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. Obtain oxygen saturation by pulse oximetry at rest. Vital signs must be collected immediately prior to the start of treatment at each visit. Extended monitoring of vital signs

Table 2-2: On Treatment Procedural Outline (Part 1, Groups A, B, B2, and C)

Procedure[a,b]	Cycle [redacted]		Cycle 1						Cycles 2 and 3		Cycle 4+	EOT[d]	Notes 1 Cycle = 4 Weeks Exception: Group B2 (Cycle 0 = 2 Weeks)
	D1	D8	D1	D2	D8	D15	D16	D22	D1	D15	D1		
Visit Window (days)		±2			±2	± 2	± 2	± 2	±2	± 2	± 2		**The C1D15 and C1D16 visits must occur within the visit window stated and must be 24 h apart.**
													on [redacted] post administration of BMS-986408.
Blood Pressure [redacted]			X			X							Participants will be supplied with an [redacted]. See Section 5.1.2.
Body Weight			X						X		X	X	
Triplicate 12-lead Electrocardiogram (ECG)	X		X			X							Triplicate 12-lead ECGs 5 minutes apart to be performed per Table 9.5-2. All triplicate ECGs should be recorded on the Sponsor-provided ECG machine and results should be transmitted electronically to the central laboratory.
Electrocardiogram (ECGs)				X	X		X	X	X		X	X	All single 12-lead ECGs should be recorded on the site's ECG machine (locally) predose after the participant has been supine for at least 5 minutes and prior to blood draws.

Table 2-2: On Treatment Procedural Outline (Part 1, Groups A, B, B2, and C)

Procedure[a,b]	Cycle [redacted]		Cycle 1						Cycles 2 and 3		Cycle 4+	EOT[d]	Notes 1 Cycle = 4 Weeks Exception: Group B2 (Cycle 0 = 2 Weeks)
	D1	D8	D1	D2	D8	D15	D16	D22	D1	D15	D1		
Visit Window (days)		±2			±2	± 2	± 2	± 2	±2	± 2	± 2		**The C1D15 and C1D16 visits must occur within the visit window stated and must be 24 h apart.**
Concomitant Medication Use	X	X	X	X	X	X	X	X	X	X	X	X	
ECOG Performance Status	X		X			X			X		X	X	
AE Reporting													
Monitor for Non-serious AEs and SAEs	Continuously												All AEs (including non-serious AEs and SAEs) must be collected continuously during the treatment period.
Laboratory Tests													
Clinical Laboratory Assessments	X		X		X	X		X	X	X	X	X	Perform onsite/local laboratory testing within 72 hours prior to each dose. For the first treatment visit, labs need not be repeated if they were performed within 72 hours and the results are available and have been reviewed for eligibility. See Section 9.4.4 and Table 9.4.4-1.
Thyroid Function Test (TSH)	X		X						X		X	X	If TSH is abnormal, free T3 and free T4 should be collected. See Section 9.4.4 and Table 9.4.4-1.

Table 2-2: On Treatment Procedural Outline (Part 1, Groups A, B, B2, and C)

Procedure[a,b]	Cycle [redacted]		Cycle 1						Cycles 2 and 3		Cycle 4+	EOT[d]	Notes 1 Cycle = 4 Weeks Exception: Group B2 (Cycle 0 = 2 Weeks)
	D1	D8	D1	D2	D8	D15	D16	D22	D1	D15	D1		
Visit Window (days)		±2			±2	± 2	± 2	± 2	±2	± 2	± 2		**The C1D15 and C1D16 visits must occur within the visit window stated and must be 24 h apart.**
Urinalysis	X		X			X			X		X	X	See Section 9.4.4 and Table 9.4.4-1.
Pregnancy Test (WOCBP only)	X		X						X		X	X	Serum or urine pregnancy test (minimum sensitivity equivalent units 25 IU/L or equivalent units of hCG). Sample should be drawn within 24 h of Day 1 of each cycle, and results must be available and reviewed prior to administration of study treatment on Day 1 of each cycle while on study treatment. An extension up to 72 h prior to the start of study treatment or Day 1 of Cycles 2 and beyond is permissible in situations where results cannot be obtained within standard 24 h window.
PK Assessments													
PK Collections			See Table 9.5-2										Includes plasma and urine samples. Refer to Section 9.5 for timing of collections

Table 2-2: On Treatment Procedural Outline (Part 1, Groups A, B, B2, and C)

Procedure[a,b]	Cycle [redacted]		Cycle 1						Cycles 2 and 3		Cycle 4+	EOT[d]	Notes 1 Cycle = 4 Weeks Exception: Group B2 (Cycle 0 = 2 Weeks)
	D1	D8	D1	D2	D8	D15	D16	D22	D1	D15	D1		
Visit Window (days)		±2			±2	± 2	± 2	± 2	±2	± 2	± 2		**The C1D15 and C1D16 visits must occur within the visit window stated and must be 24 h apart.**
Biomarker Assessments													
Biomarker Sample Collections			See Table 9.8-1.										Refer to biomarker collection table in Section 9.8 for timing of collections.
Tumor Biopsy										X		X	Biopsies are optional at the discretion of the Investigator and/or Participant for Part 1, Groups A, B, and B2 (if evaluated). Part 1, Group C only: Mandatory on-treatment biopsy should be performed on C2D15 (± 7 days) only. EOT biopsy is optional at the discretion of the Investigator and/or Participant. An on-treatment biopsy does not need to be performed if a fresh biopsy was not collected at screening or the screening biopsy or biopsies did not contain adequate tumor tissue for biomarker analysis. The screening and on-treatment tumor biopsies should be preferentially collected from the same site, if feasible. See Section 9.8 and Table 9.8-1. [redacted]

Table 2-2: On Treatment Procedural Outline (Part 1, Groups A, B, B2, and C)

Procedure[a,b]	Cycle [redacted]		Cycle 1						Cycles 2 and 3		Cycle 4+	EOT[d]	Notes 1 Cycle = 4 Weeks Exception: Group B2 (Cycle 0 = 2 Weeks)
	D1	D8	D1	D2	D8	D15	D16	D22	D1	D15	D1		
Visit Window (days)		±2			±2	± 2	± 2	± 2	±2	± 2	± 2		The C1D15 and C1D16 visits must occur within the visit window stated and must be 24 h apart.
													[redacted]
Imaging Assessments													
Body Imaging			Contrast-enhanced CT of the chest, CT/MRI of the neck (required only for HNSCC participants), abdomen, pelvis, and all other known and/or suspected sites of disease should occur every 8 weeks (± 7 days) starting from C1D1 for the first 48 weeks, then every 12 weeks (± 7 days) until disease progression or discontinuation of all study treatment, whichever occurs later. See Section 9.1.1 for further details.										
Brain Imaging			Participants with a history of brain metastasis or symptoms should have a surveillance MRI performed per standard of care (approximately every 12 weeks ± 7 days), or sooner if clinically indicated. CT of the brain without and with contrast can be performed if MRI is contraindicated. See Section 9.1.1 for further details.										
Other Assessments													
BMS-986408 [redacted]			X						X (Cycle 3 only)				Only for participants administered BMS-986408 [redacted] See Section 9.10 and [redacted]

Table 2-2: On Treatment Procedural Outline (Part 1, Groups A, B, B2, and C)

Procedure[a,b]	Cycle [redacted]		Cycle 1						Cycles 2 and 3		Cycle 4+	EOT[d]	Notes 1 Cycle = 4 Weeks Exception: Group B2 (Cycle 0 = 2 Weeks)
	D1	D8	D1	D2	D8	D15	D16	D22	D1	D15	D1		
Visit Window (days)		±2			±2	± 2	± 2	± 2	±2	± 2	± 2		**The C1D15 and C1D16 visits must occur within the visit window stated and must be 24 h apart.**
Study Intervention													
Dispense BMS-986408 Q4W	X		X						X		X		BMS-986408 to be supplied by BMS and issued to the participant at the beginning of every cycle (see Section 7.1).

Abbreviations: AE, adverse event; C, cycle; CRF, case report form; CT, computed tomography; D, day; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; EOT, end of treatment; h, hour; hCG, human chorionic gonadotrophin; HNSCC, squamous cell carcinoma of the head and neck; min, minute; MRI, magnetic resonance imaging; PE, physical examination; PK, pharmacokinetics; Q4W, every 4 weeks; SAE, serious adverse event; T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone; WOCBP, women of childbearing potential

[a] If all components of study treatment are delayed, the procedures scheduled for that same time point should be delayed to coincide with when the time point's dosing actually occurs (except radiographic tumor assessments).

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

[redacted]

[d] EOT is defined as the visit where the decision is made to discontinue the participant from treatment. Evaluations will be performed prior to study discharge, or for participants who are prematurely discontinued. 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 (eg, C26D1) and the start of the safety follow-up period. 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); it does not need to be repeated and will be considered as the start of the safety follow-up period.

Table 2-3: On Treatment Procedural Outline (Parts 2 and 3, Groups D, D2, E, F, F2, and G)

Procedure[a,b]	Cycle 0				Cycle 1					Cycle 2 and Cycle 3		Cycle 4+	EOT[d]	Notes Groups D, D2, E, and G: 1 Cycle = 4 Weeks Groups F and F2: 1 Cycle = 3 Weeks (Exception: Group G Cycle 0 = 11 Days)
	D-4	D1	D2	D3-D5	D1	D2	D8	D 15	D 22[e]	D1	D15	D1		
Visit Window (± days)							± 2	± 2	± 2	± 2	± 2	± 2		
Safety Assessments														
Physical Examination (PE)		X			X					X		X	X	If there are any new or worsening clinically significant changes since the last examination, report changes on the appropriate nonserious or serious AE CRF page.
Targeted PE			X	X		X	X	X	X		X			Symptom directed as clinically indicated.
Vital Signs (including oxygen saturation)		X			X	X	X	X	X	X	X	X	X	Includes body temperature, respiratory rate, 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. Obtain oxygen saturation by pulse oximetry at rest. Vital signs must be collected immediately prior to the start of treatment at each visit.
Body Weight		X			X					X		X	X	

Table 2-3: On Treatment Procedural Outline (Parts 2 and 3, Groups D, D2, E, F, F2, and G)

Procedure[a,b]	Cycle [redacted]				Cycle 1					Cycle 2 and Cycle 3		Cycle 4+	EOT[d]	Notes Groups D, D2, E, and G: 1 Cycle = 4 Weeks Groups F and F2: 1 Cycle = 3 Weeks (Exception: Group G Cycle 0 = 11 Days)
	D-4	D1	D2	D3-D5	D1	D2	D8	D 15	D 22[e]	D1	D15	D1		
Visit Window (± days)							± 2	± 2	± 2	± 2	± 2	± 2		
Triplicate 12-lead Electrocardiogram (ECG)		X			X (Group G only)									Triplicate 12-lead ECGs 5 minutes apart to be performed per Table 9.5-5. All triplicate ECGs from C0 and C1 should be recorded on the Sponsor-provided ECG machine and results should be transmitted electronically to the central laboratory.
Electrocardiogram (ECGs)					X[f]	X		X		X		X	X	All single 12-lead ECGs should be recorded on the site's ECG machine (locally) predose after the participant has been supine for at least 5 minutes and prior to blood draws. On Cycle 1 Day 1, a single safety ECG to be done predose and at 6 hours after dosing BMS-986408. Only a pre-dose ECG is required at all other timepoints.
Concomitant Medication Use	X	X	X	X	X	X	X	X	X	X	X	X	X	

Table 2-3: On Treatment Procedural Outline (Parts 2 and 3, Groups D, D2, E, F, F2, and G)

Procedure[a,b]	Cycle [redacted]				Cycle 1					Cycle 2 and Cycle 3		Cycle 4+	EOT[d]	Notes Groups D, D2, E, and G: 1 Cycle = 4 Weeks Groups F and F2: 1 Cycle = 3 Weeks (Exception: Group G Cycle 0 = 11 Days)
	D-4	D1	D2	D3-D5	D1	D2	D8	D 15	D 22[e]	D1	D15	D1		
Visit Window (± days)							± 2	± 2	± 2	± 2	± 2	± 2		
ECOG Performance Status		X			X			X		X		X	X	
AE Reporting														
Monitor for non-serious AEs and SAEs	Continuously													All AEs (including non-serious AEs and SAEs) must be collected continuously during the treatment period.
Laboratory Tests														
Clinical Laboratory Assessments	X				X		X	X	X	X	X	X	X	Perform onsite/local laboratory testing within 72 hours prior to each dose. For the first treatment visit, laboratory assessments need not be repeated if they were performed within 72 hours and the results are available and have been reviewed for eligibility. See Section 9.4.4 and Table 9.4.4-1.
Thyroid Function Test (TSH)					X					X		X	X	If TSH is abnormal, free T3 and free T4 should be

Table 2-3: On Treatment Procedural Outline (Parts 2 and 3, Groups D, D2, E, F, F2, and G)

Procedure[a,b]	Cycle [redacted]				Cycle 1					Cycle 2 and Cycle 3		Cycle 4+	EOT[d]	Notes Groups D, D2, E, and G: 1 Cycle = 4 Weeks Groups F and F2: 1 Cycle = 3 Weeks (Exception: Group G Cycle 0 = 11 Days)
	D-4	D1	D2	D3-D5	D1	D2	D8	D 15	D 22[e]	D1	D15	D1		
Visit Window (± days)							± 2	± 2	± 2	± 2	± 2	± 2		
														collected. See Section 9.4.4 and Table 9.4.4-1.
Urinalysis					X					X		X	X	See Section 9.4.4 and Table 9.4.4-1.
Pregnancy Test (WOCBP only)	X				X					X		X	X	Serum or urine pregnancy test (minimum sensitivity equivalent units 25 IU/L or equivalent units of hCG). Sample should be drawn within 24 h of Day 1 of each cycle, and results must be available and reviewed prior to administration of study treatment on Day 1 of each cycle while on study treatment. An extension up to 72 h prior to the start of study treatment or Day 1 of Cycles 2 and beyond is permissible in situations where results cannot be obtained within standard 24 h window.

Table 2-3: On Treatment Procedural Outline (Parts 2 and 3, Groups D, D2, E, F, F2, and G)

Procedure[a,b]	Cycle [redacted]				Cycle 1					Cycle 2 and Cycle 3		Cycle 4+	EOT[d]	Notes Groups D, D2, E, and G: 1 Cycle = 4 Weeks Groups F and F2: 1 Cycle = 3 Weeks (Exception: Group G Cycle 0 = 11 Days)
	D-4	D1	D2	D3-D5	D1	D2	D8	D 15	D 22[e]	D1	D15	D1		
Visit Window (± days)							± 2	± 2	± 2	± 2	± 2	± 2		
PK and Immunogenicity Assessments														
PK sample Collection	See Table 9.5-3, Table 9.5-4, and Table 9.5-5.													Refer to Section 9.5 for timing of collections.
Biomarker Assessments														
Biomarker Sample Collection					See Table 9.8-1.									Refer to Section 9.8 for timing of collections
Tumor Biopsy											X (Cycle 2 only)		X	Biopsies are optional at the discretion of the investigator and/or participant for Part 3, Groups D2 and F2. Mandatory on-treatment biopsy should be performed on C2D15 (± 7 days) for Part 2, Groups D, E, F, and G. EOT biopsy is optional at the discretion of the Investigator and/or participant. An on-treatment biopsy does not need to be performed if a fresh biopsy was not collected at screening or the screening biopsy or biopsies did not

Table 2-3: On Treatment Procedural Outline (Parts 2 and 3, Groups D, D2, E, F, F2, and G)

Procedure[a,b]	Cycle [redacted]				Cycle 1					Cycle 2 and Cycle 3		Cycle 4+	EOT[d]	Notes Groups D, D2, E, and G: 1 Cycle = 4 Weeks Groups F and F2: 1 Cycle = 3 Weeks (Exception: Group G Cycle 0 = 11 Days)
	D-4	D1	D2	D3-D5	D1	D2	D8	D 15	D 22[e]	D1	D15	D1		
Visit Window (± days)							± 2	± 2	± 2	± 2	± 2	± 2		
														contain adequate tumor tissue for biomarker analysis. The screening and on-treatment tumor biopsies should be preferentially collected from the same site, if feasible. [redacted] Refer to Table 9.8-1 for timing of collections.
Efficacy Assessments														
Body Imaging					Contrast-enhanced CT of the chest, CT/MRI of the neck (required only for HNSCC participants), abdomen, pelvis, and all other known and/or suspected sites of disease should occur every 8 weeks (± 7 days) starting from C1D1 for the first 48 weeks, then every 12 weeks (± 7 days) until disease progression or discontinuation of all study treatment, whichever occurs later. See Section 9.1.1 and Section 5.1.2 for further details.									
Brain Imaging					Participants with a history of brain metastasis or symptoms should have a surveillance MRI performed per standard of care (approximately every 12 weeks ± 7 days), or sooner if clinically indicated. CT of the brain without and with contrast can be performed if MRI is contraindicated. See Section 9.1.1 for further details.									

Table 2-3: On Treatment Procedural Outline (Parts 2 and 3, Groups D, D2, E, F, F2, and G)

Procedure[a,b]	Cycle [redacted]				Cycle 1					Cycle 2 and Cycle 3		Cycle 4+	EOT[d]	Notes Groups D, D2, E, and G: 1 Cycle = 4 Weeks Groups F and F2: 1 Cycle = 3 Weeks (Exception: Group G Cycle 0 = 11 Days)
	D-4	D1	D2	D3-D5	D1	D2	D8	D 15	D 22[e]	D1	D15	D1		
Visit Window (± days)							± 2	± 2	± 2	± 2	± 2	± 2		
Other Assessments														
BMS-986408 [redacted]					X					X (Cycle 3 only)				Only for participants administered BMS-986408 [redacted]. See Section 9.10 and [redacted]
Study Intervention														
Dispense BMS-986408 Q4W (Groups D, D2, E, and G)		X [redacted]			X					X		X		BMS-986408 to be supplied by BMS and issued to the participant at the beginning of every cycle. See Section 7.1.
Nivolumab Infusion Q4W (Groups D, D2, E, and G)					X					X		X		Nivolumab will be supplied by BMS.
Ipilimumab infusion Q8W (Group E)					X					X (Cycle 3 only)		X (Cycle 5 and every 2 cycles thereafter)		Ipilimumab will be supplied by BMS. Ipilimumab infusions on Day 1 of every second cycle; therefore, on Day 1 of Cycles 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, and 25.

Table 2-3: On Treatment Procedural Outline (Parts 2 and 3, Groups D, D2, E, F, F2, and G)

Procedure[a,b]	Cycle [redacted]				Cycle 1					Cycle 2 and Cycle 3		Cycle 4+	EOT[d]	Notes Groups D, D2, E, and G: 1 Cycle = 4 Weeks Groups F and F2: 1 Cycle = 3 Weeks (Exception: Group G Cycle 0 = 11 Days)
	D-4	D1	D2	D3-D5	D1	D2	D8	D 15	D 22[e]	D1	D15	D1		
Visit Window (± days)							± 2	± 2	± 2	± 2	± 2	± 2		
Dispense BMS-986408 Q3W + Nivolumab Infusion Q3W + 4 Cycles of PDCT Infusion Q3W (Groups F and F2)					X					X		X		BMS-986408 to be supplied by the Sponsor and issued to the participant at the beginning of every cycle. Nivolumab will be supplied by the Sponsor. See Section 7.1 for details on PDCT sourcing and administration.
Dispense Rabeprazole (Group G)	X													[redacted]

Abbreviations: AE, adverse event; C, cycle; CRF, case report form; CT, computed tomography; D, day; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; EOT, end of treatment; h, hour; hCG, human chorionic gonadotrophin; MRI, magnetic resonance imaging; PDCT, platinum-doublet chemotherapy; PE, physical examination; PK, pharmacokinetics; Q3W, every 3 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; SAE, serious adverse event; T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone; WOCBP, women of childbearing potential.

[a] If all components of study treatment are delayed, the procedures scheduled for that same time point should be delayed to coincide with when the time point's dosing actually occur (except radiographic tumor assessments).

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

[redacted]

[d] EOT is defined as the visit where the decision is made to discontinue the participant from treatment. Evaluations will be performed prior to study discharge, or for participants who are prematurely discontinued. 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 (eg, C26D1) and the start of the safety follow-up period. 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); it does not need to be repeated and will be considered as the start of the safety follow-up period.

[e] Cycle 1 Day 22 visit is not applicable to Groups F and F2.

[f] Single 12-lead ECG on Cycle 1 Day 1 is not applicable to Group G.

Table 2-4: Follow-up Procedural Outline (CA099003)

Procedure	Follow-up 1 [redacted] days (±7 Days)	Follow-up 2[a] 60 days (±7 Days)	Follow-up 3[a] 100 days (±7 Days)	Survival Follow-up	Notes **Part 1 has a safety follow-up period of [redacted] with 1 follow-up visit at 30 days after EOT.** [redacted] **Follow-up visits should be conducted in person and occur relative to the last dose of study treatment or EOT visit, whichever is later.**
Safety Assessments					
Targeted PE, Measurements, Vital Signs, Oxygen Saturation, and ECOG Performance Status	X	X	X		Weight, blood pressure, heart rate, body temperature, oxygen saturation by pulse oximetry, and ECOG Performance Status (Appendix 6).
Concomitant Medication Use	Continuously				Record at each visit. Record continuously for a minimum of [redacted] (Part 1) or [redacted] (Parts 2 and 3), except if a participant has started a new anti-neoplastic therapy. However, any concomitant medication used to treat an AE suspected to be related to the study treatment by the investigator occurring after the start of a new treatment will be reported.
Subsequent Cancer Treatment	X	X	X	X	
Monitor for AEs and SAEs	Continuously				Record at each visit. **Part 1**: Collect continuously for a minimum of [redacted] following discontinuation of study treatment, except in cases where a study participant has started a new anti-neoplastic therapy. However, any AE occurring after the start of a new treatment that is suspected to be related to study treatment by the Investigator will be reported. Beyond [redacted] from the last dose of study therapy, participants will be followed for drug-related AEs/SAEs [redacted]

Table 2-4: Follow-up Procedural Outline (CA099003)

Procedure	Follow-up 1 [redacted] days (±7 Days)	Follow-up 2[a] 60 days (±7 Days)	Follow-up 3[a] 100 days (±7 Days)	Survival Follow-up	Notes **Part 1 has a safety follow-up period of [redacted], with 1 follow-up visit at 30 days after EOT.** **Part 2 and Part 3 have a safety follow-up period of [redacted] with 3 follow-up visits at [redacted] after EOT.** **Follow-up visits should be conducted in person and occur relative to the last dose of study treatment or EOT visit, whichever is later.**
					Parts 2 and 3: Collect continuously for a minimum of [redacted] following discontinuation of study treatment, except in cases where a study participant has started a new anti-neoplastic therapy. However, any AE occurring after the start of a new treatment that is suspected to be related to study treatment by the Investigator will be reported. Beyond [redacted] from the last dose of study therapy, participants will be followed for drug-related AEs/SAEs [redacted]
Laboratory Tests					
Clinical Laboratory Assessments	X	X	X		See Section 9.4.4 for the list of laboratory tests.
Urinalysis	X	X	X		
Pregnancy Test (WOCBP only)	X	X	X		Serum or urine test. Pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG.
PK and Immunogenicity Assessments					
PK and Immunogenicity Collections	See Table 9.5-2 (Part 1, Groups A, B, B2, and C), Table 9.5-3 (Part 2, Groups D, F, and G and Part 3), Table 9.5-4 (Part 2, Group E), and Table 9.5-5 (Part 2, Group G, Cycle 0).				Refer. to PK/immunogenicity collection tables in Section 9.5 for timing of collections.

Table 2-4: Follow-up Procedural Outline (CA099003)

Procedure	Follow-up 1 [redacted] days (±7 Days)	Follow-up 2 60 days (±7 Days)	Follow-up 3 100 days (±7 Days)	Survival Follow-up	Notes **Part 1 has a safety follow-up period of [redacted], with 1 follow-up visit at [redacted] after EOT.** **Part 2 and Part 3 have a safety follow-up period of [redacted] with 3 follow-up visits at [redacted] days after EOT.** **Follow-up visits should be conducted in person and occur relative to the last dose of study treatment or EOT visit, whichever is later.**
Biomarker Assessments					
Biomarker Sample Collections	See Table 9.8-1.				Refer to Section 9.8 for timing of collections, including a tumor biopsy.
Efficacy Assessments					
Body Imaging	See notes.				Participants will have imaging assessments completed every 12 weeks (± 7 days) from EOT until withdrawal of consent, death, study termination, or initiation of another anti-cancer treatment, whichever occurs first, for up to [redacted] after EOT. Contrast enhanced CT of the chest, abdomen, pelvis, and all other known and/or suspected sites of disease should be completed. CT/MRI of the neck is required for HNSCC participants. See Section 9.1.1.1 for further details. If pregnancy is the reason for study drug discontinuation, no imaging is performed.
Brain Imaging	See notes.				Participants with a history of brain metastasis or symptoms should have a surveillance MRI study per standard of care (approximately every 12 weeks ± 7 days), or sooner if clinically indicated, until discontinuation of body imaging. CT of the brain without and with contrast can be performed if MRI is contraindicated. See Section 9.1.1.1 for further details.
Assessment of Participant Survival Status	X	X	X	X	During Safety Follow-up (clinic visits) and every 12 weeks ± 2 weeks (clinic visit or by telephone) during survival phase for up to [redacted] after EOT. Include documentation of subsequent cancer treatments.

Abbreviations: AE, adverse event; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; EOT, end of treatment; hCG, human chorionic gonadotrophin; HNSCC, squamous cell carcinoma of the head and neck; MRI, magnetic resonance imaging; PE, physical exam; PK, pharmacokinetics; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome-coronavirus 2; WOCBP, women of childbearing potential.

[redacted]

In the event that multiple procedures are required at a single time point after dosing BMS-986408 during any visit, the procedures should occur with the following priority:

1) Post-dose electrocardiograms (ECGs) for PK-QT relationship analysis.
2) Post-dose pharmacokinetic (PK) sampling.

3 INTRODUCTION

CA099003 is a Phase 1/2 first-in-human (FIH) study of BMS-986408, an oral inhibitor of diacylglycerol kinase (DGK)α and DGKζ, in participants with advanced solid tumors. The main goals of the study are to characterize the safety profile of BMS-986408 as monotherapy and in combination with nivolumab, nivolumab plus ipilimumab, or nivolumab plus chemotherapy and to establish the maximum tolerated dose (MTD) and the recommended Phase 2 dose(s) (RP2D) that optimize the pharmacokinetic/pharmacodynamic (PK/PD) relationship of BMS-986408. Additional goals are to evaluate preliminary PD and anti-tumor activity through analyses of several biomarkers aimed at establishing proof-of-mechanism for DGKα/ζ inhibition in human tumors.

3.1 Study Rationale

The discovery of T cell checkpoint inhibitor therapy has revolutionized the treatment of a multitude of previously fatal cancers, resulting in improved quality of life and long-term survival benefit for a substantial number of patients. However, a significant fraction of patients continue to demonstrate resistance to existing therapies, underscoring the need for a next generation of immune-modulating approaches that will expand the life-saving benefits of immune therapy.

DGKs are a family of lipid kinases that terminate diacylglycerol (DAG)-mediated signaling through the direct conversion of DAG into phosphatidic acid. In T cells, the diacylglycerol kinase (DGK)α and DGKζ isozymes serve as intra-cellular T cell receptor (TCR)-signaling, negative-regulatory checkpoints. DGKα and DGKζ are broadly expressed among human T cell populations, enabling the DGK checkpoint to regulate all phases of T cell activation including T cell priming, effector response, and memory recall responses. As such, DGKα and DGKζ impede T cell-mediated anti-tumor immunity and serve as a resistance mechanism to both anti-programmed death protein-1 (PD-1) and anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) therapy.

BMS-986408 is a novel small-molecule dual inhibitor of DGKα and DGKζ, [redacted]

3.2 Background

A detailed description of the chemistry, pharmacology, and preclinical toxicity of BMS-986408 is provided in the BMS-986408 Investigator's Brochure (IB).[1] Detailed information on nivolumab and ipilimumab is provided in their respective IB.[2,3] A summary of the data is provided below.

3.2.1 BMS-986408

3.2.1.1 BMS-986408 Mechanism of Action

BMS-986408 is a substrate-competitive inhibitor of both the DGKα and DGKζ lipid kinases. Inhibition of the DGK intracellular T cell checkpoint is differentiated from and complementary to both anti-PD-1 and anti-CTLA-4 blockade.

3.2.1.2 BMS-986408 Nonclinical Pharmacology

BMS-986408 exhibits superior potentiation of T cell activation in a human mixed lymphocyte reaction assay compared to either nivolumab (BMS-986558, anti-PD-1 monoclonal antibody [mAb]) or ipilimumab (BMS-734016, anti-CTLA-4) alone, and the combination of BMS-986408 with either nivolumab or ipilimumab is additive compared to each of the single agents. [redacted].[6]

[redacted]

[redacted]

[redacted]

[redacted]

3.2.1.4 BMS-986408 Nonclinical Toxicology

[redacted]

[redacted]

Collectively, the results of the nonclinical toxicology studies indicate an acceptable monitorable and manageable safety profile and supports the continued clinical development of BMS-986408.

3.2.1.5 BMS-986408 Clinical Activity

As of the data cut-off 19-Jun-2023, [redacted] participants have been treated across 5 dose levels of BMS-986408 monotherapy: [redacted] and [redacted] has been treated in combination with nivolumab (BMS-986408 [redacted] plus nivolumab 480 mg intravenously [IV] once every 4 weeks [Q4W]). [redacted]

To date, the preliminary clinical safety data are consistent with the nonclinical assessment of toxicity, and the data support the continued exploration of BMS-986408 alone and in combination.

3.2.2 Nivolumab

3.2.2.1 Nivolumab Mechanism of Action

Nivolumab (also referred to as BMS-936558, MDX1106, or ONO-4538) is a human monoclonal antibody (immunoglobulin G4 [IgG4]-S228P) that targets the PD-1 CD279 cell-surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes. Binding of PD-1 to its ligands, programmed death ligands 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T cell responses to both foreign antigens as well as self-antigens. Nivolumab is expressed in Chinese hamster ovary cells and is produced using standard mammalian cell cultivation and chromatographic purification technologies. The clinical study product is a sterile solution for parenteral administration.

Nivolumab (OPDIVO^{TM}) is approved for the treatment of several types of cancer in multiple regions including the US (Dec-2014), the European Union (EU, Jun-2015), and Japan (Jul-2014).

3.2.2.2 Nivolumab Clinical Activity

Nivolumab has demonstrated durable responses exceeding 6 months as monotherapy in several tumor types, including non-small cell lung cancer (NSCLC), melanoma, renal cell carcinoma (RCC), classical Hodkin lymphoma, small cell lung cancer, gastric cancer, squamous cell carcinoma of the head and neck (HNSCC), urothelial cancer, hepatocellular carcinoma (HCC), and colorectal cancer. In confirmatory trials, nivolumab as monotherapy demonstrated a statistically significant improvement in overall survival (OS) as compared with the current standard of care in patients with advanced or metastatic NSCLC, unresectable or metastatic melanoma, advanced RCC, or recurrent or metastatic HNSCC. Details of the clinical activity in these various malignancies are provided in the United States Prescribing Information (USPI)[10] and Summary of Product Characteristics (SmPC).[11]

3.2.3 Ipilimumab Mechanism of Action

Ipilimumab (BMS-734016, MDX010, MDX-CTLA4) is a fully human monoclonal immunoglobulin G1 kappa specific for human CTLA-4 (CD152), which is expressed on a subset of activated T cells. CTLA-4 is a negative regulator of T cell activity. Ipilimumab is a monoclonal antibody that binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T cell activation and proliferation, including the activation and proliferation of tumor-infiltrating T effector cells. Inhibition of CTLA-4 signaling can also reduce T-regulatory cell function, which may contribute to a general increase in T cell responsiveness, including the anti-tumor response.

3.2.4 Nivolumab Combined with Ipilimumab Clinical Activity

Multiple clinical studies have evaluated nivolumab combined with ipilimumab at different doses and schedules. Based on Phase 3 data showing improved survival over standard-of-care therapies, nivolumab combined with ipilimumab has been approved in multiple countries for the treatment of patients with cancer in various settings, including unresectable or metastatic melanoma, intermediate or poor risk previously untreated advanced RCC, first line metastatic NSCLC

expressing PD-L1 (≥ 1%) and [redacted] in these various malignancies are provided in the USPI and SmPC.[10,11]

3.2.5 Nivolumab Combined with Ipilimumab Clinical Pharmacology

Nivolumab PK was assessed using a population PK approach for both single-agent nivolumab and nivolumab with ipilimumab.

Nivolumab as a single agent: The PK of single-agent nivolumab was studied in patients over a dose range of 0.1 to 20 mg/kg administered as a single dose or as multiple doses of nivolumab as a 60-minute intravenous (IV) infusion every 2 or 3 weeks. Nivolumab clearance (CL) decreases over time, with a mean maximal reduction (% coefficient of variation [CV%]) from baseline values of 24.5% (47.6%) resulting in a geometric mean steady-state clearance (CLss) (CV%) of 8.2 mL/h (53.9%) in patients with metastatic tumors; the decrease in CLss is not considered clinically relevant. Nivolumab CL does not decrease over time in patients with completely resected melanoma, as the geometric mean population clearance is 24% lower in this patient population compared with patients with metastatic melanoma at steady state. The geometric mean Vss (CV%) is 6.8 L (27.3%), and geometric mean elimination half-life is 25 days (77.5%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg every 2 weeks, and systemic accumulation was 3.7-fold. The exposure to nivolumab increases dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks. The predicted exposure (average concentration [Cavg] and Cmax) of nivolumab after a 30-minute infusion is comparable to that observed with a 60-minute infusion.

Nivolumab with ipilimumab: When nivolumab 1 mg/kg was administered in combination with ipilimumab 3 mg/kg, the CL of nivolumab was increased by 29%, and the CL of ipilimumab was unchanged compared to nivolumab administered alone. When nivolumab 3 mg/kg once every 2 weeks (Q2W), was administered in combination with ipilimumab 1 mg/kg, the CL of nivolumab and ipilimumab were unchanged. When nivolumab was administered in combination with ipilimumab, the presence of anti-nivolumab antibodies increased the CL of nivolumab by 20% and the CL of ipilimumab was unchanged in presence of anti-ipilimumab antibodies.

Specific Populations: The population PK analysis suggested that the following factors had no clinically important effect on the CL of nivolumab: age (29 to 87 years), weight (35 to 160 kg), gender, race, baseline lactate dehydrogenase (LDH), PD-L1 expression, solid tumor type, tumor size, renal impairment, and mild hepatic impairment.

Renal Impairment: The effect of renal impairment on the CL of nivolumab was evaluated by a population PK analysis in patients with mild (estimated glomerular filtration rate [eGFR] 60 to 89 mL/min/1.73 m^2), moderate (eGFR 30 to 59 mL/min/1.73 m^2), or severe (eGFR 15 to 29 mL/min/1.73 m^2) renal impairment. No clinically important differences in the CL of nivolumab were found between patients with renal impairment and patients with normal renal function.

Hepatic Impairment: The effect of hepatic impairment on the CL of nivolumab was evaluated by population PK analyses in patients with HCC and in patients with other tumors with mild hepatic impairment (total bilirubin [T. bili] less than or equal to the upper limit of normal [ULN] and AST greater than ULN or T. bili greater than 1 to 1.5 times ULN and any AST) and in HCC patients with moderate hepatic impairment (T. bili greater than 1.5 to 3 times ULN and any AST). No clinically important differences in the clearance of nivolumab were found between patients with mild/moderate hepatic impairment.

Full details on the clinical pharmacology aspects of nivolumab can be found in the IB and product label.[3,10]

Nivolumab 480 mg Q4W dose levels are approved in the following indications: unresectable or metastatic melanoma; adjuvant treatment of melanoma; advanced RCC as monotherapy or in combination with cabozantinib; recurrent or metastatic HNSCC; urothelial cancer (adjuvant or treatment of locally advanced metastatic disease); microsatellite instability-high metastatic colorectal cancer; esophageal squamous cell carcinoma and adjuvant treatment of resected esophageal or gastroesophageal cancer, and it will be used in this study.

Nivolumab 360 mg (Q2W) / ipilimumab 1 mg/kg once every 6 weeks (Q6W) is approved in the following indications: malignant pleural mesothelioma and metastatic NSCLC (in combination with 2 cycles of PDCT), and it will be used in this study.

3.2.6 Nivolumab plus PDCT Clinical Activity

Clinical activity of nivolumab plus PDCT in chemotherapy-naïve NSCLC has been demonstrated in 2 clinical studies. In Study CA209012, a multi-arm Phase 1 safety study of nivolumab in chemotherapy naïve NSCLC, 56 participants received nivolumab in combination with cisplatin/gemcitabine, cisplatin/pemetrexed, or carboplatin/paclitaxel. The objective response rate (ORR) with the different combinations ranged from 33% to 47%.[12] Nivolumab in combination with histology-based PDCT was also studied in Part 2 of the Phase 3 trial CA209227.[15] In this trial, due to the hierarchical nature of the statistical design and because the primary end point of OS in the non-squamous population was not statistically significant, additional endpoints were purely descriptive. However, it is important to note that ORR, progression-free survival (PFS), and OS demonstrated trends towards improved efficacy with nivolumab in combination with chemotherapy versus chemotherapy alone after a minimum follow-up of 19.5 months for OS and 18.4 months for all other data. The OS hazard ratio (HR) in all randomized participants was 0.81 (95.62% confidence interval [CI]: 0.67,0.97). The median PFS and OS were numerically higher in participants who received nivolumab plus chemotherapy, with a median OS of 18.27 months versus 14.72 months in the chemotherapy group, and a median PFS of 8.38 months with the nivolumab plus chemotherapy group versus 5.52 months in the chemotherapy group. In addition, ORR was higher with nivolumab plus chemotherapy when compared with chemotherapy alone in the randomized population as well as in the non-squamous (48.1% vs 25.7%) and the squamous (59.8% vs 32.4%) participant sub-groups.

3.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably anticipated adverse event (AEs) of BMS-986408 may be found in the IB.[1]

BMS-986408 is a novel small-molecule dual inhibitor of DGKα and DGKζ that has demonstrated robust preclinical efficacy as monotherapy and in combination with anti-PD-1, anti-PD-1 plus anti-CTLA4, and anti-PD-1 plus chemotherapy. It is hypothesized [redacted]

It is unknown whether the study treatments increase the risk for contracting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or increase the severity or duration of symptoms. This unknown risk must be considered when enrolling a participant. No additional safety monitoring or routine screening tests will be required due to SARS-CoV-2.

The study has been designed with study visits that allow for close monitoring of participants' safety throughout the clinical trial (Section 2), and participants are encouraged to contact the Investigator if an intercurrent illness develops between study visits. Testing for COVID-19 to inform decisions about clinical care during the study should follow local standard practice.

3.3.1 Risk Assessment

Participants who enroll on this proposed study will have an unmet medical need due to advanced cancer without curative treatment options. While this study may not provide clinical benefit to the enrolled participants, taking into account the measures taken to minimize risk to participants in this study, BMS-986408 is a novel immunotherapy that has the potential to significantly improve outcomes in a similar population of patients once an optimal human dose and schedule is identified, supporting its evaluation in clinical studies.

[redacted] in Table 3.3.1-1.

Extensive details on the safety profile of nivolumab alone or in combination with ipilimumab, including results from other clinical studies, are available in the nivolumab and ipilimumab IBs.[2,3]

The combination of BMS-986408 and nivolumab may have overlapping toxicities, including immune-mediated adverse events (IMAEs). A pattern of IMAEs, [redacted] has been defined for both nivolumab and the combination of nivolumab and ipilimumab. Most high-grade events were manageable with the

use of corticosteroids or hormone replacement therapy (endocrinopathies) as indicated in these algorithms.

BMS-986408 in combination with nivolumab plus PDCT may have overlapping toxicities. Nivolumab in combination with chemotherapy has been assessed in a variety of studies and has demonstrated an acceptable safety profile that was consistent with the established safety profile of each component of the regimen.[13] The combination of BMS-986408 and PDCT may have overlapping toxicities [redacted]. Dose modification criteria for study treatments, [redacted] are provided.

Table 3.3.1-1: Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Interventions(s)		
[redacted]	BMS-986408 IB[1] Carboplatin USPI Cisplatin USPI Paclitaxel USPI Pemetrexed USPI	[redacted] • [redacted] • Dose modification criteria [redacted]
[redacted]	BMS-986408 IB[1] Carboplatin USPI Cisplatin USPI Paclitaxel USPI Pemetrexed USPI	• Routine scheduled clinical laboratory monitoring throughout treatment of [redacted] for early detection of abnormalities.
[redacted]	BMS-986408 IB[1]	• [redacted] [redacted]

Table 3.3.1-1: Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		• Inclusion of a comprehensive list of QTc modulators that should be avoided in the study [redacted]
[redacted]	BMS-986408 IB[1] Carboplatin USPI Cisplatin USPI Paclitaxel USPI Pemetrexed USPI	• Routine scheduled clinical laboratory monitoring throughout treatment of hematologic, hepatic, and metabolic parameters for early detection of abnormalities. • [redacted]
[redacted]		
IMAEs (eg, pneumonitis, colitis, hepatitis, myocarditis, nephritis, endocrinopathy, neurologic and skin AEs)	Nivolumab IB[3], ipilimumab IB[2], BMS-986408 IB[1]	• Recommended IMAE [redacted] or per institutional protocol/Investigator discretion.
Potential Developmental Toxicity	Nivolumab IB[3], ipilimumab IB[2], BMS-986408 IB[1] Carboplatin USPI Cisplatin USPI Paclitaxel USPI Pemetrexed USPI	• Exclusion criteria (Section 6.2), pregnancy testing, contraception per protocol (Section 6.1).
Study Procedures		
Tumor Biopsy (eg, pain, infection)	Not applicable	• Per institutional protocol/Investigator discretion.
Phlebotomy (eg, pain, ecchymosis, bleeding, syncope)	Not applicable	• Per institutional protocol/Investigator discretion.
Other (if applicable)		
Allergy to Contrast Agent (eg, hives, anaphylaxis)	Not applicable	• Prophylaxis and/or treatment per institutional protocol/Investigator discretion.

Abbreviations: AE, adverse event; [redacted] IB, Investigator's Brochure; IMAE, immune-mediated adverse event; [redacted]; QTc, corrected QT interval, USPI, United States Prescribing Information.

3.3.2 Benefit Assessment

CA099003 is the first Phase 1 clinical trial evaluating the safety of BMS-986408 in human participants with advanced solid tumors. Although benefits might be hypothesized based on mechanism of action and/or preclinical observations, actual clinical benefits of BMS-986408 to patients with advanced cancer have not been established. Clinical activity of nivolumab plus PDCT in chemotherapy-naïve NSCLC has been demonstrated (see Section 3.2.6) with participants that express PDL1 having the greatest benefit.

3.3.3 Overall Benefit/Risk Conclusion

Taking into account the measures implemented to minimize risk to participants in this study, the potential risk identified and associated with BMS-986408 are justified by the anticipated benefits that may be afforded to participants with advanced cancers. In addition, first-line therapy of BMS-986408 in combination with nivolumab and PDCT has the potential to improve efficacy compared to PDCT in combination with anti-PD-1 therapy.

The Sponsor will evaluate the risk/benefit profile of the study on an ongoing basis. This evaluation will be based on all available data – with particular attention to: (i) AEs or other safety trends in this or any other clinical study of BMS-986408 whose character, severity, and/or frequency suggest that participants would be exposed to an unreasonable and significant risk of illness or injury; (ii) new nonclinical data suggesting unreasonable and significant risk of illness or injury.

If such evaluation suggests that the risk/benefit profile of the study has become unfavorable to participants, the Sponsor will pause enrollment and/or treatment until further evaluation of data, and interaction with the appropriate Health Authority(ies) can take place on potential actions. Such actions may include (but are not limited to) study continuation, substantial amendment, or termination of the study.

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Primary • To characterize the safety and tolerability, and to establish the MTD, maximum administered dose, and/or RP2D(s), and optimal schedule of oral BMS-986408, administered as monotherapy and in combination with nivolumab ± ipilimumab or chemotherapy to participants with advanced cancer.	**Primary** • Incidence of DLTs, AEs, SAEs, AEs leading to discontinuation, and deaths.

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Secondary • To characterize the PK profile of BMS-986408 following oral administration as monotherapy and in combination with nivolumab ± ipilimumab or chemotherapy to participants with advanced solid tumors.	**Secondary** • Summary measures of BMS-986408 PK parameters in plasma, such as, but not limited to, Cmax, Tmax, and AUC(0-T), from concentration-time data during BMS-986408 monotherapy and in combination with nivolumab ± ipilimumab or chemotherapy.
• To evaluate the preliminary anti-tumor activity of BMS-986408 as monotherapy and in combination with nivolumab ± ipilimumab or chemotherapy in participants with advanced cancer.	• ORR and DOR per RECIST v1.1.
[redacted]	[redacted]

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
[redacted]	

Abbreviations: AE, adverse event; AUC(0-T), area under the concentration-time curve from time 0 to time of last quantifiable concentration; Cmax, maximum concentration; DLT, dose-limiting toxicity; DOR, duration of response; ORR, objective response rate; PDCT, platinum-doublet chemotherapy; PK, pharmacokinetics; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended Phase 2 dose; SAE, serious adverse event; Tmax, time of maximum observed concentration.

5 STUDY DESIGN

5.1 Overall Design

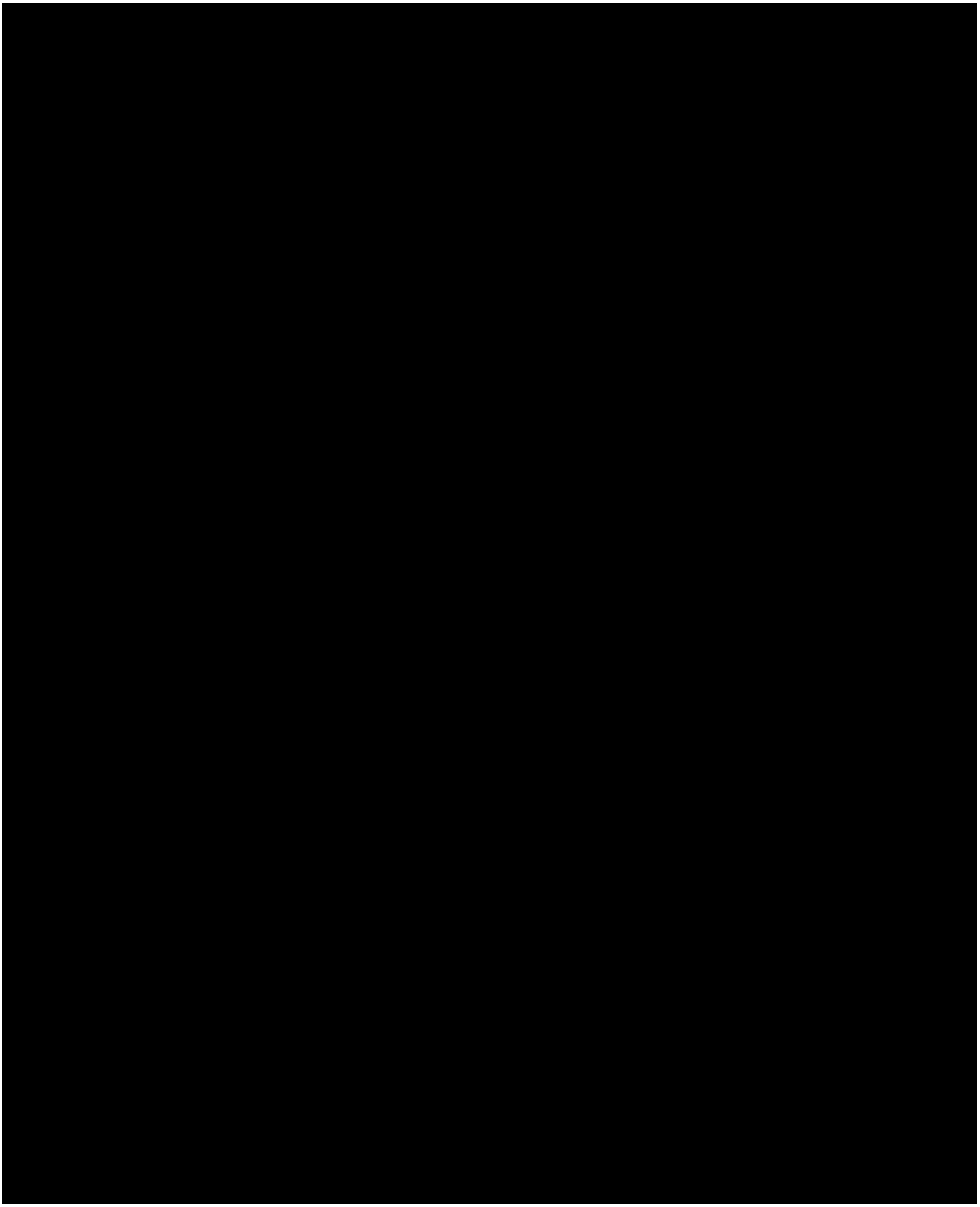
CA099003 is a Phase 1/2, FIH, multi-center, open-label study of oral BMS-986408 administered as a single agent, and in combination with nivolumab, nivolumab and ipilimumab, or nivolumab and chemotherapy in participants with advanced solid tumors. The primary objectives of the proposed study are to characterize the safety and tolerability; to establish the maximum tolerated dose (MTD), if reached; to evaluate the maximum administered dose if the MTD is not reached; and to establish the recommended Phase 2 dose/s (RP2D[s]), at the optimal dosing schedule. Secondary objectives of the study are to characterize the PK profile and evaluate preliminary anti-tumor activity of BMS-986408 as both monotherapy and in combination with nivolumab, nivolumab and ipilimumab, or nivolumab and PDCT.

The study is composed of 3 parts, with monotherapy dose escalation evaluated in Part 1 and combination therapy of escalating doses of BMS-986408 with nivolumab, nivolumab and ipilimumab, or nivolumab and PDCT evaluated in Part 2. Part 3 will include expansion cohorts to evaluate the combination of BMS-986408 with nivolumab or nivolumab and PDCT. Part 3 combination with nivolumab and ipilimumab may be added in a future amendment.

All participants will complete 3 study periods: Screening [redacted], Treatment [redacted] and Follow-up [redacted] The duration of study participation for individual participants will be approximately 4 years.

5.1.1 Part 1 Monotherapy Cohorts

Part 1 will evaluate BMS-986408 monotherapy [redacted]



[redacted]

5.1.2 Part 2 Combination Therapy Cohorts

Part 2 will evaluate BMS-986408 in combination with nivolumab in Group D, nivolumab and ipilimumab in Group E, or nivolumab and PDCT in Group F. In Group G, single-dose BMS-986408 with and without a proton pump inhibitor (PPI) will be evaluated followed by continuous dosing of BMS-986408 and nivolumab. [redacted]

[redacted]

[redacted]

5.1.2.1 BMS-986408 in Combination with Nivolumab with or without Ipilimumab (Groups D and E)

The dual combination of BMS-986408 and nivolumab (480 mg once every 4 weeks [Q4W]) will be evaluated in participants with HNSCC, NSCLC, melanoma, and RCC, who have previously experienced disease progression during checkpoint inhibitor therapy. Triple combination therapy of BMS-986408 with nivolumab (480 mg Q4W) and ipilimumab (1 mg/kg once every 8 weeks [Q8W]) will be evaluated in participants with HNSCC, NSCLC, melanoma, and RCC who have previously experienced disease progression during checkpoint inhibitor therapy (prior PD-[L]1

treatment or CTLA-4 treatment as monotherapy or in any combination). [redacted]

[redacted]

5.1.2.2 BMS-986408 in Combination with Nivolumab and PDCT (Group F)

The combination of BMS-986408 with nivolumab (360 mg Q3W) and PDCT will be evaluated in participants with advanced/metastatic NSCLC who have not had systemic therapy for advanced/metastatic disease. Participants with non-squamous NSCLC will be treated with carboplatin or cisplatin and pemetrexed, while participants with squamous histology will be treated with carboplatin and paclitaxel (see Section 7.1 for additional information on dosing). [redacted]

5.1.2.3 pH Effect PK Sub-study [redacted] (Group G)

Group G will be an open-label, single dose PK cohort to explore the potential pH effect on the single dose PK [redacted] of BMS-986408 followed by continuous dosing with BMS-986408 in combination with nivolumab. [redacted] Prolonged increases in gastric pH occur with administration of rabeprazole (model PPI), which irreversibly bind to and inactivate the proton pump (H+ -K+-ATPase), resulting in suppression of stimulated and basal acid secretion produced by acetylcholine and histamine release.[14] In general, the PD effects of PPIs take up to 3 days with [redacted] dosing to reach steady state. [redacted]

[redacted]

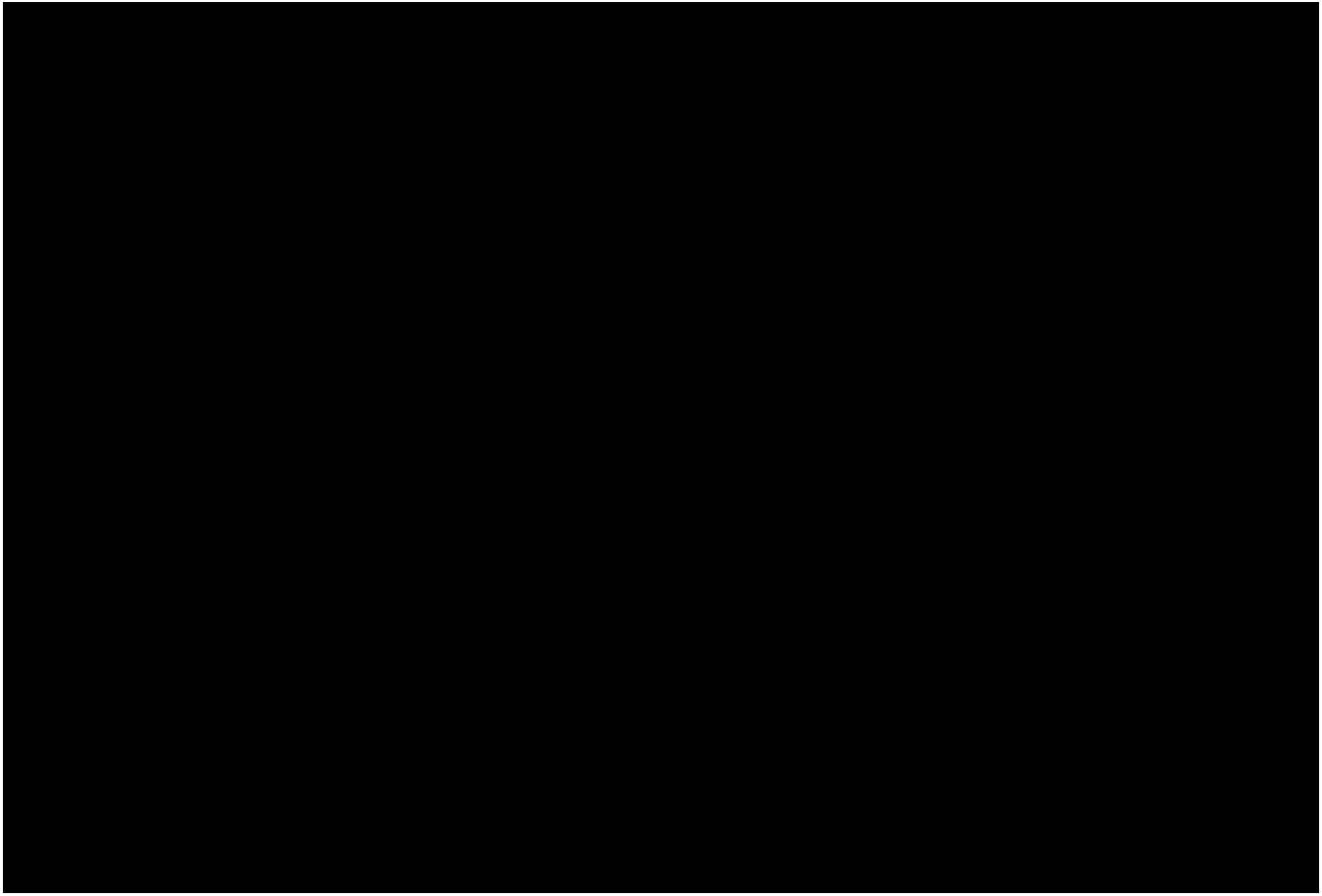
[redacted]

5.1.3 Part 3 Expansion Cohorts

Part 3 is an open-label, dose expansion part to assess the preliminary efficacy, safety, and tolerability of the optimal dose level(s) of BMS-986408 in combination with nivolumab (Group D2) or nivolumab and PDCT (Group F2). [redacted]

[redacted]

[redacted]



[redacted]

5.1.4 Screening

The screening period will be [redacted] and begins by establishing the participant's initial eligibility after signing of the informed consent form. Participants will be enrolled using interactive response technology (IRT). The screening assessments are shown in Table 2-1.

For Part 1, Group C and Part 2, tumor tissue must be obtained and submitted to central laboratory prior to treatment assignment except if biopsy was attempted but was not completed due to safety concerns. See Section 6.1 (Inclusion Criteria) and Section 9.8 (Biomarkers) for specifications and the laboratory manual for additional details.

If a participant exceeds [redacted] screening period due to a study-related procedure (eg, scheduling of a tumor biopsy or waiting for a study-related laboratory value) or a SARS-CoV-2 infection, the participant must be reconsented, but does not require a new participant identification number (see Section 6.4.1). In this situation, the Medical Monitor should be notified, and the fewest number of procedures from the initial screening should be repeated to qualify the participant, while maintaining participant safety and eligibility.

5.1.5 Treatment Period

The treatment period for monotherapy and combination treatment will last approximately 104 weeks from the first dose of study treatment. [redacted]

On-treatment monitoring will include planned clinic visits with standard safety monitoring and blood draws for laboratory testing, PK, and biomarkers as indicated in Table 2-2 (Part 1) and Table 2-3 (Parts 2 and 3). Imaging for tumor assessment will occur every 8 weeks during the first 48 weeks of treatment, followed by every 12 weeks until 104 weeks and the end of study treatment phase (all groups). For cardiovascular monitoring, safety ECGs are planned for all groups and multiple additional ECGs are planned for the monotherapy portion of the study to evaluate for [redacted]. Participants will be supplied with an [redacted] All participants will be supplied with a mechanism to capture daily pill intake of BMS-986408.

5.1.6 Follow-up Period

The follow-up period includes a safety follow-up and a survival follow-up, which begin in parallel after the end of treatment (EOT) visit. EOT is defined as the visit where the decision is made to discontinue the participant from treatment. Evaluations will be performed prior to study discharge, or for participants who are prematurely discontinued. 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 (eg, C26D1) and the start of the safety follow-up period. 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); it does not need to be repeated and will be considered as the start of the safety follow-up period.

The safety follow-up period is [redacted] for participants in Part 1, with a visit at [redacted] after the EOT visit. For Part 2 combinations, Groups D and E, the safety follow-up period will be [redacted] days after the end-of-treatment visit, with visits to occur at [redacted] after the end of treatment visit. Survival follow-up for all parts will begin at the EOT visit and last for a period of [redacted], or until death, lost to follow-up, withdrawal of consent, conclusion of the study, or study termination, whichever comes first.

5.1.7 Data Monitoring Committee and Other Committees

A data monitoring committee (DMC) will not be used in the study.

Although there is not a formal DMC for this study, BMS has developed a multi-layered process to ensure safety monitoring through close collaboration of study site Investigators, the BMS study team and the BMS Worldwide Patient Safety (WWPS)-led Safety Management Team (SMT) and this will be employed in this study. Dose escalation decisions and decisions to continue enrollment according to the outlined study protocol will be made by the Sponsor in collaboration with Investigators, and take into consideration all available safety, PK, and PD data.

To support safety oversight, BMS has established ongoing processes for collection, review, analysis, and submission of individual AE reports and their aggregate analyses. Signal detection will be performed at least monthly and ad hoc throughout the study. Because this is an open-label study, WWPS, the BMS Medical Monitor, and the investigators will have access to all data necessary for safety evaluation.

BMS WWPS is an internal group that operates independently from the clinical team to monitor safety across all BMS protocols and analyze all data in an unblinded fashion. Within BMS, an SMT is established for investigational therapies under clinical development, and a member of WWPS chairs this team. In addition, signal detection is performed at least quarterly and ad hoc throughout the study by the SMT composed, at a minimum, of the WWPS medical safety assessment physician (Chair of the SMT), the Study Physician, Global Regulatory Lead, and Pharmacovigilance Scientist; all of whom, analyze the data in an unblinded fashion. Extended SMT members may include medical review safety physician(s), epidemiologist(s), clinical safety strategy and solutions, Global Risk Management, toxicologist, clinical pharmacologist, biostatistician, clinical scientist(s), labeling, Medical Affairs, legal representative, and project lead and/or project manager. Furthermore, the SMT routinely monitors for actual or potential issues related to participant safety that could result in a change in the medical benefit-risk balance associated with the use of study treatment(s).

5.2 Number of Participants

The approximate total number of participants treated will be 402 for Parts 1, 2, and 3:

- Part 1 Monotherapy: The total sample size is approximately [redacted] participants: approximately [redacted] participants for Group A dose escalation, [redacted] participants each for Groups B and B2 (if evaluated), and [redacted] participants for Group C.
- Part 2 Combination Therapy: The total sample size is approximately [redacted] participants: [redacted] participants each for Groups D and E, [redacted] participants for Group F, and [redacted] participants for Group G.
- Part 3 Combination Therapy Expansion cohorts: The total sample size is approximately [redacted] participants: [redacted] participants per indication for Groups D2 and F2.

5.3 End of Study Definition

The start of the trial is defined as the first participant first visit.

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 were or are expected to be collected, if this is not the same.

A participant is considered to have completed the study if he/she has completed the last visit shown in the Schedule of Activities.

5.4 Scientific Rationale for Study Design

BMS-986408 is a novel small-molecule dual inhibitor of DGKα and DGKζ, intracellular check-points broadly expressed in T cells. [redacted]. Due to the broad expression of DGKα and DGKζ among T cell lineages, [redacted]. The FIH study is designed to thoroughly evaluate the safety, PK, and peripheral blood and tumor PD of BMS-986408 alone and in combination with other check-point inhibitors in a broad population of patients with solid tumors.

In Part 1, the monotherapy evaluation of BMS-986408 will guide dosing and schedule selection for combination testing, with the objective of identifying a dose and schedule [redacted],[6] while remaining safe and well tolerated. [redacted]

[redacted]

Parts 2 and 3 are focused on evaluating the safety and preliminary efficacy of BMS-986408 in combination with either nivolumab (Groups D and D2), nivolumab and ipilimumab (Group E), or nivolumab and PDCT (Groups F and F2). Given the growing knowledge around check-point inhibitor therapy and the landscape of single-agent versus combination efficacy,[15,16,17,18] evaluation of combination regimens in this FIH study will provide important safety and PD insights on targeted, rational combination approaches that can be employed within a variety of tumor indications. The study design includes the following:

- Screening period [redacted]
- Treatment period of approximately [redacted]
- Safety follow-up period of [redacted] from EOT for participants receiving monotherapy and [redacted] from EOT for participants receiving combination therapy
- Survival follow-up period of up to [redacted] from EOT.

The rationales for individual elements of the study design are given below.

[redacted]

5.4.2 Rationale for 2-Year Duration of Treatment

The optimal duration of immunotherapy is an important question and continues to be investigated. Clinical trials across different tumor types in the nivolumab and ipilimumab development program indicate that most of the responses occur early, with a median time to response of 2-4 months, and emerging data suggest that benefit can be maintained in the absence of continued treatment. A retrospective pooled analysis of 2 melanoma studies suggests the majority of patients who

discontinue nivolumab and/or ipilimumab for toxicity maintain disease control in the absence of further treatment.[21] Furthermore, a limited duration of ipilimumab, including only 4 induction doses, resulted in long term survival in patients with metastatic melanoma, with a sustained plateau in survival starting around 2 years after the start of treatment.[22]

Accumulating data suggest that 2 years of PD-1 checkpoint inhibitor treatment may be sufficient for long term benefit. CA209003, a dose-escalation cohort expansion trial evaluating the safety and clinical activity of nivolumab in patients with previously treated advanced solid tumors (including 129 patients with NSCLC), specified a maximum treatment duration of 2 years. Among 16 patients with NSCLC who discontinued nivolumab after completing 2 years of treatment, 12 patients were alive > 5 years and remained progression-free without any subsequent therapy. In the CA209003 NSCLC cohort, the overall survival (OS) curve begins to plateau after 2 years, with an OS rate of 25% at 2 years and 18% at 3 years.[23] These survival outcomes are similar to Phase 3 studies in previously treated NSCLC, in which nivolumab treatment was continued until progression or unacceptable toxicity (2-year OS rates of 23% and 29%, and 3-year OS rates of 16%-18% for squamous and non-squamous NSCLC respectively).[24]

Taken together, these data suggest that treatment beyond 2 years is unlikely to confer additional clinically meaningful benefit and that the risk of progression after discontinuing treatment at 2 years is low.

In contrast, a shorter duration of nivolumab of only 1 year was associated with increased risk of progression in previously treated patients with NSCLC, suggesting that treatment beyond 1 year is likely needed. In CA209153, patients with previously treated advanced NSCLC who completed 1 year of nivolumab therapy were randomized to either continue or stop treatment, with the option of retreatment upon progression. Among 163 patients still on treatment at 1 year and without progression, those who were randomized to continue nivolumab had significant improvement in PFS compared to those who were randomized to stop treatment, with median PFS (post-randomization) not reached vs 10.3 months, respectively; hazard ratio (HR)=0.42 (95% CI, 0.25 to 0.71). With a median follow-up of 14.9 months post-randomization, there also was a trend for patients on continued treatment to live longer (OS HR = 0.63 [95% confidence interval (CI): 0.33, 1.20]). Of note, the PFS curves in both groups plateau approximately 1 year after randomization (ie, 2 years after treatment initiation), suggesting that there may be minimal benefit in extending treatment beyond a total of 2 years.[25]

Collectively, these data suggest that there is minimal if any benefit derived from continuing immuno-oncology (IO) treatment beyond 2 years in advanced tumors. Even though immunotherapy is well tolerated, patients will be at risk for additional toxicity with longer term treatment. Therefore, in this study, treatment will be given for a maximum of 2 years from the start of study treatment.

5.4.3 Rationale for BMS-986408 in Combination with Nivolumab and PDCT

The Food and Drug Administration approvals of pembrolizumab in combination with PDCT and nivolumab in combination with ipilimumab and PDCT in first-line NSCLC increase the

armamentarium of immunotherapy combinations and have improved the prognosis in this population. However, less than 50% of patients are expected to benefit from anti-PD-1/PD-L1 combination therapy, highlighting the need for further investigation into other strategies, such as simultaneous inhibition of multiple immune checkpoints in combination with chemotherapy.

[redacted] The safety profile of nivolumab in combination with chemotherapy has been manageable. [redacted]

5.5 Justification for Dose

[redacted]

[redacted]

5.5.2 Nivolumab

The nivolumab dose of 480 mg Q4W was selected for Part 2, Groups D, E, and G and Part 3, Group D2 based on clinical data and modeling and simulation approaches using population PK (PPK) and exposure-response (E-R) analyses of data from studies in multiple tumor types (melanoma, NSCLC, and RCC) where body weight normalized dosing (mg/kg) was used. The nivolumab dose of 360 mg Q3W was selected for Part 2, Group F and Part 3, Group F2.

Nivolumab PK has been extensively studied in multiple tumor types, including melanoma, NSCLC, RCC, classical Hodgkin's lymphoma, HNSCC, colorectal cancer, and urothelial carcinoma and has been safely administered at doses up to 10 mg/kg Q2W. Nivolumab monotherapy was originally approved as a body-weight based dose of 3 mg/kg Q2W, and was updated to 240 mg Q2W or 480 mg Q4W in multiple indications.[10,11] Nivolumab 360 mg Q3W is also under evaluation in monotherapy and in combination therapy studies. When used in combination with ipilimumab and chemotherapy, nivolumab 360 mg Q3W is approved for the treatment of first line (1L) NSCLC. Less frequent 360 mg Q3W and 480 mg Q4W dosing regimens can reduce the burden to patients of frequent, lengthy IV treatments and allow combination of nivolumab with other agents using alternative dosing regimens.

The benefit-risk profiles of nivolumab 240 mg Q2W, 360 mg Q3W, and 480 mg Q4W are predicted to be comparable to 3 mg/kg Q2W. This assessment is based on a comprehensive characterization of nivolumab PK, safety, efficacy, and E-R relationships across indications. Population PK (PPK) analyses have shown that the PK of nivolumab is linear with proportional exposures over a dose range of 0.1 to 10 mg/kg; no clinically meaningful differences in PK across ethnicities and tumor types were observed. Using the PPK model, the exposures following administration of several dosing regimens of nivolumab administered as a flat dose were simulated, including 240 mg Q2W, 360 mg Q3W, and 480 mg Q4W. The simulated average serum concentration at steady state [Cavgss] following administration of nivolumab 360 mg Q3W and 480 mg Q4W are predicted to be similar to those following administration of nivolumab 240 mg Q2W and nivolumab 3 mg/kg Q2W administered to patients over a wide body weight range (34 to 180 kg) across tumor types.

Extensive E-R analyses of multiple PK measures (maximum serum concentration at Day 1 [Cmax1], average serum concentration at Day 28 [Cavg28], and trough serum concentration at Day 28 [Cmin28]) and efficacy and safety endpoints indicated that the efficacy of the flat-dose 480 mg IV regimen is similar to that of the 3 mg/kg Q2W IV regimen. In E-R efficacy analyses for OS and objective response rate (ORR) conducted in melanoma, RCC, and NSCLC using Cavg28 as the exposure measure, probabilities of achieving a response and survival probabilities at 1 year and 2 years for IV 480 mg Q4W were similar to that of IV 3 mg/kg Q2W. In E-R safety analyses, it was demonstrated that the exposure margins for safety are maintained following nivolumab 480 mg Q4W, and the predicted risks of discontinuations due to AEs or death, AE Grade 3+, and immune-mediated AEs (IMAEs) Grade 2+ are similar following nivolumab 480 mg Q4W relative to nivolumab 3 mg/kg Q2W across tumor types. In addition, nivolumab exposures with 240 mg Q2W, 360 mg Q3W, and 480 mg Q4W flat-dose IV regimens across tumor types are maintained well below the corresponding exposures observed with the well-tolerated 10 mg/kg IV nivolumab Q2W dose regimen.

5.5.3 Ipilimumab

Ipilimumab at a dose of 1 mg/kg Q8W infused over 30 minutes will be administered in combination with BMS-986408 and nivolumab 480 mg Q4W in Part E.

Ipilimumab is approved as monotherapy for the treatment of advanced melanoma and adjuvant melanoma with 3 mg/kg Q3W for 4 doses and 10 mg/kg Q3W for 4 doses followed by maintenance dose, respectively. Ipilimumab is also approved in combination with nivolumab for the treatment of various cancers, including melanoma, RCC, colorectal cancer, and HCC with a dosing regimen of 1 mg/kg Q3W or 3 mg/kg Q3W for 4 doses, depending on tumor type. In addition, a less frequent but continuous ipilimumab regimen (1 mg/kg once every 6 weeks [Q6W]) was evaluated in combination with nivolumab or nivolumab plus chemotherapy in a number of pivotal studies, including 1L NSCLC studies (Studies CA209227 and CA2099LA), 1L HNSCC study (Study CA209651), and 1L mesothelioma study (Study CA209743). Ipilimumab 1 mg/kg Q6W is currently approved for the treatment of 1L NSCLC in combination with nivolumab or with nivolumab and 2 cycles of chemotherapy and is also approved for the treatment of 1L mesothelioma in combination with nivolumab.[26]

In CA209012, ipilimumab 1 mg/kg using Q6W and once every 12 weeks (Q12W) schedules were assessed and were found to have acceptable safety in combination with nivolumab 3 mg/kg once every 2 weeks (Q2W). Both the Q6W and Q12W arms were associated with improved and manageable tolerability compared to the arms with more frequent ipilimumab dosing (once every 3 weeks; [Q3W]). Both arms also had encouraging efficacy in all participants and enhanced benefit in participants with PD-L1 expression, with Q6W arm having numerically higher median progression-free survival (PFS) compared to the Q12W arm. There were some imbalances observed between the Q6W and Q12W arms, as follows:

- There were more never-smokers in Arm Q (Q6W schedule) than Arm P (Q12W schedule). Current and former smokers have been shown to respond better to immunotherapy.
- Participants in Arm Q progressed, died, or came off treatment more frequently in the first 3 months; however, this did not appear to be related to the schedule.
  - Overall rates of treatment-related AEs leading to discontinuation were 11% and 13% in the Q12W and Q6W arm, respectively. While there were more AEs leading to discontinuation in the first 3 months in Arm Q (n=3) versus Arm P (n=1), 2 of the [redacted] who discontinued < 3 months on arm Q discontinued before receiving the second dose of ipilimumab; therefore, these discontinuations are unlikely to be due to the more frequent dosing on the Q6W arm.
  - There were early clinical progressors and (unrelated) deaths in the Q6W arm compared to the Q12W arm (8% and 15%, respectively), more likely due to imbalances in baseline characteristics, rather than differences in treatment schedule.

With both schedules showing a similar safety and efficacy profile and considering imbalances in treatment arms favoring the Q12W arm, for this study a Q8W schedule was chosen for the ipilimumab administration, to align with nivolumab dosing and maintain expected safety and efficacy.

6 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1) Signed Written Informed Consent

a) Participants (see Appendix 13 for country- and region-specific requirements) must have signed and dated an Institutional Review Board/Independent Ethics Committee (IRB/IEC) institutional guideline. This signature must be obtained before the performance of any protocol-related procedures that are not part of normal patient care.

b) Participants must be willing and able to comply with scheduled visits, treatment schedule, laboratory testing, and other requirements of the study.

2) Type of Participant and Target Disease Characteristics

a) Participants in Part 1, Groups A, B, and B2 must have a histologically or cytologically confirmed, advanced, unresectable/metastatic, solid malignancy of any histology measurable by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, and have received, be refractory to, ineligible for, or intolerant of existing therapy(ies) known to provide clinical benefit for the condition of the participant.

b) Participants in Part 1, Group C and Part 2, Groups D and E must have a histologically or cytologically confirmed, advanced, unresectable/metastatic malignancy measurable by RECIST v1.1, with the following histologies: HNSCC, NSCLC, melanoma, or RCC, and have received, be refractory to, ineligible for, or intolerant of existing therapy(ies) known to provide clinical benefit for the condition of the participant.

i) [redacted]

v) Participants with melanoma should have documentation of mutation status for BRAF and NRAS, if known.

c) Not applicable per Protocol Amendment 04.

d) Participants in Part 1, Group C and Part 2, Groups D, E, F, and G must have tumor lesions that can be biopsied at acceptable risk and must consent to undergo pre-treatment and on-treatment biopsy collection. Only core, excisional, incisional, or surgical biopsies are acceptable. A formalin-fixed, paraffin-embedded (FFPE) tissue block of tumor tissue from a core biopsy, punch biopsy, excisional or incisional biopsy, or surgical specimen obtained during screening or within 3 months before start of screening period, with no intervening systemic anti-cancer treatment between time of acquisition and enrollment, must be sent to the central laboratory. Fine needle aspirates or other cytology samples are not acceptable.

e) Participants in Part 1, Group C and Part 2, Groups D and E must have received previous treatment with PD-1, PD-L1, and/or CTLA-4 checkpoint inhibitor (CPI) [redacted]

f) Participants must have experienced radiographically documented progressive disease on or after the most recent therapy.

g) Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.

h) Participants in Part 2, Group G and Part 3, Group D2:
   i) Measurable disease by RECIST v1.1.

[redacted]

i) Part 2, Group F and Part 3, Group F2:
   i) Documented histologically or cytologically confirmed metastatic Stage IV A/B NSCLC of non-squamous or squamous histology (as defined by the 8th International Association for the Study of Lung Cancer Classification).
   ii) Must be eligible to receive PDCT based on local guidelines.
   iii) [redacted]
   iv) [redacted]
   v) [redacted]
   vi) [redacted]
   vii) [redacted]
   viii) Part 3, Group F2 only: A formalin-fixed, paraffin-embedded (FFPE) tumor tissue block or unstained slides of tumor tissues obtained during screening or prior to enrollment (within 3 months of enrollment and with no intervening systemic anti-cancer therapies between the time of acquisition and enrollment) must be sent for confirmation of PD-L1 status to the central laboratory prior to treatment assignment. Results are not required prior to starting treatment. Samples may be from core biopsy,

punch biopsy, excisional biopsy, or surgical specimen. On-treatment biopsies are optional.

3) Age of Participant

a) Participant must be age ≥ 18 years or local age of majority at the time of consent.

4) Reproductive Status

- Investigators shall counsel women of childbearing potential (WOCBP), and male participants who are sexually active with WOCBP, on the importance of pregnancy prevention, the implications of an unexpected pregnancy, and the potential of fetal toxicity occurring due to transmission of study intervention, present in seminal fluid, to a developing fetus, even if the participant has undergone a successful vasectomy or if the partner is pregnant.
- The Investigator shall evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.
- Local laws and regulations may require the use of alternative and/or additional contraception methods.

a) Female Participants:

i) Female participants must have documented proof that they are not of childbearing potential.

ii) Women who are not of childbearing potential are exempt from contraceptive requirements.

iii) WOCBP must have a negative highly sensitive urine or serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [hCG]) within 24 hours prior to the start of study intervention. An extension up to 72 hours prior to the start of study treatment is permissible in situations where results cannot be obtained within the standard 24-hour window.

- Additional requirements for pregnancy testing during and after study intervention are located in Section 2, Schedule of Activities.
- The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

iv) WOCBP must agree to follow instructions for method(s) of contraception defined in Appendix 4 and as described below and included in the informed consent form (ICF).

- WOCBP are permitted to use hormonal contraception methods (as described in Appendix 4) but WOCBP using hormonal contraceptives must also be utilizing a second contraception method that is highly effective (with a failure rate of < 1% per year) as described in Appendix 4, due to the potential for lack of efficacy of hormonal contraception methods from potential drug-drug interactions with BMS-986408. Oral contraceptives alone do not fulfill the contraception requirement for this study. WOCBP that are not utilizing hormonal contraceptives must be utilizing 1 highly effective contraceptive method, as described in Appendix 4.

v) A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

(1) Is not a WOCBP

OR

(2) Is a WOCBP and using a contraceptive method that is not a hormonal contraceptive method and is highly effective (with a failure rate of < 1% per year) as described in Appendix 4. Duration of required contraception use is described in Appendix 4, during the intervention period and for the following time periods and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction for the same time periods:

(a) [redacted]

(b) For the duration of chemotherapy plus 7 months after last dose of chemotherapy (applicable to paclitaxel, pemetrexed, and carboplatin) or a total of 14 months after the last dose of cisplatin and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction for the same time period as contraception requirements listed above.

b) Male Participants:

i) Male participants, including azoospermic males, will be required to always use a latex or other synthetic condom during any sexual activity (eg, vaginal, anal, oral) with WOCBP, even if the participants have undergone a successful vasectomy or if their partner is already pregnant or breastfeeding. Males should continue to use a condom during the intervention period, [redacted] and at least [redacted] after the last chemotherapy (applicable to paclitaxel, pemetrexed, and carboplatin) dose of study intervention (or a total of 11 months for male participants receiving cisplatin).

ii) Female partners of males participating in the study should be advised to use a highly effective method of contraception during the intervention period, [redacted], and at least [redacted] after the last chemotherapy (applicable to paclitaxel, pemetrexed, and carboplatin) dose of study intervention (or a total of 11 months for male participants receiving cisplatin).

iii) Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from sexual activity or use a male condom during any sexual activity (eg, vaginal, anal, oral), even if the participants have undergone a successful vasectomy, during the intervention period, [redacted] and for at least [redacted] after the last chemotherapy (applicable to paclitaxel, pemetrexed, and carboplatin) dose of study intervention (or a total of 11 months for male participants receiving cisplatin).

iv) Male participants must refrain from donating sperm during the intervention period, [redacted] and for at least [redacted] after the last chemotherapy (applicable to paclitaxel, pemetrexed, and carboplatin) dose of study intervention (or a total of 11 months for male participants receiving cisplatin).

v) Breastfeeding partners should be advised to consult their health care providers about using appropriate highly effective contraception during the time the participant is required to use condoms.

6.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1) Medical Conditions

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

b) Conditions requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) within 14 days or other immunosuppressive medications within 30 days of the first dose of study treatment. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

c) [redacted]

f) Current or recent (within 3 months of study drug administration) gastrointestinal disease or gastrointestinal surgery (eg, intestinal/gastric/colon resection) that could impact the absorption of study drug.

g) 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 treatment.

h) [redacted]

[redacted]

k) Untreated central nervous system (CNS) metastases. [redacted]

[redacted]

2) Reproductive Status

a) Women who are breastfeeding or are pregnant.

3) Prior/Concomitant Therapy

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

[redacted]

[redacted]

4) Physical and Laboratory Test Findings

[redacted]

5) Allergies and Adverse Drug Reaction

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

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

c) Any contraindication to any of the study drugs. Investigators should refer to local package insert or summary of product characteristics (SmPC).

6) Other Exclusion Criteria

a) Prisoners or participants who are involuntarily incarcerated. (Note: Under certain specific circumstances and only in countries where local regulations permit, 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) Inability to comply with restrictions as listed in Section 6.3, Lifestyle Restrictions.

c) Participation in another clinical trial concurrent with this 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

[redacted]

[redacted]

.

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but who are not subsequently entered in the study/included in the analysis population.

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, as applicable, 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 [redacted] Period

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

The most current result prior to administration of study intervention is the value by which study inclusion will be assessed, because it represents the participant's most current clinical state.

Laboratory parameters and/or assessments that are included in Table 2-1, Screening Procedural Outline, 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.

Testing for asymptomatic SARS-CoV-2 infection by reverse transcription polymerase chain reaction (RT-PCR) or viral antigen is not required. However, participants may develop suspected or confirmed symptomatic SARS-CoV-2 infection or be discovered to have asymptomatic SARS-CoV-2 infection during the screening period. In such cases, participants may be considered eligible for the study after meeting all inclusion/exclusion criteria related to active infection, and after meeting the following criteria:

- At least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared or positive RT-PCR or viral antigen test result.
- At least 24 hours have passed since last fever without the use of fever-reducing medications.
- Acute symptoms (eg, cough, shortness of breath) have resolved.
- In the opinion of the Investigator, there are no COVID-19 sequelae that may place the participant at a higher risk of receiving investigational treatment.

In the instance of a SARS-CoV-2 infection during screening, the screening period may be extended beyond the protocol-specified timeframe with Medical Monitor approval. Any screening tests already performed which could potentially be affected by the SARS-CoV-2 infection or its complications on an individual basis and agreed upon with the Medical Monitor (eg safety laboratory assessments, oxygen saturation, chest computed tomography [CT] scan) should be repeated.

7 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, procedure(s) or medical device intended to be administered to a study participant according to the study protocol.

Study intervention includes Investigational [Medicinal] Product (IP/IMP) as indicated in Table 7-1.

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 from the

authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as non-IPs/auxiliary medicinal products (AxMPs).

Table 7-1: Study Intervention(s) for CA099003

Product Description/Class and Dosage Form	Potency	IMP/ Non-IMP	Blinded or Open Label	Packaging/ Appearance	Storage Conditions (per label)
BMS-986408 Formulation 1, Formulation 2, and Formulation 3 Tablets	Formulation 1: 0.75 mg and 5 mg Formulation 2: 5 mg and 15 mg Formulation 3: 5 mg	IMP	Open Label	Bottle	Refer to the label on container and/or pharmacy manual
Nivolumab (BMS-936558-01) Solution for Injection	100 mg/vial (10 mg/mL)	IMP	Open Label	Vial	Refer to the label on container and/or pharmacy manual
Ipilimumab Solution for Injection (BMS-734016)	50 mg/vial (5 mg/mL)	IMP	Open Label	Vial	Refer to the label on container and/or pharmacy manual
Carboplatin	450 mg/vial	IMP	Open Label	Vial	Refer to the label on container and/or pharmacy manual
Paclitaxel	100 mg/vial	IMP	Open Label	Vial	Refer to the label on container and/or pharmacy manual
Pemetrexed	500 mg/vial	IMP	Open Label	Vial	Refer to the label on container and/or pharmacy manual
Cisplatin	100 mg/vial	IMP	Open Label	Vial	Refer to the label on container and/or pharmacy manual
Rabeprazole	20 mg	IMP	Open Label	Bottle	Refer to the label on container and/or pharmacy manual

Abbreviations: IMP, investigational medicinal product; Non-IMP, non- investigational medicinal product.

7.1 Study Interventions Administered

Dose and route of administration for study intervention in each arm are presented in Table 7.1-1.

Table 7.1-1: Study Intervention(s) Administered

ARM Name	Part 1, Groups A, B, B2, and C	Part 2, Group D Part 2, Group G (Starting C1D1) Part 3, Group D2	Part 2, Group E	Part 2, Group G (Cycle 0)	Part 2, Group F Part 3, Group F2
Intervention Name	BMS-986408 monotherapy	BMS-986408 + nivolumab	BMS-986408 + nivolumab + ipilimumab	BMS-986408 Rabeprazole	BMS-986408 + nivolumab + PDCT
Type	Drug	Drug + Biologic	Drug + Biologics	Drugs	Drugs + Biologics
Dose Formulation	BMS-986408 Formulations 1 and 2: tablet	Nivolumab: Solution in a single-use vial Part 2, Group D: BMS-986408 Formulations 1 and 2: tablet Part 2, Group G and Part 3, Group D2: BMS-986408 Formulations 1, 2, and 3: tablet	Nivolumab and ipilimumab: Solutions in single-use vials BMS-986408 Formulations 1 and 2: tablet	BMS-986408 Formulation 1, 2, and 3: tablet Rabeprazole: tablet	Nivolumab and PDCT: solutions in single-use vials Part 2, BMS-986408 Formulation 1 and 2: tablet Part 3, BMS-986408 Formulation 1, 2, and 3: tablet
Unit Dose Strength(s)	BMS-986408: 0.75 mg, 5 mg, and 15 mg	Nivolumab: 100 mg/vial BMS-986408: Same as Part 1	Nivolumab: 100 mg/vial Ipilimumab: 50 mg/vial BMS-986408: Same as Part 1	BMS-986408: 5 mg Rabeprazole: 20 mg	Nivolumab: 100 mg/vial BMS-986408: same as Part 1 Carboplatin: 450 mg/45 mL vial Pemetrexed 500 mg/vial Cisplatin: 100 mg/100 mL vial Paclitaxel: 100 mg/16.7 mL vial
Dosage Level(s)	BMS-986408 QD* (mg): 0.75, 1.5, 3, 5, 10, 20, 30, 45, and 60. *Alternative BID schedule may be evaluated in Group B.	Nivolumab: 480 mg Q4W BMS-986408: Dose TBD	Nivolumab: 480 mg Q4W Ipilimumab: 1 mg/kg Q8W BMS-986408: Dose TBD	BMS-986408: 5 mg once Rabeprazole: 20 mg QD	Nivolumab: 360 mg Q3W BMS-986408: Dose TBD Carboplatin AUC 6 + paclitaxel 200 mg/m^2 Carboplatin AUC 5 or 6 or cisplatin 75 mg/m^2 + pemetrexed 500 mg/m^2

Table 7.1-1: Study Intervention(s) Administered

ARM Name	Part 1, Groups A, B, B2, and C	Part 2, Group D Part 2, Group G (Starting C1D1) Part 3, Group D2	Part 2, Group E	Part 2, Group G (Cycle 0)	Part 2, Group F Part 3, Group F2
Route of Adminis-tration	Oral	BMS-986408: oral Nivolumab: IV infusion	BMS-986408: oral Nivolumab and ipilimumab: IV infusion	Oral	BMS-986408: oral Nivolumab and PDCT: IV infusion
Use	Experimental	Experimental	Experimental	Experimental	Experimental
IMP and NIMP/ AxMP	IMP	IMP	IMP	IMP	IMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor	BMS-986408: Provided centrally by the Sponsor Rabeprazole: Provided locally by the study site[a]	BMS-986408, nivolumab: Provided centrally by the Sponsor PDCT: Provided locally by the study site[a]
Packaging and Labeling	BMS-986408 will be provided in bottles. Each bottle will be labeled as required per country requirement.	Nivolumab will be provided in vials. BMS-986408 will be provided in bottles. Each bottle and vial will be labeled as required per country requirement.	Ipilimumab and nivolumab will be provided in vials. BMS-986408 will be provided in bottles. Each vial and bottle will be labeled as required per country requirement.	BMS-986408 will be provided in bottles. Each bottle will be labeled as required per country requirement.	PDCT and nivolumab will be provided in vials. BMS-986408 will be provided in bottles. Each vial and bottle will be labeled as required per country requirement.
Current/ Former Name(s) or Alias(es)	DGK inhibitor (BMS-986408)	DGK inhibitor (BMS-986408) Anti-PD-1 (nivolumab)	DGK inhibitor (BMS-986408) Anti-PD-1 (nivolumab) Anti-CTLA-4 (ipilimumab)	DGK inhibitor (BMS-986408)	DGK inhibitor (BMS-986408) Anti-PD-1 (nivolumab)

Abbreviations: AxAMP, auxillary medicinal product; BID, twice daily; CTLA-4, cytotoxic T lymphocyte associated protein 4; DGK, diacylglycerol kinase; IMP, investigational medicinal product; IV, intravenous;

NIMP, noninvestigational medicinal product; PD-1, programmed death protein-1; QD, once daily; QxW, once every x weeks; SOC, standard of care; TBD, to be determined.

[a] The Sponsor may provide in regions where it is not available through insurance or as part of SOC.

Restrictions related to food and fluid intake are described in Section 6.3.

7.1.1 BMS-986408 Dosing

For Part 1, Groups A and B2 (if evaluated), participants will take oral BMS-986408 [redacted] For scheduled clinic visit days, BMS-986408 will be administered to the participant in the clinical facility. [redacted] For scheduled clinic visit days, the first dose of BMS-986408 will be administered to the participant in the clinical facility. [redacted] . For all parts of the

study, under certain circumstances. [redacted]

Dosing information for BMS-986408 should be recorded in the study diary and the case report form (CRF). If a dose of BMS-986408 is missed, the dose should be skipped, and dosing should resume at the next scheduled dose.

[redacted]. Missed dosing information should be recorded in the study diary, the CRF, and medical record along with a description of the reason for the missed dose. The next dosing day should be kept on schedule. If the participant misses a dose, BMS must be notified.

Participants should bring all containers for BMS-986408 to each study visit for drug reconciliation. Empty drug containers should be collected at each visit (or reconciled at least once every cycle, whichever is prior). Table 7.1-1 indicates the dose and dosage form for treatments to be administered in this study. Refer to the current IB and/or pharmacy manual for further details regarding storage of BMS-986408.

[redacted]

7.1.2 *BMS-986408 in Combination with Nivolumab or with Nivolumab and Ipilimumab*

For the combination of BMS-986408 and nivolumab, participants will receive nivolumab at a dose of 480 mg over an approximately 30-minute infusion on Day 1 of each treatment cycle until progression, unacceptable toxicity, withdrawal of consent, completion of 104 weeks of treatment, or the study ends, whichever occurs first. The IV line must be flushed with an appropriate amount of diluent (eg, 0.9% sodium chloride or 5% dextrose in water) to ensure that the complete dose is administered over approximately 30 minutes. [redacted]. BMS-986408 will be administered as described in Section 7.1.1.

[redacted] Participants will receive nivolumab at a dose of 480 mg infusion every cycle Q4W (28 days) and ipilimumab at 1 mg/kg every 2 cycles Q8W (56 days) until progression, unacceptable toxicity, withdrawal of consent, completion of 26 cycles of treatment (104 weeks) from first treatment regardless of treatment delays, or the study ends, whichever occurs first. Nivolumab will be administered over an approximately 30 minutes infusion period and must be promptly followed by a flush of diluent to clear the line of nivolumab before starting the ipilimumab infusion. The second infusion will always be the ipilimumab study treatment and will

start after the infusion line has been flushed, filters changed, and participant has been observed to ensure no infusion reaction has occurred. There should be a 30-minute waiting period between the completion of the nivolumab infusion and the start of the ipilimumab infusion. The duration of the ipilimumab infusion should be approximately 30 minutes.

7.1.3 BMS-986408 in Combination with Nivolumab and PDCT

In Groups F (Part 2) and F2 (Part 3), 4 cycles of the histology-based PDCT option selected by the investigator will be administered on Day 1 Q3W. Participants with non-squamous (NSQ) histology may also receive optional maintenance therapy with 500 mg/m^2 pemetrexed alone on Day 1 of each 3-week cycle until disease progression, unacceptable toxicity, or other reasons specified in the protocol.

Histology-based PDCT:

- Squamous histology: Carboplatin AUC 6 plus paclitaxel 200 mg/m^2
- Non-squamous histology: Carboplatin AUC 5 or 6 or cisplatin 75 mg/m^2 plus pemetrexed 500 mg/m^2 (optional maintenance therapy with 500 mg/m^2 Q3W pemetrexed)

BMS-986408 and nivolumab will be administered as described in Sections 7.1.1 and 7.1.2. All chemotherapy agents' preparation, premedication, administration, monitoring, and management of complications are to follow local prescription guidelines and regulations. The dose of chemotherapy may be capped per local standards.

Note: The investigator must decide prior to starting treatment whether or not a participant with NSQ histology will receive cisplatin, if eligible.

7.1.3.1 Paclitaxel and Carboplatin

Participants will receive paclitaxel 200 mg/m^2 as a 180-minute IV infusion with carboplatin at a dose of AUC 6 as a 30-minute IV infusion on Day 1 of a 3-week cycle, or at doses per the local prescribing information. The infusion time can follow local institutional standards.

Paclitaxel dosing calculations should be based on the body surface area calculation. The dose may remain the same if the participant's weight is within 10% of the baseline weight or prior dose weight.

Carboplatin should be given following paclitaxel on Day 1 of each cycle. The carboplatin dose will be calculated using the Calvert formula as follows:

$$\text{Carboplatin dose (mg)} = \text{target AUC} \times (\text{CrCl [mL/min]} + 25)$$

Creatinine clearance (CrCl) calculation is based on the Cockcroft-Gault formula and should include the most recent serum creatinine and most recent weight. NOTE: If calculation of the CrCl by the Cockcroft-Gault formula yields a result of > 125 mL/min, then a CrCl should be calculated by an alternative formula per institutional standards or capped at 125 mL/min.

The dose of carboplatin may be capped per local standards.

Premedications for use with paclitaxel include the following:

- Oral or IV corticosteroid should be given according to local standard at a dose equivalent to dexamethasone 20 mg 12 and 6 hours prior to paclitaxel administration (oral or IV).
- IV diphenhydramine (or its equivalent) 50 mg and histamine H2-blocker (per local standard of care) should be administered 30 to 60 minutes prior to paclitaxel infusion.
- Doses of paclitaxel and/or carboplatin may be interrupted, delayed, reduced, or discontinued, depending on how well the participant tolerates the treatment.

7.1.3.2 Pemetrexed and Cisplatin

Pemetrexed dosing calculations should be based on the body surface area calculation. The dose may remain the same if the participant's weight is within 10% of the weight used to calculate the previous dose.

Premedications for use with pemetrexed include the following:

- Oral or IV corticosteroid should be given according to local standards at a dose equivalent to dexamethasone 4 mg BID on the day prior to, the day of, and the day after the administration of pemetrexed.
- Oral folic acid 350 to 1000 μg daily should be given starting 1 week prior to the first dose of pemetrexed, with at least 5 doses of folic acid administered in the 7 days prior to the first dose. Oral folic acid should be continued daily throughout the treatment with pemetrexed and for 21 days after the last dose of pemetrexed. Intramuscular (IM) injection of vitamin B12 1000 μg should be given approximately 1 week prior to the first dose of pemetrexed and repeated every 3 cycles thereafter during pemetrexed treatment. Subsequent injections of vitamin B12 may be given on the same day as pemetrexed (participant with NSQ histology may begin folic acid and vitamin B12 prior to randomization in anticipation of pemetrexed).
- Antiemetic premedication will be administered according to local standards. Recommended antiemetic treatments are dexamethasone (dosing according to local standards; an equivalent dose of another corticosteroid may be substituted) and a 5-HT3 receptor antagonist (type per investigator discretion and local standards of care). Additional use of antiemetic premedications may be employed at the discretion of the investigator.

Participants will receive pemetrexed at a dose of 500 mg/m^2 as a 10-minute IV infusion on Day 1 with cisplatin at a dose of 75 mg/m^2 infusion per local standard practice on Day 1 of a 3-week treatment cycle for up to 4 cycles.

Dosing calculations should be based on the body surface area calculation and may be capped per local standards. The dose may remain the same if the participant's weight is within 10% of the weight or prior dose weight.

Cisplatin will be administered to participants at least 30 minutes following the end of the pemetrexed infusion. Pretreatment hydration for cisplatin can follow local standard of care or use 1 to 2 liters of fluid (per local standards) infused IV for 8 to 12 hours prior to cisplatin infusion (recommended). Adequate hydration and urinary output must be maintained for at least 24 hours following cisplatin administration. Administration and monitoring should be performed according to local standards. Use of mannitol following the cisplatin infusion should also follow local standards of care.

Doses of pemetrexed and/or cisplatin may be interrupted, delayed, reduced, or discontinued, depending on how well the participant tolerates the treatment.

All participants who will receive cisplatin should have audiometric testing performed prior to initiation of therapy and prior to subsequent doses of cisplatin or per local standards of care (SOC).

Participants who discontinue cisplatin alone may, at the investigator's discretion, be switched to pemetrexed/carboplatin for the remainder of the PDCT (up to 4 cycles in total). Dosing for pemetrexed/carboplatin for such participants should follow the instructions in Section 7.1.3.3.

7.1.3.3 Pemetrexed and Carboplatin

Pemetrexed dosing calculations should be based on the body surface area calculation. The dose may remain the same if the participant's weight is within 10% of the weight used to calculate the previous dose.

Premedications for use with pemetrexed:

- Oral or IV corticosteroid premedication for pemetrexed should be given according to local standards at a dose equivalent to dexamethasone 4 mg BID on the day prior to, the day of, and the day after the administration of pemetrexed.
- Oral folic acid 350 to 1000 μg daily should be given starting 1 week prior to the first dose of pemetrexed, with at least 5 doses of folic acid administered in the 7 days prior to the first dose. Oral folic acid should be continued daily throughout the treatment with pemetrexed and for 21 days after the last dose of pemetrexed. IM injection of vitamin B12 1000 μg should be given approximately 1 week prior to the first dose of pemetrexed and repeated every 3 cycles thereafter during pemetrexed treatment. Subsequent injections of vitamin B12 may be given on the same day as pemetrexed (participant with NSQ histology may begin folic acid and vitamin B12 prior to randomization in anticipation of pemetrexed).

Participants will receive pemetrexed at a dose of 500 mg/m^2 as a 10-minute IV infusion on Day 1, followed by carboplatin at a dose of AUC 5 or 6 as a 30-minute IV infusion on Day 1 of a 3-week treatment cycle for up to 4 cycles.

Pemetrexed dosing calculations should be based on the body surface area calculation. The dose may remain the same if the participant's weight is within 10% weight used to calculate the previous dose.

The carboplatin dose will be calculated using the Calvert formula as follows:

Carboplatin dose (mg) = Target AUC × (CrCl [mL/min] + 25)

CrCl calculation is based on the Cockcroft-Gault formula (see inclusion criterion in Section 6.1) and should include the most recent serum creatinine and most recent weight. NOTE: If calculation of the CrCl by the Cockcroft-Gault formula yields a result of > 125 mL/min, then a CrCl should be calculated by an alternative formula per institutional standards or capped at 125 mL/min.

Doses of pemetrexed and/or carboplatin may be interrupted, delayed, reduced, or discontinued, depending on how well the participant tolerates the treatment. All chemotherapy agents' preparation, premedication, administration, monitoring, and management of complications are to follow local prescription guidelines and regulations. The dose of chemotherapy may be capped per local standards.

7.1.3.4 Optional Continuation Maintenance

After Cycle 4 of chemotherapy, participants with NSQ histology who have stable disease or response are permitted to receive pemetrexed 500 mg/m^2 Q3W alone as maintenance therapy until disease progression, unacceptable toxicity, or the maximum duration of treatment (2 years) has been reached.

7.2 Method of Study Intervention Assignment

All participants will be centrally assigned to treatment using IRT. Before the study is initiated, each user will receive log-in information and directions on how to access the IRT.

Study intervention will be dispensed at the study visits as listed in Schedule of Activities (Section 2).

Enrolled participants, including those not dosed, will be assigned sequential participant numbers starting with [redacted] Those enrolled participants meeting inclusion and exclusion criteria will be eligible to be dosed. Sequential numbering may restart at [redacted] for each participating site as the distinct patient identification number (PID) will ultimately be comprised of the site number and participant number [redacted]

Once it is determined that the participant meets the eligibility criteria following the screening visit, the investigative site will utilize the IRT to centrally assign the participant into the open dose level within 3 days of starting the treatment. If multiple cohorts are simultaneously enrolling in Part 2, Group G or Part 3, Groups D2 and F2, participants may be randomized to treatment assignment.

7.3 Blinding

This is a non-randomized open-label study. It has been determined that blinding is not required to meet study objectives. Blinding procedures are not applicable and access to treatment assignment information is unrestricted. The specific treatment to be taken by a participant will be assigned using IRT. The site will contact the IRT prior to the start of study intervention administration for each participant. The site will record the treatment assignment on the applicable CRF, if required.

7.4 Dosage Modification

Participants will be monitored for AEs during 3 phases of the study: screening, treatment, and safety follow-up. Participants experiencing Grade ≥ 3 treatment-related AEs that do not qualify as DLT events will hold study treatment until symptoms resolve or return to baseline. Intraparticipant dose escalation of BMS-986408 is permitted per Section 5.1.1. Intraparticipant schedule modifications of BMS-986408 are not permitted at any time. Intraparticipant dose reductions of BMS-986408 are allowed after specific DLT criteria are met. No dose reductions or escalations of nivolumab or ipilimumab will be allowed throughout the study treatment period. Dose reductions of PDCT are permitted per Section 7.4.3.

The assessment for dose delays and modifications should be made separately for each study intervention administered. Dose modifications are required only for the study treatment considered to be related to the AE. Thus, in case of an AE relationship assignment to PDCT alone, dose modifications for PDCT alone are allowed. Similarly, in case of assignment of AE relationship to BMS-986408 and nivolumab, dose reduction for PDCT is not mandated. If criteria for discontinuation of BMS-986408 and nivolumab are met, PDCT may continue until 4 cycles have been completed. If criteria for discontinuation of PDCT are met, BMS-986408 and nivolumab may continue until progression or unacceptable toxicity, whichever occurs first. In case of doubt, all study treatments should be modified.

For participants who require delay of study treatment, re-evaluate weekly, or more frequently, if clinically indicated, and resume dosing when criteria to resume treatment are met (see Section 7.4.4). Continue tumor assessments per protocol even if dosing is delayed.

[redacted]

See Section 7.4.4 for criteria to resume treatment.

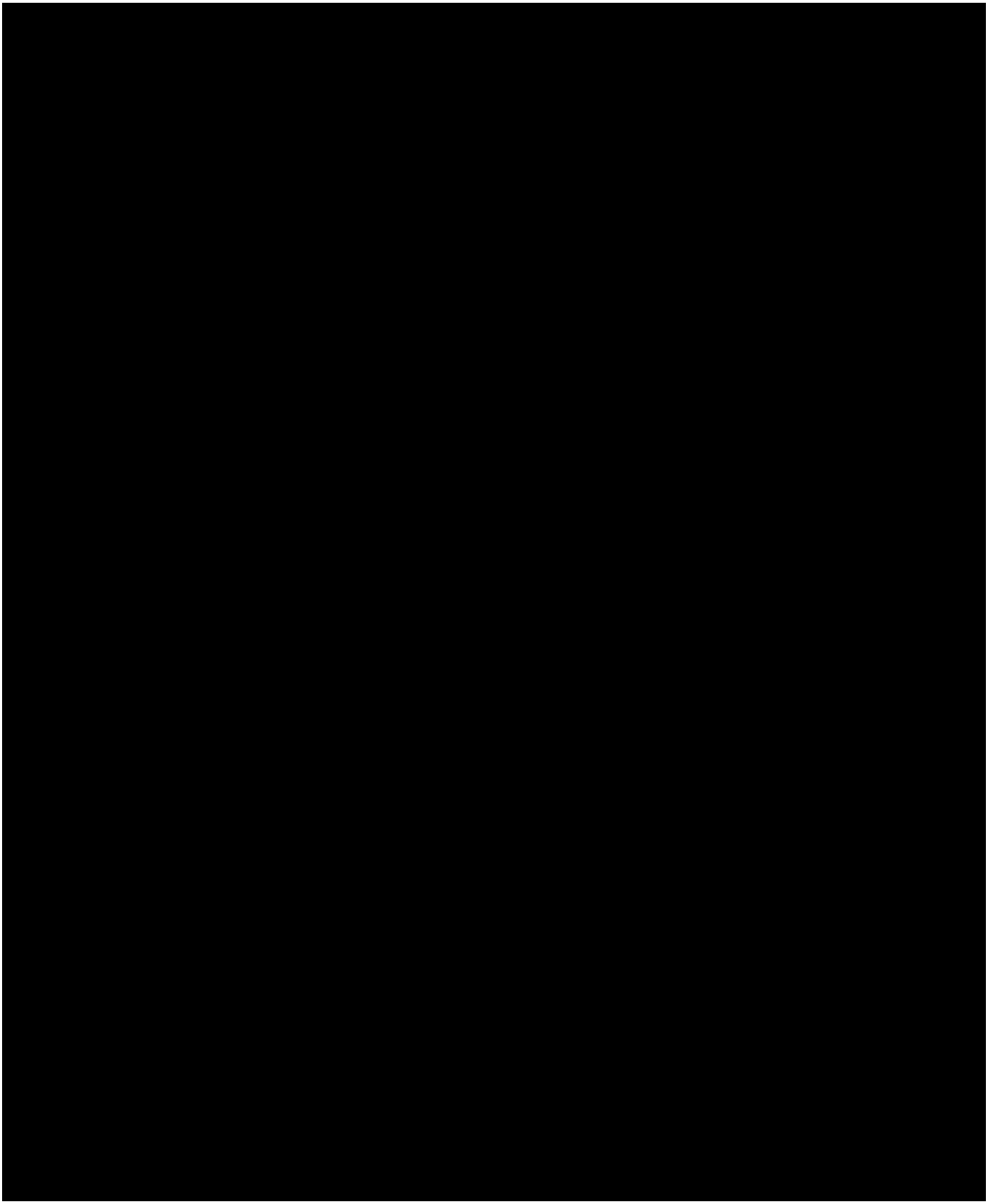
Criteria for participants who are required to permanently discontinue study drugs are listed in Section 8.1. Participants not meeting guidelines for permanent discontinuation will be permitted to resume therapy as soon as criteria for resuming therapy specified in Section 7.4.4 are fulfilled.

7.4.1 Dose Delay and Discontinuation Criteria for BMS-986408, Nivolumab and Ipilimumab

Dose delay criteria apply for all drug-related AEs. Delay administration of all treatment if any of the delay criteria [redacted] are met. Delay all treatment dosing for any AE, laboratory

abnormality, or intercurrent illness which, in the judgment of the Investigator, warrants delaying the dose of study medication.

[redacted]



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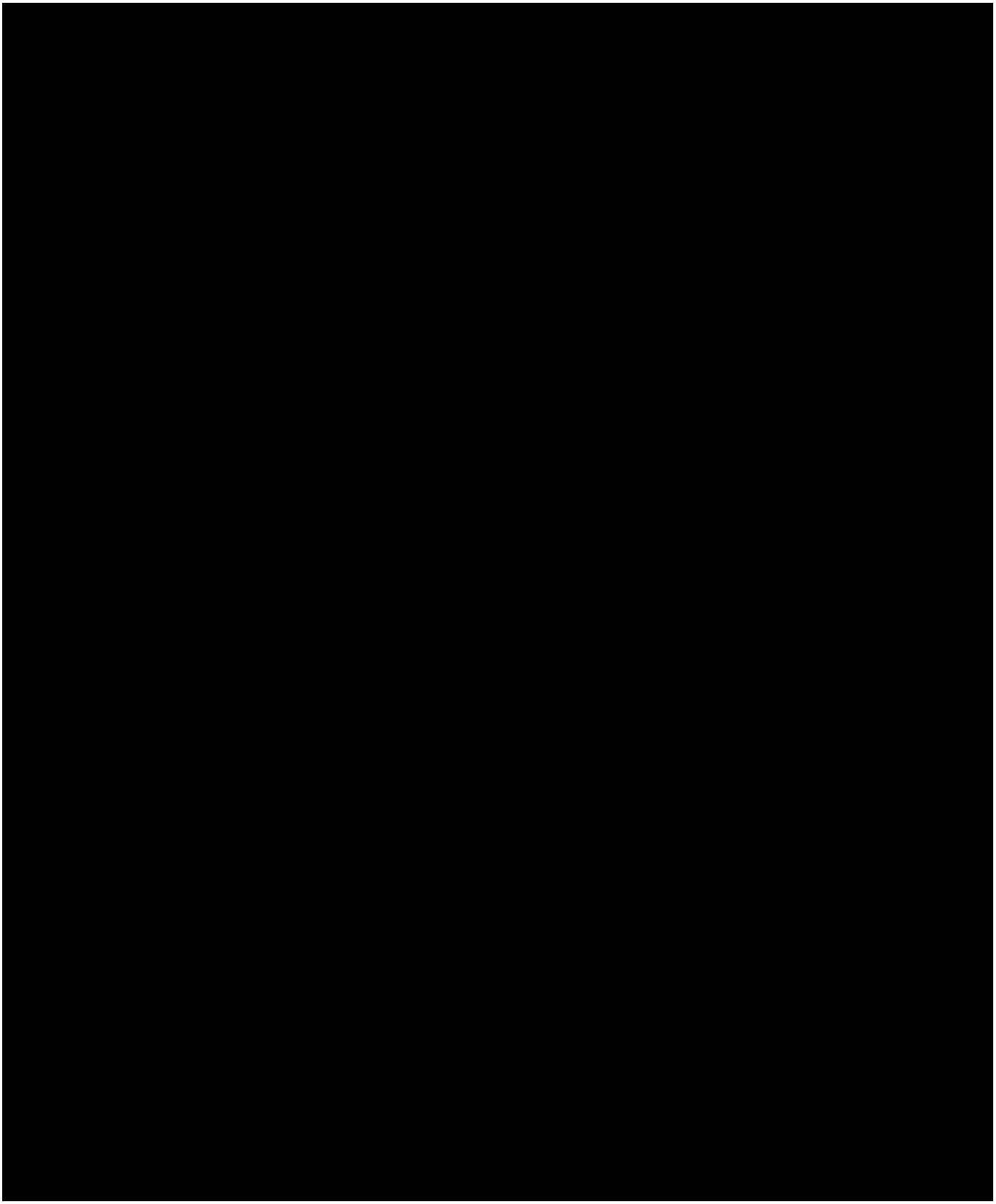
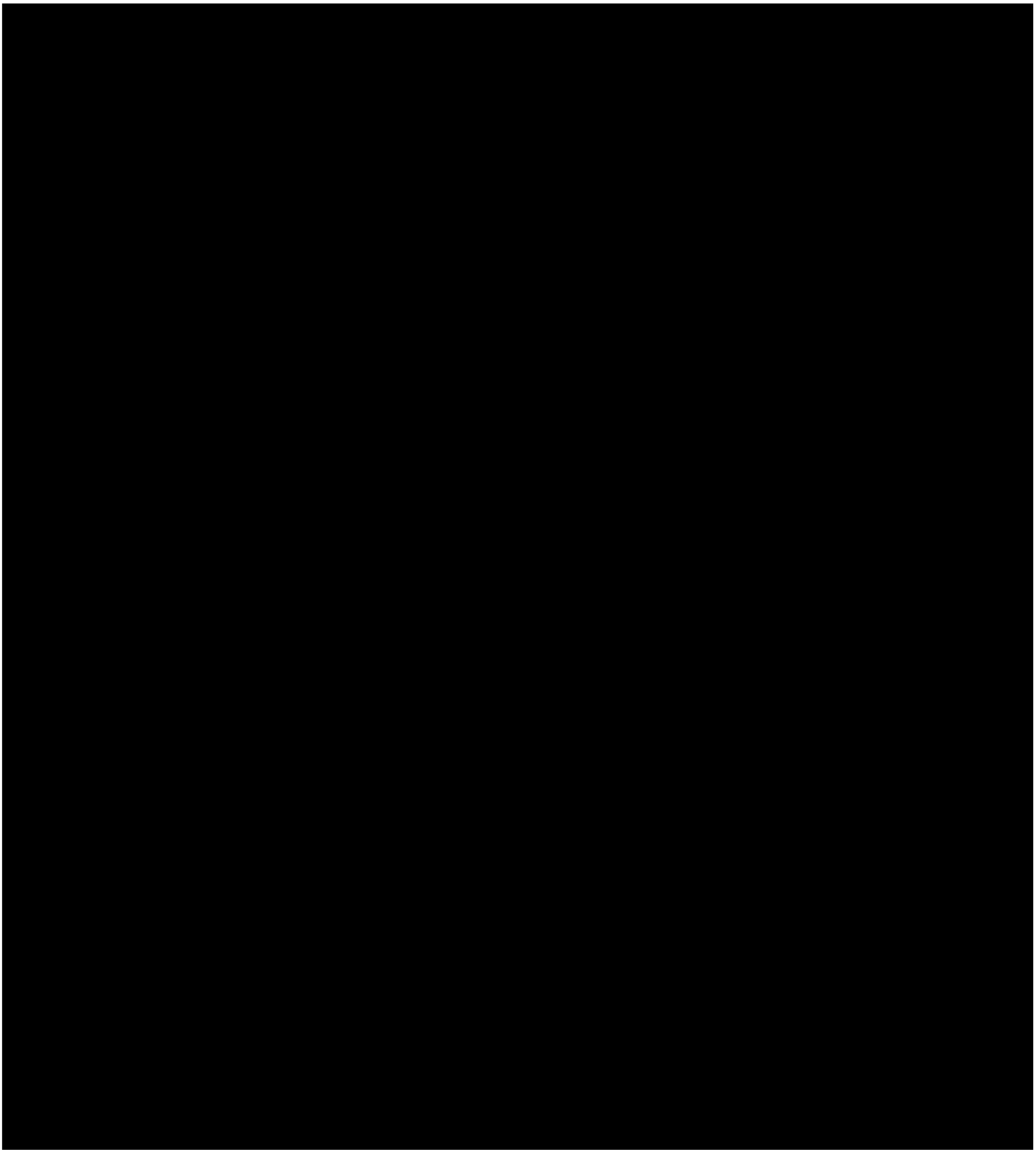
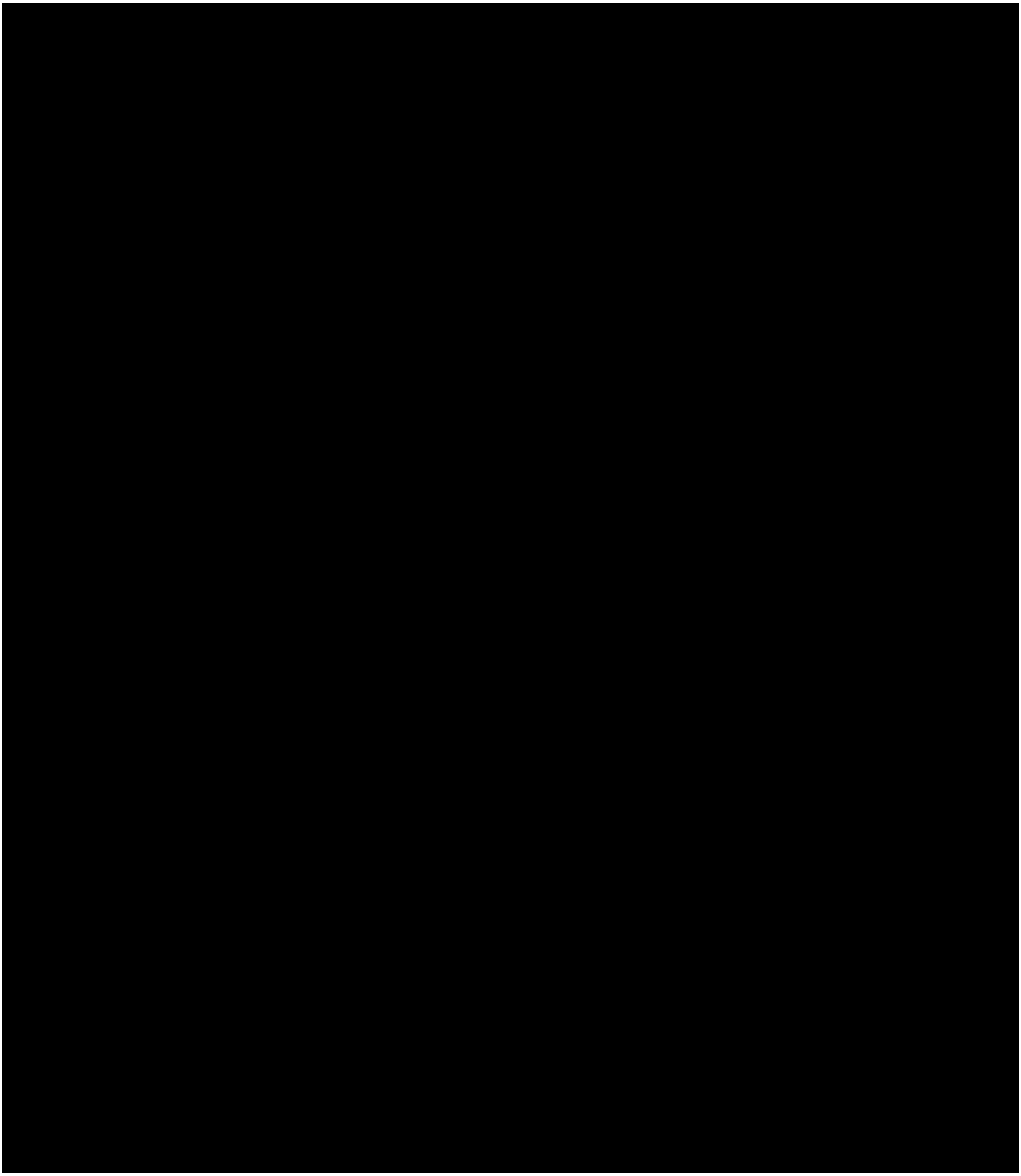
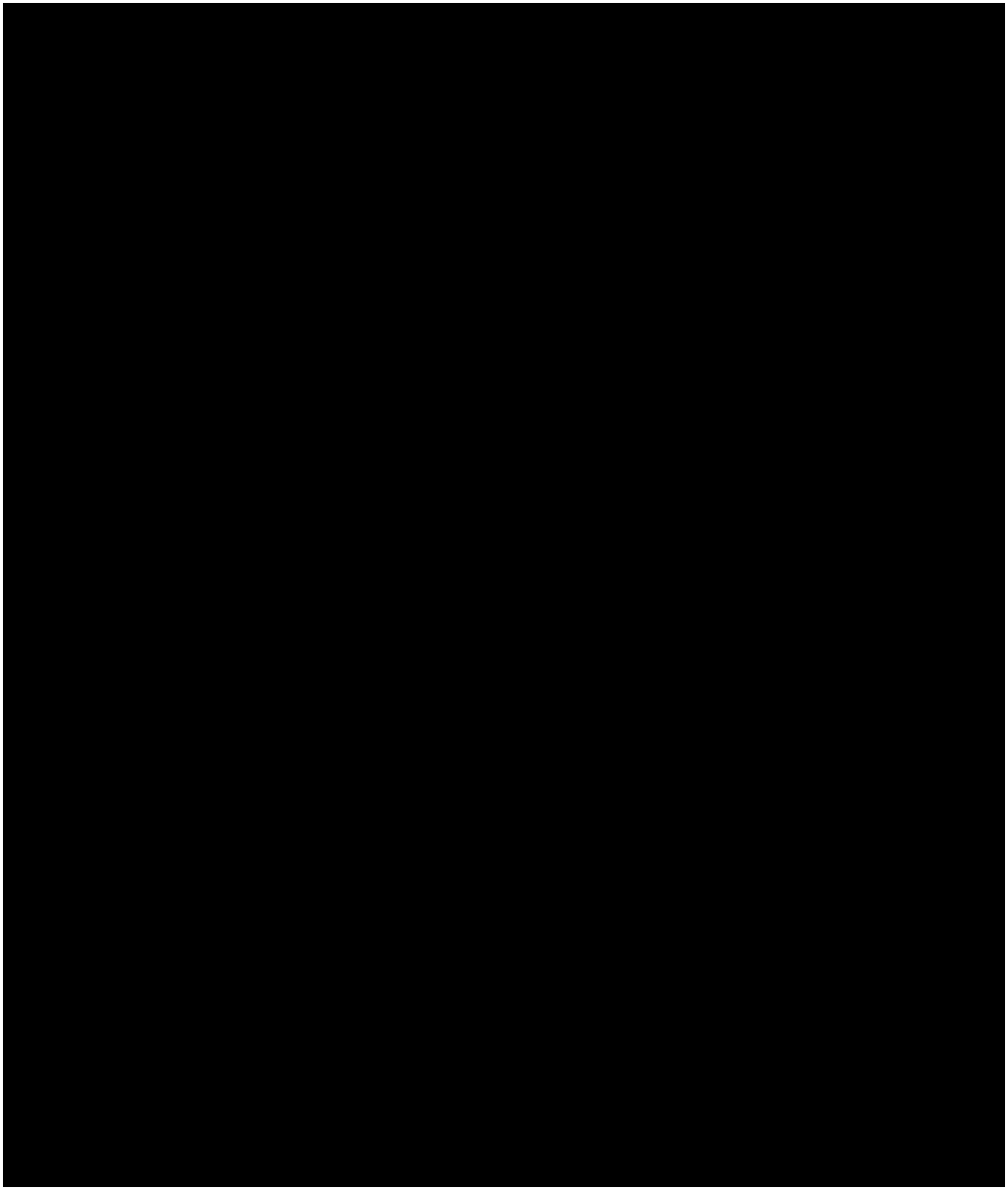
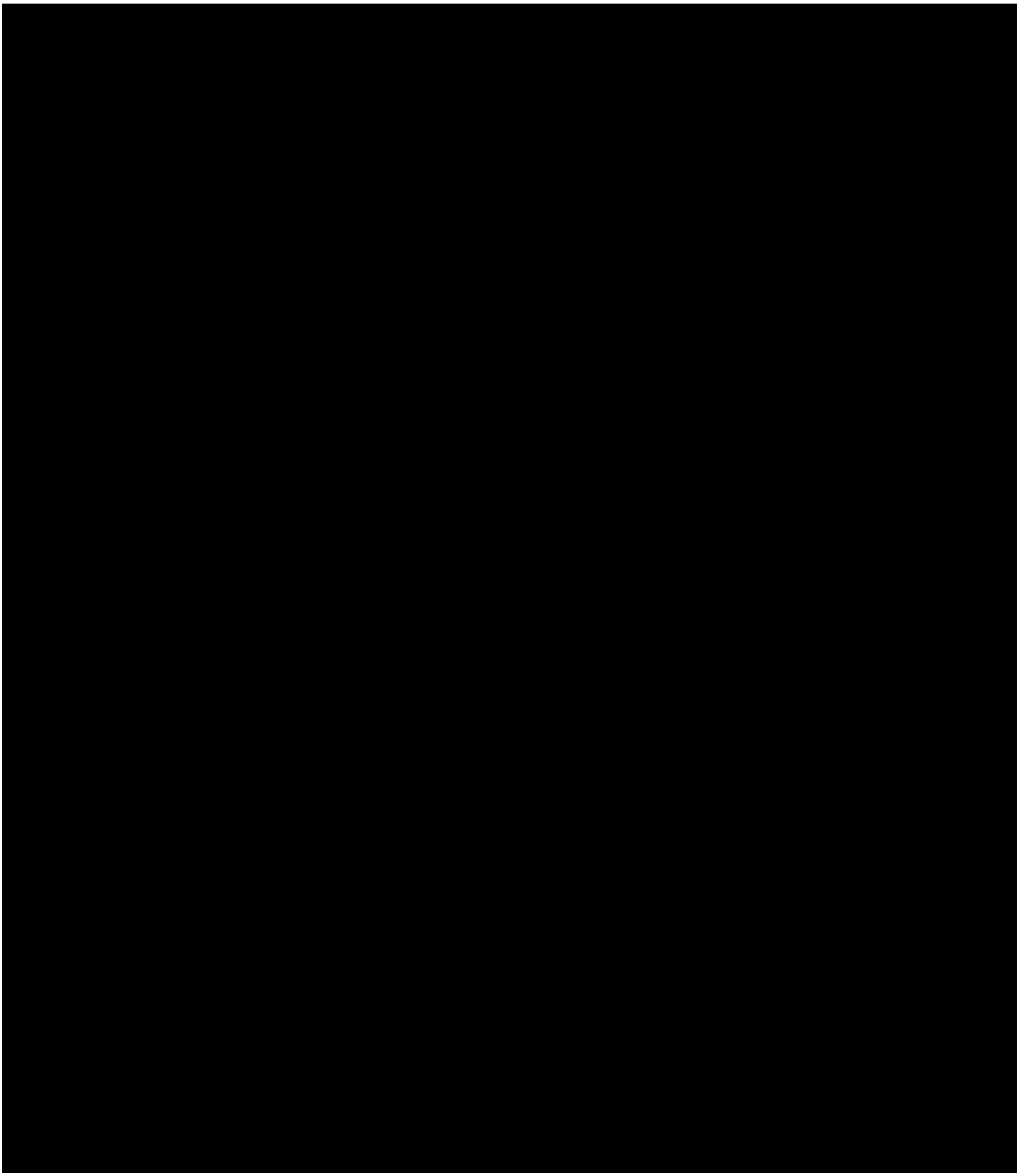
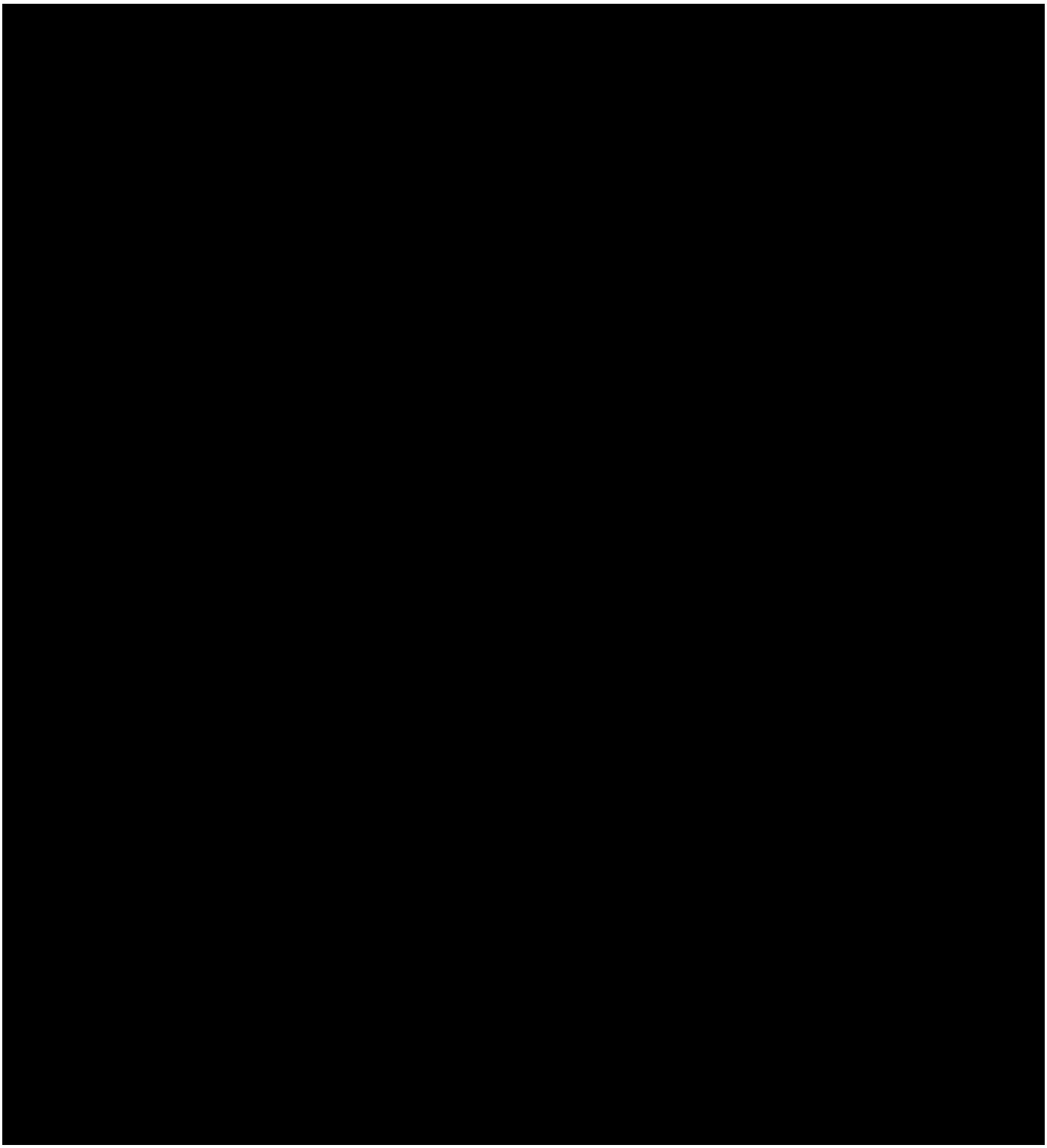












7.4.2 Dose Delays for Chemotherapy

Chemotherapy drugs should be delayed for any of the events listed below. The delay should occur on treatment Day 1.

- Absolute neutrophil count < 1500/μL (SI units: < 1.5×10^9/L)
- Platelets < 100,000/μL (SI units: < 100×10^9/L)
- Any Grade ≥ 2 non-skin, non-hematologic, drug-related AE (excluding Grade 2 alopecia, Grade 2 fatigue, and Grade 2 laboratory abnormalities)
- Any Grade ≥ 3 skin, drug-related AE
- Any Grade ≥ 3 drug-related laboratory abnormality, with the following exceptions for AST, ALT, or total bilirubin:
  - If a participant has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity.
  - If a participant has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity.
- Any AE, laboratory abnormality, or intercurrent illness that, in the judgment of the investigator, warrants delaying the dose of study medication. Investigators should consult local labeling for the chemotherapy drugs being administered to any given participant for additional guidance on dose delays.

Dose modifications listed are specific to US Prescribing Information (USPI). Variations may apply per local label. Participants receiving cisplatin with pemetrexed must discontinue cisplatin if the calculated CrCl decreases to < 50 mL/min (based on the Cockcroft-Gault formula). The other drug (pemetrexed) may be continued, and the platinum agent may, at the investigator's discretion, be switched to carboplatin for the rest of the cycles when the participant meets retreatment criteria. Note that pemetrexed can only be administered if CrCl is ≥ 45 mL/min (calculated per Cockcroft-Gault formula).

If a participant receiving carboplatin with paclitaxel must discontinue carboplatin, paclitaxel may be continued at the investigator's discretion.

If any non-hematologic AE meeting the dose delay criteria above is felt to be related to only 1 particular agent in the PDCT regimen, then that agent alone may be omitted for that cycle while the other agent is given. To maintain synchronized dosing of the regimen, the omitted agent should be resumed with the next scheduled cycle once the AE has improved and retreatment criteria are met. Please refer to Section 7.4.3 to determine if dose reduction of the resumed agent is required.

If both drugs in the PDCT regimen are delayed, then the participant should be re-evaluated weekly or more frequently if clinically indicated until re-treatment criteria are met (see Section 7.4.4).

7.4.3 Dose Reduction for Chemotherapy

Dose reductions for chemotherapy may be required and will be performed as described below or per institutional guidelines. Chemotherapy dose reductions are permanent: once the dose of any

chemotherapy agent is reduced, it may not be re-escalated in subsequent cycles, except as noted when starting pemetrexed maintenance therapy. The dose reductions for each agent in the PDCT regimen are not linked and may be adjusted independently as summarized in Table 7.4.3.1-1.

Table 7.4.3-1: Dose Reduction for Chemotherapy[a]

Dose Level	Carboplatin	Pemetrexed	Paclitaxel	Cisplatin
Starting Dose	AUC 6 or AUC 5	500 mg/m^2	200 mg/m^2	75 mg/m^2[b]
First Dose Reduction	AUC 5 (if starting dose is AUC 6) or AUC 4 (if starting dose is AUC 5)	375 mg/m^2	150 mg/m^2	56 mg/m^2
Second Dose Reduction	AUC 4 (if starting dose is AUC 6) or AUC 3 (if starting dose is AUC 5)	250 mg/m^2	100 mg/m^2	38 mg/m^2
Third Dose Reduction	Discontinue	Discontinue	Discontinue	Discontinue

Abbreviations: AUC, area under the curve; CrCl, creatinine clearance.

[a] Starting dose and dose reductions per table or institutional guidelines.

[b] If CrCl ≥ 60 mL/min, then starting dose is cisplatin 75 mg/m^2. If CrCl is 50-59 mL/min, then decrease by 75% or per local guidelines.

Dose modifications listed are specific to USPI. Variations may apply per local label.

Any participant with 2 prior dose reductions for 1 agent who experiences a toxicity that would cause a third dose reduction must be discontinued from that agent.

7.4.3.1 Chemotherapy: Dose Reductions for Hematologic Toxicity

Dose modifications for hematologic toxicities (according to Common Terminology Criteria for Adverse Events [CTCAE] v5) are summarized in Table 7.4.3.1-1. Dose adjustments are based on nadir blood counts (assessed per local standards) since the preceding drug administration. Dose level adjustments for PDCT are relative to that of the preceding administration. Generally, both chemotherapy agents in the PDCT regimen should be dose reduced together for hematologic toxicity. After the first cycle, growth factors may be used to assist hematologic recovery. For incidences of chemotherapy-induced anemia or cancer-associated anemia, red blood cell transfusions are highly recommended. In participants who refuse RBC transfusions, erythropoiesis-stimulating agents may be administered per local standards.

Use local standards of care for other previously described supportive measures. Additionally, prophylactic antibiotics may be used according to local standards of care. Investigators are strongly recommended to have a high index of suspicion for infection and consider starting broad spectrum antibiotics early for any fever or signs of infection in participants with neutropenia. Please report any antibiotic or growth factor use on the electronic case report form (eCRF).

Dose modifications listed are specific to USPI. Variations may apply per local label.

Table 7.4.3.1-1: Dose Modification for Hematologic Toxicity (Based on Nadir Counts)

Toxicity	Carboplatin	Paclitaxel	Pemetrexed	Cisplatin
Neutrophil Count Decreased				
Grade 4 (< 500/mm^3 or < 0.5× 10^9/L)	Reduce 1 dose level	Reduce 1 dose level	Reduce 1 dose level	Reduce 1 dose level
Platelet Count Decreased				
Grade 3 (< 50,000-25,000/mm^3; < 50.0-25.0× 10^9/L)	Reduce 1 dose level	Reduce 1 dose level	Reduce 1 dose level	Reduce 1 dose level
Grade 4 (< 25,000/mm^3; < 25.0× 10^9/L)	Reduce 1 dose level	Reduce 1 dose level	Reduce 1 dose level	Reduce 1 dose level

7.4.3.2 Chemotherapy: Dose Reductions for Non-hematologic Toxicities

Dose adjustments for chemotherapy for non-hematologic toxicities during treatment are described in Table 7.4.3.2-1. All dose reductions should be made based on the worst-grade toxicity. Participants experiencing any of the toxicities during the previous cycle should have chemotherapy delayed until retreatment criteria are met and then reduced for all subsequent cycles by 1 dose level or discontinued as appropriate. Dose levels for the 2 drugs in the PDCT regimen are not linked and may be reduced independently as summarized in Table 7.4.3-1.

Table 7.4.3.2-1: Dose Modification for Non-Hematologic Toxicity

Toxicity	Carboplatin	Paclitaxel	Pemetrexed	Cisplatin
Febrile Neutropenia Grade ≥ 3	Reduce 1 dose level	Reduce 1 dose level	Reduce 1 dose level	Reduce 1 dose level
Diarrhea Grade ≥ 3	No change	Reduce 1 dose level	Reduce 1 dose level	No change
Allergic Reaction Grade ≥ 3	Discontinue	Discontinue	Discontinue	Discontinue
Neuropathy Grade 2	Reduce 1 dose level	Reduce 1 dose level	No change	Reduce 1 dose level
Neuropathy Grades 3 or 4	Discontinue	Discontinue	Discontinue	Discontinue
CrCl < 50 mL/min	No change	Discontinue if CrCl < 20 mL/min	No change	Discontinue

Table 7.4.3.2-1: Dose Modification for Non-Hematologic Toxicity

Toxicity	Carboplatin	Paclitaxel	Pemetrexed	Cisplatin
Other Grade ≥ 3 toxicity (except for fatigue and transient arthralgia and myalgia)	Adjust as medically indicated	Adjust as medically indicated	Adjust as medically indicated	Adjust as medically indicated

Abbreviation: CrCl, creatinine clearance.

7.4.4 Criteria to Resume Treatment

7.4.4.1 Criteria to Resume Treatment with BMS-986408, Nivolumab, or Ipilimumab

Participants in all groups must not meet any relevant criteria for discontinuation described in Section 8.1 to be considered for resumption of study treatment. Medical Monitor should be consulted for any delay of study treatment > 4 weeks for non-drug-related AEs before resuming study treatment.

Participants may resume study treatment if they have completed AE management (ie, corticosteroid taper) or are on ≤ 10 mg prednisone or equivalent and meet the requirements [redacted].

Prior to re-initiating treatment in a participant with a dosing delay lasting > 10 weeks for Part 2 or Part 3, the Medical Monitor (or designee) must be consulted. Continue tumor assessments per protocol even if dosing is delayed. Continue periodic study visits to assess safety and laboratory studies per protocol or more frequently if clinically indicated during such dosing delays.

For Part 2, Group E, when doses of both nivolumab and ipilimumab have been delayed and criteria to resume treatment are subsequently met, resume both nivolumab and ipilimumab on the same day unless the Investigator determines that one of the agents must be discontinued due to toxicity attributed to that agent alone. Decisions to eliminate any component of the assigned study regimen must be discussed with and approved by the medical monitor.

7.4.4.2 Criteria to Resume Treatment with Chemotherapy

Participants may resume treatment with chemotherapy when the absolute neutrophil count returns to ≥ 1500/µL (≥ 1.5× 10^9/L), the platelet count returns to ≥ 100,000/µL (≥ 100× 10^9/L), and all other drug-related toxicities have returned to baseline or Grade 1 (or Grade 2 for alopecia and fatigue).

If a participant fails to meet criteria for re-treatment, then re-treatment should be delayed, and the participant should be re-evaluated weekly or more frequently as clinically indicated. Any participant who fails to recover from toxicity attributable to chemotherapy to baseline or Grade 1 (except Grade 2 alopecia and fatigue) within 6 weeks from the last dose given should discontinue the drug(s) that caused the delay.

When resuming chemotherapy treatment, follow the dose-reduction recommendations in Section 7.4.3.

7.4.5 [redacted]

Immuno-oncology (IO) agents are associated with AEs that can differ in severity and duration from AEs caused by other therapeutic classes. Nivolumab, ipilimumab, and BMS-986408 are considered IO agents and the [redacted] provide guidance on assessing and managing the following groups of AEs:

- Gastrointestinal
- Renal
- Pulmonary
- Hepatic
- Endocrinopathy
- Skin
- Neurological
- Myocarditis

[redacted]

[redacted]

[redacted]

7.4.7 Treatment of Immunotherapy Infusion-related Reactions

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

Treatment recommendations are provided below based on CTCAE v5 grading definitions 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):

- [redacted].

For Grade 2 symptoms: (Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours**)**:

- [redacted]

For Grade 3 or 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 clinical sequelae. Grade 4: Life-threatening consequences; urgent intervention indicated):

- [redacted]

In 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).

7.5 Preparation/Handling/Storage/Accountability

The IP/AxMP must be stored in a secure area according to local regulations. It is the responsibility of the Investigator, or designee where permitted, to ensure that IP/AxMP is only dispensed to study

participants. The IP/AxMP must be dispensed only from official study sites by authorized personnel according to local regulations.

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

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

IP/AxMP documentation (whether supplied by BMS or not) must be maintained that includes all processes required to ensure the 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).

- The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study interventions are provided in Appendix 2.

7.6 Treatment Compliance

Study intervention compliance will be periodically monitored by drug accountability (including review of dosing diary). Drug accountability should be reviewed by the site study staff at each visit to confirm treatment compliance. Sites should discuss discrepancies with the participant at each on-treatment study visit and document these discussions and discrepancies within medical records.

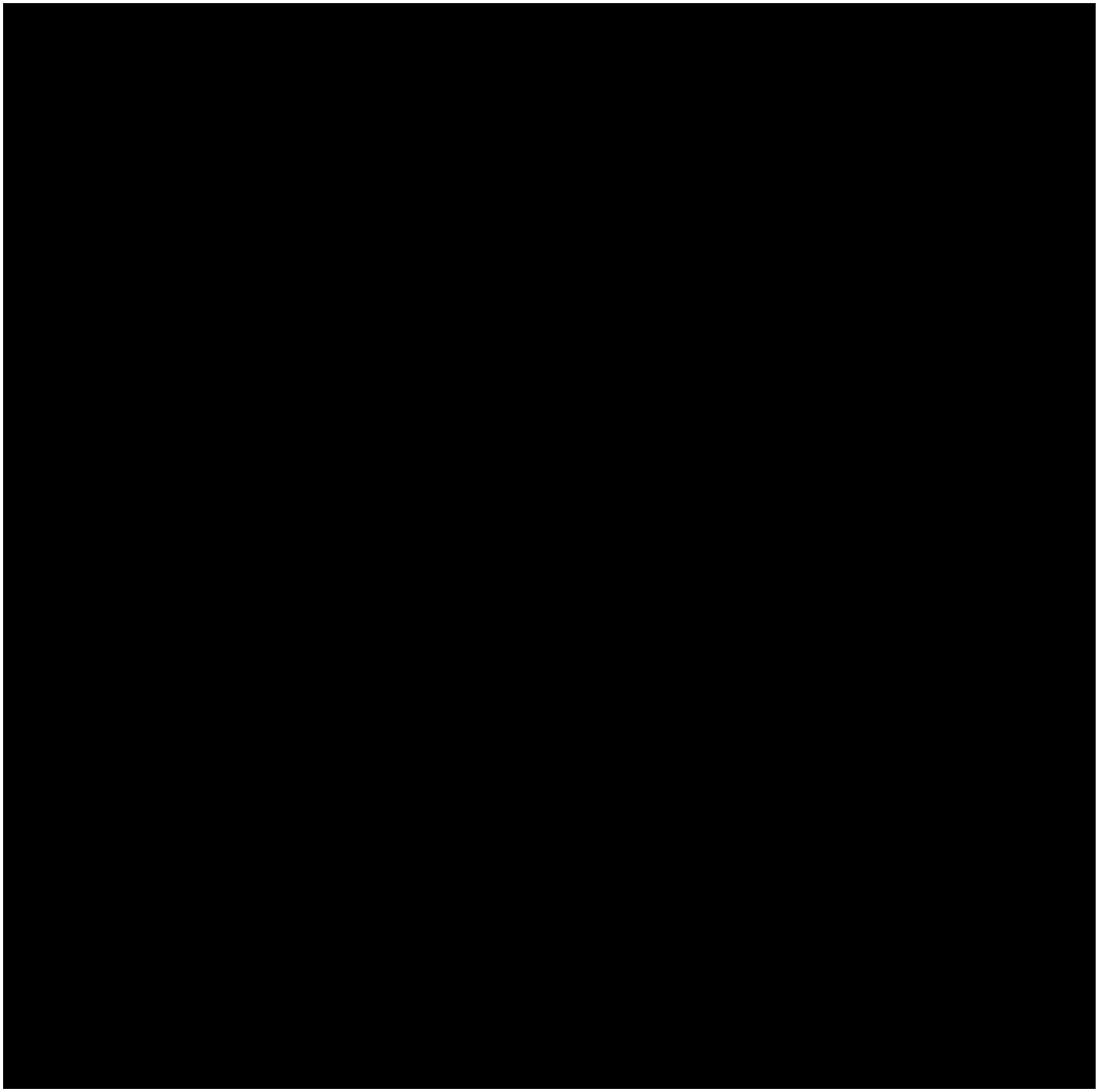
- When participants are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. Study site staff will examine each participant's mouth to ensure that the study intervention was ingested.
- When participants self-administer BMS-986408 at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning, counting returned tablets/capsules, and review of Participant Diary (supplied by BMS) during the site visits and documented in the source documents and relevant form. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.
- A record of the quantity of BMS-986408 dispensed to and administered by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions, will also be recorded in the CRF.

During Study Visit days, all study treatment(s) will be administered in the clinical facility.

7.7 Concomitant Therapy

7.7.1 Prohibited and/or Restricted Treatments

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



- [redacted]
- The investigator must also adhere to the contraindications, precautions, and drug interactions found in the USPI or local label for each chemotherapy agent.

7.7.2 Other Restrictions and Precautions

Participants are prohibited from joining another clinical trial while they are participating in this study.

- [redacted]

7.7.2.1 Imaging Restriction and Precautions

It is the local imaging facility's responsibility to determine, based on participant attributes (eg, allergy history, diabetic history, and renal status), the appropriate imaging modality and contrast regimen per imaging study. Imaging contraindications and contrast risks are to be considered in this assessment. Participants with renal insufficiency are to be assessed as to whether or not they should receive contrast and, if so, which contrast agent and dose is appropriate. Specific to magnetic resonance imaging (MRI), participants with severe renal insufficiency (ie, eGFR< 30 mL/min/1.73 m^2) are at increased risk of nephrogenic systemic fibrosis, therefore MRI contrast is contraindicated. In addition, participants may be excluded from MRI if they have tattoos, metallic implants, pacemakers, etc. This will be outlined in the image manual.

Gentle hydration before and after IV contrast should follow local standard of care. The ultimate decision to perform MRI in an individual participant in this study rests with the site radiologist, the Investigator, and standards set by the local Ethics Committee.

7.7.2.2 Palliative Local Therapy

Palliative local therapy to non-target lesions, including palliative radiation therapy and palliative surgical resection, to symptomatic non-target bone lesions, skin lesions, or CNS lesions is permitted prior to discontinuation of the study intervention for participants who do not have evidence of overall clinical or radiographic progression per RECIST v1.1. The case must be discussed with the Sponsor/Medical Monitor (or designee).

Participants requiring palliative local therapy should be evaluated for objective evidence of disease progression prior to the initiation of such therapy, particularly if the most recent tumor assessment was more than 4 weeks prior to the start of local therapy. If progression per RECIST v1.1 is identified on any tumor assessments prior to the initiation of palliative local therapy, then

participants must either discontinue the study intervention or meet criteria to continue treatment beyond progression (Section 8.1.1) in order to resume immunotherapy after palliative local therapy.

The potential for overlapping toxicities with radiotherapy and the study interventions is not known. As concurrent radiotherapy and the regimens evaluated in this study have not been formally evaluated, whenever palliative radiotherapy is required for a tumor lesion, then treatment should be withheld for at least 1 week before, during, and 1 week after radiation if medically feasible. Participants should be closely monitored for any potential toxicity during and after receiving radiotherapy and AEs should resolve to Grade ≤ 1 prior to resuming treatment.

7.8 Continued Access to Study Intervention 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 Intervention

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

- [redacted]

- [redacted]

Study treatment must be permanently discontinued per criteria in [redacted] Section 7.4. Discontinue nivolumab and/or ipilimumab for any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the participant with continued nivolumab dosing and/or ipilimumab.

Part 1 (BMS-986408 Monotherapy):

[redacted]

Parts 2 and 3:

[redacted]

All Study Parts:

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

All participants who discontinue study intervention 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 intervention 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 per local regulatory requirements in each region/country and entered on the appropriate CRF page.

8.1.1 Treatment Beyond Disease Progression

Accumulating evidence indicates a minority of participants treated with immunotherapy may derive clinical benefit despite initial evidence of progressive disease.[28]

Participants treated with study treatment will be permitted to continue all components of study treatment beyond initial RECIST v1.1 defined progressive disease, assessed by the Investigator up to a maximum of 24 months from date of first dose as long as they meet the following criteria:

- Investigator-assessed clinical benefit.
- Tolerance of study treatment.
- Stable performance status.
- Participant provides written informed consent prior to receiving additional treatment. All other elements of the main consent including description of reasonably foreseeable risks or discomforts, or other alternative treatment options will still apply.

Treatment beyond progression may be administered during or after localized interventions (surgery/radiation therapy).

Continue radiographic assessment/scan(s) in accordance with the Section 2 Schedule of Activities for the duration of the treatment beyond progression and submit to the central imaging vendor. Balance the assessment of clinical benefit with clinical judgment as to whether the participant is clinically deteriorating and unlikely to receive any benefit from continued treatment with the study intervention.

For the participants who continue the study therapy beyond progression, further progression is defined as an additional 10% increase in tumor burden with a minimum 5 mm absolute increase from time of initial progressive disease. This includes an increase in the sum of diameters of all target lesions and/or the diameters of new measurable lesions compared to the time of initial progressive disease. Upon documentation of further progression, permanently discontinue treatment unless the clinical judgement of the Investigator is that continuing the treatment is in the participant's best interest.

New lesions are considered measurable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). Any new lesion considered non-measurable at the time of initial progression may become measurable and therefore included in the tumor burden if the longest diameter increases to at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). In situations where the relative increase in total tumor burden by 10% is solely due to inclusion of new lesions which become measurable, these new lesions must demonstrate an absolute increase of at least 5 mm.

The assessment of clinical benefit should take into account whether the participant is clinically deteriorating and unlikely to receive further benefit from continued treatment. If the Investigator believes that the participant continues to achieve clinical benefit by continuing treatment with the study treatments, then the participant should remain on the trial and continue to receive monitoring

according to the Schedule of Activities (see Section 2). All decisions to continue treatment beyond initial progression must be discussed with and agreed upon by the BMS Medical Monitor (or designee) prior to treatment beyond progression, and an assessment of the benefit-risk of continuing with study therapy must be documented in the study records (see Appendix 2).

8.1.2 Post-study Intervention Study Follow-up

In this study, safety and efficacy are key endpoints of the study. Post-study follow-up is of critical importance and is essential to preserving participant safety and the integrity of the study. Participants who discontinue study intervention must continue to be followed (in this study or a rollover study) for collection of outcome and/or survival follow-up data as required and in line with Section 5 until death or the conclusion of the study.

8.2 Discontinuation From the Study

Participants who request to discontinue study intervention 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.
- 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 intervention 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.

8.2.1 Individual Discontinuation Criteria

- A participant may withdraw completely from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon. Stopping study intervention is not considered withdrawal from the study.
- At the time of discontinuing from the study, if possible, an early termination visit should be conducted, as shown in the Schedule of Activities. See the Schedule of Activities (Section 2) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- 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

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- 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 (3)** documented phone calls, faxes, or emails, as well as lack of response by participant to one (1) 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 the 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 the 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.

8.4 Study Stopping Criteria

Systematic review of SAEs experienced through the duration of therapy will serve as a key basis for pausing or prematurely stopping the study. Review of these SAEs, and any decision to stop enrollment or terminate the study, will be determined by the Sponsor in collaboration with the investigators regarding possible study continuation, adjustment of the dose/schedule, health authority consultation, and study termination.

During Parts 1 and 2, stopping rules based on [redacted] will be used to continuously monitor for excess toxicity, defined as the occurrence of AEs during any cycle that would fulfill the DLT criteria or AEs leading to dose reduction or treatment discontinuation.

The Sponsor and investigators will convene regularly to review all the available safety, PK, PD and efficacy data and the results of [redacted] and in the event of any of the following occurrences:

- [redacted].
- Unanticipated SAEs that are related to study treatment are reported.
- Death attributable to study treatment is reported.

- The Sponsor or IRB/IEC decides that subject safety may be compromised by continuing the study.

Decisions to stop the enrollment or terminate the study will be communicated promptly to investigators, to the IRBs/IECs, Institutional Biosafety Committees, if applicable, and to the appropriate regulatory authorities.

9 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the Schedule of Activities.
- Protocol waivers or exemptions are not allowed.
- All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.
- Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before study treatment assignment. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before 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.
- Evaluate participant immediately to rule out cardiac or pulmonary toxicity if participant shows cardiac or pulmonary-related signs (hypoxia, abnormal heart rate, or changes from baseline) or symptoms (eg, dyspnea, cough, chest pain, fatigue, palpitations).
- Some of the assessments referred to in this section may not be captured as data in the electronic case report form (eCRF). They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.
- Perform additional measures, including non-study required laboratory tests, as clinically indicated or to comply with local regulations. Laboratory toxicities (eg, suspected drug induced liver enzyme evaluations) will be monitored during the follow-up phase via on-site/local laboratory assessments until all study drug-related toxicities resolve, return to baseline, or are deemed irreversible.

9.1 Efficacy Assessments

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

Section 9.1.1. Imaging should continue until disease progression or discontinuation of all study treatment, whichever occurs later.

Efficacy assessments for the anti-tumor activity of BMS-986408, alone and in combination with nivolumab or with nivolumab and ipilimumab, will be based on tumor measurements using RECIST v1.1 with CT and/or MRI, as appropriate, at baseline, and during the treatment period.

For all study parts, tumor assessments will occur every 8 weeks (Q8W; ± 7 days) for the first 48 weeks of study treatment, then every 12 weeks (± 7 days) until disease progression or discontinuation of all study treatment, whichever occurs later.

During Follow-up for all groups, participants will continue to have imaging assessments completed every 12 weeks (± 7 days) until withdrawal of consent, death, or initiation of another anti-cancer treatment, whichever occurs first, for up to 2 years from the date of EOT.

Only data for the procedures and assessments specified in this protocol should be submitted to the Sponsor or designee on a CRF. Additional procedures and assessments may be performed as part of standard of care. However, data for these assessments should remain in the participant's medical record and should not be provided to the Sponsor or designee, unless specifically requested from BMS or designee.

9.1.1 Efficacy Assessment for the Study

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

If a participant has a contraindication for CT IV contrast, then a non-contrast CT of the chest and a contrast-enhanced MRI of the abdomen, pelvis, and other known/suspected sites of disease should be obtained.

If a participant has a contraindication for both MRI and CT IV contrasts, then 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.

If a participant has a contraindication for MRI (eg, incompatible pacemaker) in addition to contraindication to CT IV contrast, then a non-contrast CT of the chest, abdomen, pelvis, and other known/suspected sites of disease is acceptable.

Use of CT component of a PET-CT scanner: Combined modality scanning, such as with positron emission tomography (PET)-CT, is increasingly used in clinical care and is a modality/technology that is in rapid evolution; therefore, the recommendations outlined here may

change rather quickly with time. At present, low-dose or attenuation correction CT portions of a combined PET-CT are of limited use in anatomically based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast-enhanced CT scans for anatomically based RECIST v1.1 measurements. However, if a site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the PET-CT can be used for RECIST v1.1 measurements. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

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

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

MRI of the brain (without and with contrast) should be acquired as outlined in Section 2 (Schedule of Activities). CT of the brain (without and with contrast) can be performed if MRI is contraindicated.

9.1.1.1 Imaging and Clinical Assessment

Tumor assessments should continue on the protocol defined imaging schedule regardless if dosing is delayed or discontinued. Changes in tumor measurements and tumor responses will be assessed by the same investigator or designee using RECIST v1.1 criteria. Investigators will report the number and size of new lesions that appear while on study. The time point of tumor assessments will be reported on the electronic case report form (eCRF) based on the Investigator's assessment using RECIST v1.1 criteria (see Appendix 5 for specifics of RECIST v1.1 criteria to be used in this study). Assessments of partial response and complete response must be confirmed at least 4 weeks (28 days) after initial response. See Appendix 5, Section 5.3.3 for determination of best overall response.

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, or a surrogate).

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

Use CTCAE v5 definitions and grading for safety reporting of all AEs and SAEs on the CRF.

IMAEs are AEs consistent with an immune-mediated mechanism or immune-mediated component for which non-inflammatory etiologies (eg, infection or tumor progression) have been ruled out.

IMAEs can include events with an alternate etiology which were exacerbated by the induction of autoimmunity. Information supporting the assessment will be collected on the participant's CRF.

Refer to Appendix 3 for SAE reporting. Refer to the eCRF instructions for additional guidance regarding the capture of an AE or SAE within the database.

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

All SAEs and AEs, including those associated with SARS-CoV-2 infection, must be collected from the time of signing the consent, including those thought to be associated with protocol-specified procedures, and within [redacted] following discontinuation for Part 1 monotherapy or within [redacted] following discontinuation of dosing for Parts 2 and 3 combinations.

The Investigator must report any SAE that occurs after these time periods and that is believed to be related to study intervention or protocol-specified procedure (eg, a tumor biopsy).

- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the appropriate section of the CRF module.
- 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 or designee within 24 hours of updated information being available.

Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event reasonably related to the study intervention 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.

For participants assigned to treatment and never treated with study drug, collect SAEs for [redacted] from the date of treatment assignment.

The collection of non-serious AEs (with the exception of non-serious AEs related to SARS-CoV-2 infection) should begin at initiation of study treatment. Collect all non-serious AEs (not only those deemed to be treatment-related) continuously during the treatment period and for a minimum of [redacted] (Part 1) or [redacted] (Parts 2 and 3) following discontinuation of study treatment.

9.2.2 Method of Detecting AEs and SAEs

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

Every AE must be assessed by the Investigator with regard to whether it is considered immune-mediated. For events which are potentially immune-mediated, additional information will be collected on the participant's CRF.

9.2.3 Follow-up of AEs and SAEs

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

All SAEs will be [redacted] (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 toward the safety of participants and the safety of a product under clinical investigation are met.
- An investigator who receives an investigator safety report describing SAEs or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

The Sponsor or designee must report AEs to regulatory authorities and ethics committees according to local applicable laws and regulations. A SUSAR (suspected, unexpected serious adverse reaction) is a subset of SAEs and must be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

9.2.5 Pregnancy

If, following initiation of the study intervention, it is subsequently discovered that a participant is pregnant or may have been pregnant at the time of study exposure, [redacted], the Investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to the BMS designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Appendix 3.

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

Not applicable for women not of childbearing potential - Protocol-required procedures for study discontinuation and follow-up must be performed on the participant.

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.

If any sexual activity involving penile intercourse (eg, vaginal, anal, oral) has occurred between a male participant and a pregnant partner(s) without the use of a condom [redacted] the information should be reported to the Sponsor or designee, even if the male participant has undergone a successful vasectomy.

9.2.6 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE eCRF, 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 intervention 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 vs low hemoglobin value).

9.2.7 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 (p-DILI) event. All occurrences of p-DILIs meeting the defined criteria must be reported as SAEs (see Section 9.2 and Appendix 3 for reporting details).

Potential DILI is defined as:

- AT (ALT or AST) elevation > 3× upper limit of normal (ULN)
  AND
- Total bilirubin > 2× ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase [ALP])
  AND
- 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.

The key responsibilities for Investigators during p-DILI assessment include: (i) early detection, medical evaluation (including the exclusion of other potential causes), and rapid laboratory confirmation of liver-related abnormalities; and (ii) BMS notification of p-DILI cases via SAE forms. Following the gathering and assessment of relevant clinical information, BMS is responsible for: (i) timely evaluation and triaging of p-DILI cases; (ii) expedited reporting of p-DILI cases; and (iii) expanded review of p-DILI cases including a detailed assessment of all available clinical information, investigations, and biochemical data.

Investigators are expected to monitor ongoing routine and ad hoc hepatic laboratory test results to rapidly determine whether a participant meets p-DILI criteria. They are expected to promptly notify BMS of all p-DILI cases. p-DILI cases may be identified by abnormal liver biochemistry values, whether or not they are accompanied by liver-related signs and/or symptoms. In both cases, expedited confirmation with repeat laboratory testing should occur within 3 business days using a hepatic laboratory panel (ALT, AST, T. bili, ALP). Any participant with an abnormal hepatic laboratory panel that meets p-DILI criteria is a candidate for study treatment discontinuation. Any confirmed p-DILI events must be reported (along with a description of the clinical findings) to BMS as an SAE within 24 hours of confirmation.

An extensive clinical history, examination, and appropriate investigations should be obtained to exclude cholestatic and other apparent causes that may explain the observed abnormalities in liver function and/or hepatic signs and symptoms. Other apparent causes include, non-exhaustively and by way of example only, the following: infectious diseases (such as active hepatitis A, B, and C), congenital diseases (such as Gilbert's syndrome), neoplastic diseases, autoimmune diseases (such as primary biliary cirrhosis), and the use of concomitant hepatotoxic medications (such as antibiotics, the oral contraceptive pill, and herbal medicines). All investigations to exclude potential causes of liver function abnormalities or hepatic signs and/or symptoms should be guided by relevant factors such as the participant's age, gender, clinical history, and signs and symptoms.

9.2.8 Other Safety Considerations

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

9.3 Overdose

For this study, any dose of study treatments greater than the assigned dose within a 24-hour time period will be considered an overdose. Overdoses that meet the regulatory definition of SAE will be reported as an SAE (see Appendix 3).

In the event of an overdose, the Investigator should:

- Contact the Medical Monitor immediately
- Closely monitor the participant for AEs/SAEs and laboratory abnormalities
- Document the quantity of the excess dose as well as the duration of the overdosing in the CRF

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

9.4 Safety

Safety assessments will be based on reported AEs and the measurement results of vital signs, ECGs, physical examinations, and clinical laboratory tests. AEs will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA) and the incidence of observed AEs will be tabulated and reviewed for potential significance and clinical importance. AEs will be tabulated by system organ class, preferred term, and treatment and reviewed for potential significance and clinical importance. Clinical laboratory results will also be listed and tabulated.

AEs will be assessed continuously during the study and for a minimum of [redacted] after the last dose of BMS-986408 in the case of monotherapy. For Parts 2 and 3, AEs will be assessed continuously during the study and for a minimum of [redacted] after the last dose of nivolumab, ipilimumab, or PDCT or [redacted] after the last dose of BMS-986408 (whichever is later). Local laboratory will perform the clinical laboratory tests and will provide reference ranges for these tests. Both AEs and laboratory tests will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0.

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

9.4.1 Physical Examinations

Refer to Schedule of Activities.

9.4.2 Vital signs

Refer to Schedule of Activities.

9.4.3 Electrocardiograms

Refer to the Schedule of Activities for timing of ECG assessments for safety in Table 2-1 (Screening), Table 2-2 (Part 1), and Table 2-3 (Parts 2 and 3). The Investigators will review the 12-lead ECGs throughout the study. The corrected QTc will be applied to each ECG reading.

Refer to the schedule of specific ECG collections to analyze the effect of BMS-986408 on the QTc interval in Table 2-2 and Table 9.5-2 for all groups in Part 1. In Part 1 only, specifically on Days 1 and 15 of Cycle 1, all ECG tests will be performed in triplicate (ie, 1 ECG test equals 3 consecutive individual 12-lead ECGs performed approximately 5 minutes apart) utilizing the ECG machine supplied by the Sponsor. For Part 1, all other visits including ECGs will require a single safety ECG, which should be performed using site ECG machines.

A separate manual will include additional details and instructions.

9.4.4 Clinical Safety Laboratory Assessments

- Investigators must document their review of each laboratory safety report.
- A local laboratory will perform the analyses and will provide reference ranges for these tests. Results of clinical laboratory tests performed on Day -1 must be available prior to dosing.

- The laboratory tests that will be performed for study participants are shown in Table 9.4.4-1.
- Results of all laboratory tests required by this protocol must be provided to the Sponsor, recorded either 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.

Table 9.4.4-1: Clinical Laboratory Assessments

Hematology - CBC	
Hemoglobin	
Hematocrit	
Total leukocyte count, including differential	
Platelet count	
Activated partial thromboplastin time International normalized ratio and/or prothrombin time (at screening only)	
Chemistry	
AST ALT Total bilirubin Direct Bilirubin (reflex if total bilirubin is abnormal) ALP LDH Creatinine BUN or serum urea Glucose (fasting glucose at screening only) Lipase Amylase Total protein Troponin	Gamma-glutamyl transferase (reflex if liver function is abnormal) Albumin - screening only Sodium Magnesium Potassium Chloride Calcium Phosphorus TSH, free T3 and free T4 - screening TSH, with reflexive free T3 and free T4 if TSH is abnormal - Day 1 of each Cycle on treatment and EOT NOTE: Total T3 may be allowed if collection of free T3 is not feasible
Serology	
Hepatitis B/C, (HBsAG, HCV antibody or HCV RNA)-screening only HIV-1 and HIV-2 antibody - at screening and as mandated by local requirement	
Other Analyses	
Pregnancy test (WOCBP only: minimum sensitivity 25 IU/L or equivalent units of hCG). Serum or urine pregnancy test acceptable for eligibility and all other visits. [redacted]	
FSH screening - only required to confirm menopause in women < age 55	

Table 9.4.4-1: Clinical Laboratory Assessments

Urinalysis per Section 2
Protein
Glucose
Blood
Leukocyte esterase
Specific gravity
pH
Microscopic examination of the sediment if blood, protein, or leukocytes esterase are positive on the dipstick

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CBC, complete blood count; [redacted]; EOT, end of treatment; FSH, follicle stimulating hormone; HBsAG, hepatitis B surface antigen; hCG, human chorionic gonadotropin; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LDH, lactate dehydrogenase; [redacted]; RNA, ribonucleic acid; T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone; WOCBP, women of childbearing potential.

9.4.5 Imaging Safety Assessment

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

9.5 Pharmacokinetics

Pharmacokinetics of BMS-986408 [redacted] will be derived from plasma concentration versus time and urinary excretion data as shown in Table 9.5-1.

Plasma samples for PK assessments will be collected for all participants receiving BMS-986408, as described in Table 9.5-2 (Part 1, Groups A, B, B2, and C), Table 9.5-3 (Part 2, Groups D, F, and G, after [redacted] pH effect study period; and Part 3, Groups D2 and F2), Table 9.5-4 (Part 2, Group E), and Table 9.5-5 (Part 2, Group G, pH effect study). All on-treatment PK time points are intended to align with days on which study treatment is administered. If it is known that a dose is going to be delayed, then collect the pre-dose sample just prior to the delayed dose. However, if a pre-dose sample is collected but the dose is subsequently delayed, do not collect an additional pre-dose sample.

Blood samples should be drawn from a site other than the infusion site (ie, contralateral arm) on days of infusion for all pre-dose and end of infusion (EOI)-PK samples. Please ensure accurate documentation of the time and date of sample collection. If the infusion was interrupted, the interruption details will also be documented on the CRF. Further details of sample collection, processing, and shipment will be provided in the laboratory/procedure manual.

Urine will be collected on Cycle 1 Day 1 and Cycle 1 Day 15 in Part 1 monotherapy. The concentration of BMS-986408 [redacted] in urine will be explored. On Day 1, urine will be collected and pooled as a single block over the intervals of 0 to 6 and 6 to 24 hours post

dose. The [redacted] collected from the participant during each time interval should be recorded [redacted]. For the interval of 6 to 24 hours, participants will be asked to take the [redacted] container with them and collect all urine voided during this interval at home. They will be asked to bring the collected urine back to the site on Day 2.

[redacted] and ipilimumab (in Part 2, Group E participants) serum samples will be collected and may be used in an integrated PPK or E-R analysis along with data from other nivolumab and/or ipilimumab studies, which would be the subject of a separate report. Separate samples will be collected for PK and anti-drug antibody (ADA) assessments using validated methods.

Plasma concentrations of BMS-986408 will be measured using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. Urine concentrations of BMS-986408 will be measured using a qualified LC-MS/MS method. In addition, after the scheduled analysis of PK samples are complete, [redacted]. PK samples will be analyzed for nivolumab and ipilimumab by validated ligand-binding assays. Immunogenicity samples for nivolumab and ipilimumab will be analyzed by validated methods.

BMS-986408 PK parameters will be derived from plasma concentration-time data during BMS-986408 monotherapy, during combination treatment with nivolumab, during combination with nivolumab and chemotherapy, and during combination with nivolumab and ipilimumab. If data permit, individual participant PK parameter values as described in Table 9.5-1 will be derived by non-compartmental methods by a validated PK analysis program. Actual times will be used for the analyses. [redacted]

The PK parameters of BMS-986408 to be assessed following the first dose and at steady state administration, if data permit, include but are not limited to:

Table 9.5-1: Pharmacokinetic Parameters

Parameters to be Reported for Monotherapy Dose Escalation Cohort (Part 1, Groups A, B, and C)[a]	
Cmax	Maximum observed plasma concentration
Tmax	Time of maximum observed plasma concentration
AUC(0-T)	Area under the plasma concentration-time curve from time 0 to time of last quantifiable concentration
[redacted]	[redacted]
AUC(TAU)	Area under the concentration-time curve in 1 dosing interval
T-Halfeff	Effective terminal half life
CLT/F	Apparent total body clearance
CLR/F	Apparent renal clearance
AI	Accumulation index

Table 9.5-1: Pharmacokinetic Parameters

UR	Total amount recovered in urine
%UR	Total percent of administered dose recovered in urine over a dosing interval at steady state.
Parameters to be Reported as a Separate Listing Summary and Plot for Group D and E	
[redacted]	[redacted]
Cmax	Maximum observed plasma concentration (BMS-986408)
Nivolumab and Ipilimumab Parameters to be Reported as a Separate Listing Summary and Plot for Group D and E	
[redacted]	[redacted]
Ceoi	Observed nivolumab and ipilimumab serum concentrations at the end of infusion

[a] PK parameters will be reported as data permit.

Data may be pooled with other future studies for population PK analysis of BMS-986408, the results of which will be reported in a separate pharmacometric report.

Treatment assignments will be released to the bioanalytical laboratory in order to minimize unnecessary analysis and/or reanalysis of PK/ADA samples.

Concentration analyses for BMS-986408 in the plasma, nivolumab, and ipilimumab will be performed by validated bioanalytical method(s).

Bioanalytical samples designated for assessments (eg, immunogenicity, PK, or biomarker) from the same collection time point may be used interchangeably for analyses, if required (including, but not limited to, insufficient volume for complement assessment, to follow-up on suspected immunogenicity related AE, etc).

[redacted]

Table 9.5-2: Pharmacokinetic Sampling Schedule for Part 1, Groups A, B, B2, and C

Study Day of Sample Collection (1 Cycle = 28 days)	Event	Time Relative to BMS-986408 Dose (hr:min)	BMS-986408 PK Plasma Sample	BMS-986408 Urine Sample[a]	12-Lead Triplicate ECG[b]
Cycle 1 Day 1	Predose	0:00	X	X (0-6 h)	X
		1:00	X		X
		2:00	X		X
		4:00	X		X

Table 9.5-2: Pharmacokinetic Sampling Schedule for Part 1, Groups A, B, B2, and C

Study Day of Sample Collection (1 Cycle = 28 days)	Event	Time Relative to BMS-986408 Dose (hr:min)	BMS-986408 PK Plasma Sample	BMS-986408 Urine Sample[a]	12-Lead Triplicate ECG[b]
		6:00	X		X
Cycle 1 Day 2	Predose[c]	0:00	X	X (6-24 h)	
		4:00	X		
Cycle 1 Day 8	Predose[c]	0:00	X		
		4:00	X		
Cycle 1 Day 15	Predose[c]	0:00	X	X (0-6 h)	X
		1:00	X		X
		2:00	X		X
		4:00	X		X
		6:00	X		X
Cycle 1 Day 16	Predose[c]	0:00	X	X (6-24 h)	
Cycle 1 Day 22	Predose[c]	0:00	X		
		4:00	X		
Cycle 2 Day 1	Predose[c]	0:00	X		
Cycle 2 Day 15[d]	Predose[c]	0:00	X		
Cycle 3 Day 1	Predose[c]	0:00	X		
Cycle 3 Day 15	Predose[c]	0:00	X		
Every alternate cycle starting at Cycle 4 Day 1 up to and including EOT	Predose[c]	0:00	X		
Follow-up Period[e]					
Follow-up 30 Day			X		

Abbreviations: ECG, electrocardiogram; EOT, end of treatment; hr, hour; IV, intravenous; PK, pharmacokinetics; min, minute.

[a] Urine sample is a pooled sample for the indicated time intervals.

[b] All ECGs should be recorded after the participant has been supine for at least 5 minutes and prior to blood collections. 12-lead ECGs to be performed in triplicate (using the ECG machine supplied by the Sponsor).

[c] All pre-dose samples for BMS-986408 should be taken prior to dosing (preferably within 30 minutes). If it is known that a dose is going to be delayed, then collect the pre-dose sample just prior to delayed dose. However, if a pre-dose sample is collected but the dose is subsequently delayed, do not collect additional pre-dose sample.

[d] For participants in Group C only, C2D15 sample to be taken on the same day of on-treatment biopsy. If the on-treatment biopsy sample is delayed, then collect the C2D15 sample on the delayed biopsy sampling day.

[e] If participant discontinues study drug treatment during the sampling period, they will move to sampling at the follow-up visits.

Table 9.5-3: Pharmacokinetic and Immunogenicity Sampling Schedule for Part 2, Groups D (Combination Cohort with Nivolumab), F (Combination Cohort with Nivolumab and Chemotherapy), and G (Starting C1D1), and Part 3 Combination Expansion

Study Day of Sample Collection (1 Cycle = 28 days)	Event	Time Relative to BMS-986408 Dose (hr:min)	BMS-986408 PK plasma Sample	Nivolumab Serum PK Sample	Nivolumab Serum ADA Sample
Cycle 1 Day 1	Predose[a]	0:00	X	X	X
	EOI[b,c]	1:00	X	X	
		2:00	X		
		4:00	X		
		6:00	X		
Cycle 1 Day 2	Predose[a]	0:00	X		
Cycle 1 Day 8	Predose[a]	0:00	X		
Cycle 1 Day 15	Predose[a]	0:00	X		
Cycle 1 Day 22[d]	Predose[a]	0:00	X		
Cycle 2 Day 1	Predose[a]	0:00	X	X	X
Cycle 2 Day 15[e]	Predose[a]	0:00	X		
Every 4th cycle starting at Cycle 3 Day 1 up to and including EOT	Predose[a]	0:00	X	X	X
Follow-up Period[f]					
Follow-up 30 Day			X	X	X

Abbreviations: ADA, anti-drug antibody; C, cycle; D, day; EOI, end of infusion; EOT, end of treatment; hr, hour; IV, intravenous; min, minute; PK, pharmacokinetics.

[a] All pre-dose samples for BMS-986408 and nivolumab should be taken prior to BMS-986408 dosing (preferably within 30 minutes). If it is known that a dose is going to be delayed, then collect the pre-dose sample just prior to delayed dose. However, if a pre-dose sample is collected but the dose is subsequently delayed, do not collect an additional pre-dose sample.

[b] The EOI occurs when the entire nivolumab dose in the infusion bag is administered to the patient (after the flush is administered to clear the IV lines of the drug and to ensure delivery of the entire drug dose). Draw the EOI-PK sample within approximately 5 minutes after end of the flush. If the EOI is delayed to beyond the nominal infusion

duration (30 minutes), the collection of this sample should also be delayed accordingly. EOI samples may not be collected from the same IV access as the drug was administered.

[c] The Event label "EOI" only refers to nivolumab serum PK sample that is infused intravenously. For BMS-986408, no event label required for the 1:00 hour timepoint.

[d] Not applicable for Group F.

[e] C2D15 sample to be taken on the same day of on-treatment biopsy. If the on-treatment biopsy sample is delayed, then collect the C2D15 sample on the delayed biopsy sampling day.

[f] If participant discontinues study drug treatment during the sampling period, they will move to sampling at the follow-up visits.

Table 9.5-4: Pharmacokinetic and Immunogenicity Sampling Schedule for Part 2, Group E (Combination Cohort with Nivolumab and Ipilimumab)

Study Day of Sample Collection (1 Cycle = 28 days)	Event	Time Relative to BMS-986408 Dose (hr:min)	BMS-986408 PK plasma Sample	Nivolumab Serum PK Sample	Nivolumab Serum ADA Sample	Ipilimumab Serum PK Sample	Ipilimumab Serum ADA Sample
Cycle 1 Day 1	Predose[a]	0:00	X	X	X	X	X
		1:00	X				
	EOI[b,c]	2:00	X	X		X	
		4:00	X				
		6:00	X				
Cycle 1 Day 2	Predose[a]	0:00	X				
Cycle 1 Day 8	Predose[a]	0:00	X				
Cycle 1 Day 15	Predose[a]	0:00	X				
Cycle 1 Day 22	Predose[a]	0:00	X	X		X	
Cycle 2 Day 1	Predose[a]	0:00	X	X	X		
	EOI[b]	2:00		X			
Cycle 2 Day 15[d]	Predose[a]	0:00	X				
Cycle 3 Day 1	Predose[a]	0:00	X	X	X	X	X
	EOI[b]	2:00		X		X	
Every 4th cycle starting at Cycle 5 Day 1 up to and including EOT	Predose[a]	0:00	X	X	X	X	X

Table 9.5-4: Pharmacokinetic and Immunogenicity Sampling Schedule for Part 2, Group E (Combination Cohort with Nivolumab and Ipilimumab)

Study Day of Sample Collection (1 Cycle = 28 days)	Event	Time Relative to BMS-986408 Dose (hr:min)	BMS-986408 PK plasma Sample	Nivolumab Serum PK Sample	Nivolumab Serum ADA Sample	Ipilimumab Serum PK Sample	Ipilimumab Serum ADA Sample
Follow-up Period[e]							
Follow-up 30 Day			X	X	X	X	X

Abbreviations: ADA, anti-drug antibody; EOI, end of infusion; EOT, end of treatment; hr, hour; IV, intravenous; min, minutes; PK, pharmacokinetics.

[a] All pre-dose samples for BMS-986408 and nivolumab should be taken prior to BMS-986408 dosing (preferably within 30 minutes). If it is known that a dose is going to be delayed, then collect the pre-dose sample just prior to delayed dose. However, if a pre-dose sample is collected but the dose is subsequently delayed, do not collect additional pre-dose sample.

[b] The EOI of nivolumab and ipilimumab occurs when the entire dose of the ipilimumab in the infusion bag is administered to the participant (after the flush is administered to clear the IV lines of the drug and to ensure delivery of the entire drug dose). Draw the EOI-PK sample within approximately 5 minutes after end of the flush. If the EOI is delayed to beyond the nominal infusion duration (30 minutes), the collection of this sample should also be delayed accordingly. EOI samples may not be collected from the same IV access as the drug was administered.

[c] The Event label "EOI" only refers to nivolumab and ipilimumab that are infused intravenously. For BMS-986408, no event label required for 2:00 hour time point.

[d] C2D15 sample to be taken on the same day of on-treatment biopsy. If the on-treatment biopsy sample is delayed, then collect the C2D15 sample on the delayed biopsy sampling day.

[e] If participant discontinues study drug treatment during the sampling period, they will move to sampling at the follow-up visits.

Table 9.5-5: Pharmacokinetic Sampling Schedule for Part 2, Group G (Cycle 0 pH Effect)

Study Day of Sample Collection	Event	Time Relative to BMS-986408 Dose (hr:min)	BMS-986408 PK Plasma Sample	12-lead Triplicate ECG[a]
Cycle 0 Day 1	Predose[b]	0:00	X	X
		1:00	X	X
		2:00	X	X
		4:00	X	X
		6:00	X	X
		8:00	X	
		24:00	X	X
Cycle 0 Day 2		48:00	X	
Cycle 0 Day 3		72:00	X	
Cycle 0 Day 4		96:00	X	
Cycle 0 Day 5		120:00	X	
Cycle 1 Day 1 (Cycle 0 Day 8)	Predose[b]	168:00	See Table 9.5-3.	X
End of [redacted] Period of BMS-986408				
Additional PK sampling for cohort starting C1D1 per Table 9.5-3.				

Abbreviations: ECG, electrocardiogram; hr, hour; min, minute; PK, pharmacokinetics.

[a] All ECGs should be recorded after the participant has been supine for at least 5 minutes and prior to blood draws. 12-lead ECGs to be performed in triplicate (using the ECG machine supplied by the Sponsor).

[b] All pre-dose samples for BMS-986408 should be taken prior to dosing (preferably within 30 minutes). If it is known that a dose is going to be delayed, then collect the pre-dose sample just prior to delayed dose. However, if a pre-dose sample is collected but the dose is subsequently delayed, do not collect additional pre-dose sample.

9.6 Immunogenicity Assessments

Antibodies to nivolumab and ipilimumab will be evaluated in serum samples collected from all participants in Parts 2 and 3 (Table 9.5-3 and Table 9.5-4). Additionally, serum samples should also be collected at the final visit from participants who discontinued study intervention or were withdrawn from the study. These samples will be tested by the Sponsor/designee.

Serum samples will be screened for antibodies binding to nivolumab or ipilimumab, and the titer of confirmed positive samples will be reported. Other analyses may be performed to further characterize the immunogenicity of nivolumab or ipilimumab.

The detection and characterization of antibodies to nivolumab or ipilimumab will be performed using validated method(s) by or under the supervision of the Sponsor. All samples collected for detection of antibodies to nivolumab or ipilimumab will also be evaluated for nivolumab or ipilimumab serum concentration to enable interpretation of the antibody data. Samples may be stored for a maximum of 15 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the Sponsor to enable further analysis of immune responses to nivolumab or ipilimumab.

9.7 Genetics

Details on genetic assessments are presented in Section 9.8.

9.8 Biomarkers

Peripheral blood and tumor tissue samples will be collected in certain groups during this study at baseline and several on-treatment time points to identify pharmacodynamic markers associated with response. Additional biomarkers related to mechanism of action of BMS-986408 will be explored. The pharmacodynamic changes between baseline and on-treatment measures will also be monitored and evaluated for associations with PK data and select AEs. Samples will be collected at the times indicated in Table 9.8-1 for biomarker assessments. If biomarker samples are collected but study treatment(s) is not administered, samples will be retained. Further details of blood and tumor tissue collection and processing will be provided to the site in the laboratory manual.

Other samples may be used for research to develop methods, assays, prognostics, and/or companion diagnostics related to BMS-986408 treatment.

Table 9.8-1: Biomarker Sampling Schedule for all Participants

Study Day of Sample Collection (Cycle = 4 weeks)	Event	Time Relative to BMS-986408 Dose (hr:min)	Whole Blood: Immuno-phenotyping	Whole Blood: RNASeq	Whole Blood: TCRSeq	Tumor Biopsy: IHC, TMB/RNASeq/ TCRSeq/WES	Plasma (Soluble Analytes)
Screening						X[a]	
Cycle 1 Day 1	Predose[b]	0:00	X	X	X		X
Cycle 1 Day 8	Predose[b]	0:00	X				X
Cycle 1 Day 15	Predose[b]	0:00		X	X		
Cycle 2 Day 15	Predose[b]	0:00	X			X[a]	
Cycle 3 Day 1	Predose[b]	0:00					X
Upon Progression	EOT					X[c]	
Complete Response							X
Follow-up Period							
Follow-up Day 30							

Abbreviations: C, cycle; D, day; EOT, end of treatment; hr, hour; IHC, immunohistochemistry; min, minutes; [redacted] PD-L1, programmed death ligand 1; RNASeq, ribonucleic acid sequencing; TCRSeq, T cell receptor sequencing; TMB, tumor mutational burden; WES, whole exome sequencing.

[a] Tumor biopsy is optional for participants in Part 1, Groups A, B, and B2 and Part 3, Groups D2 and F2. During screening, tissue for PD-L1 IHC confirmation is mandatory for Part 3, Group F2, and must be submitted to central laboratory prior to treatment assignment.

[b] All pre-dose samples should be taken prior to BMS-986408 dosing (preferably within 30 minutes). If it is known that a dose is going to be delayed, then collect the pre-dose sample just prior to the delayed dose. However, if a pre-dose sample is collected but the dose is subsequently delayed, do not collect the additional pre-dose sample.

[c] EOT biopsy is optional for all participants.

9.8.1 Peripheral Biomarkers

Blood samples will be collected prior to and during treatment with BMS-986408 as monotherapy and in combination with nivolumab, nivolumab and ipilimumab, or nivolumab and chemotherapy. These blood samples may be assessed for, but not limited to, [redacted], changes in quantity, phenotype and/or functionality of immune cell subsets, changes in gene expression, presence or absence of soluble analytes, and TCR repertoire profiling.

9.8.1.1 Immunophenotyping

Pre-treatment and on-treatment whole blood samples will be analyzed to study the effects of BMS-986408 as monotherapy and in combination with nivolumab, nivolumab and ipilimumab, or nivolumab and chemotherapy on various immune cell subsets. Whole blood and/or [redacted] analyses will include, but not be limited to, monitoring the levels of regulatory T cells and detecting any change in number, phenotype, or functional status of circulating T cells and NK cells.

9.8.1.2 Peripheral Blood Gene Expression Profiling and TCR Sequencing

Total RNA and deoxyribonucleic acid (DNA) will be extracted from whole blood[redacted] obtained at time points indicated in Table 9.8-1. RNA expression may be used to identify pharmacodynamic changes caused by treatment with BMS-986408 in monotherapy or in combination with nivolumab, nivolumab and ipilimumab, or nivolumab and chemotherapy. Pharmacodynamic changes and baseline levels of genes and TCR repertoire may be explored for association with clinical outcome.

9.8.1.3 Measurement of Soluble Analytes

Plasma will be separated from whole blood at time points indicated in Table 9.8-1. Soluble analytes will be measured to assess pharmacodynamic changes and correlation with clinical outcomes following treatment with BMS-986408 alone or in combination with nivolumab, nivolumab and ipilimumab, or nivolumab and chemotherapy.

9.8.2 Tumor-based Biomarkers

Biopsy samples will be collected at screening and on-treatment from a lesion/site capable of providing sufficient tissue to characterize immune cell populations and expression of selected tumor markers during:

- Part 1, Group C and
- Part 2, Groups D, E, F, and G.

Biopsies are optional at the discretion of the investigator and/or participant in:

- Part 1, Groups A, B, and B2 and
- Part 3, Groups D2 and F2.

Tumor biopsy samples should be either core needle biopsy, surgical, excisional, or incisional; fine needle aspirates and other cytology specimens are insufficient for downstream biomarker analyses. Bone lesion biopsies are unacceptable for submission since the decalcification process is not compatible with several of the planned biomarker analyses. Pathologic confirmation by touch prep is strongly encouraged at the time of tumor biopsy to confirm adequate tissue collection and biopsy quality. Both the screening and on-treatment tumor biopsies should be preferentially collected from the same site, if feasible. On-treatment biopsies are mandated at acceptable clinical risk (as determined by the Investigator). For participants in Part 1, Group C and Part 2, a repeat biopsy at screening or on-treatment from the same or an alternative site will be required if clinically feasible (at the discretion of the Investigator), and the initial attempt was unsuccessful in obtaining adequate tissue for biomarker analysis. Only 1 repeat attempt may be performed at each time point, if clinically feasible. An unsuccessful fresh tumor biopsy at screening or on-treatment will not exclude participants from receiving or continuing study treatment. Please notify the BMS Medical Monitor if on-treatment biopsy may pose unacceptable clinical risk or if tumor at the time of on-treatment biopsy is not accessible for sampling. Institutional guidelines for the safe performance of biopsies should be followed. The screening and on-treatment biopsies will follow the same guidance methodology for sample collections, processing, and submission provided in the laboratory manual.

During screening, tissue or slides for PD-L1 IHC confirmation must be submitted to the central laboratory prior to treatment assignment for Part 3, Group F2.

9.8.2.1 Tumor Mutational Burden Assessment

DNA will be extracted from the baseline FFPE tumor tissue. Tumor mutational burden will be assessed by next generation sequencing.

9.8.2.2 Characterization of Tumor Immune Microenvironment

The number, frequency, and composition of immune infiltrates in the tumor may be assessed before and after exposure to BMS-986408 as monotherapy and in combination with nivolumab or nivolumab and ipilimumab and combination with nivolumab and chemotherapy. Formalin-fixed paraffin-embedded tissue will be assessed by methodologies including but not limited to IHC, and/or multiplex immunofluorescence.

9.8.2.3 Tumor Gene Expression Profiling and TCR Sequencing

FFPE tumor tissue may be evaluated for gene expression and TCR repertoire. Alterations in the pattern of global gene expression in tumor samples will be assessed with particular emphasis on pathways of immune function. Baseline and on-treatment TCR repertoires will be profiled and correlated to response. All samples collected will be stored and may be used for subsequent research relevant to tumor immune response.

9.9 Additional Research

This protocol will include residual sample storage for additional research.

For All sites:

Additional research is required for all study participants, except where prohibited by IRBs/ethics committees, prohibited by local laws or regulations, or academic/institutional requirements. Where one or more of these exceptions occurs, participation in the additional research should be encouraged but will not be a condition of overall study participation.

- If the IRB/ethics committees and site agree to the mandatory additional research retention and/or collection, then the study participant must agree to the mandatory additional research as a requirement for inclusion in the study.
- If optional participation is permitted and approved, then the study participants may opt out of the additional research retention and/or collection.

Additional research is intended to expand the R&D capability at Bristol-Myers Squibb and will support as yet undefined research aims that will advance our understanding of disease and options for treatment. This may also include genetic/genomic exploration aimed at exploring disease pathways, progression, and response to treatment etc.

Sample Collection and Storage

- Residual samples (see Table 9.9-1) may also be retained for additional research purposes.

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

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

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

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

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

Table 9.9-1: Residual Sample Retention for Additional Research Schedule

Sample Type	Time points for which residual samples may be retained
PK	All
ADA	All
Peripheral blood	All
Tumor Biopsy	All

Abbreviations: ADA, anti-drug antibodies; PK, pharmacokinetics.

9.10 Other Assessments

Whole blood, serum, and plasma samples will be collected at the times indicated in Table 9.8-1 for the measurement of DNA, RNA, and protein biomarkers.

[redacted] will be completed within 2 minutes (+ 3-minute window) after dosing and at 20 minutes (+ 5-minute window) after dosing per Table 2-2 and Table 2-3.

9.11 Health Economics OR Medical Resource Utilization and Health Economics

Health economics/medical resource utilization and health economics parameters will not be evaluated in this study.

10 STATISTICAL CONSIDERATIONS

10.1 Statistical Hypotheses

There is no formal primary research hypothesis for this study to be statistically tested.

10.2 Sample Size Determination

The maximum number of participants treated will be approximately [redacted]. The total sample size in Part 1 is approximately [redacted] participants, including approximately [redacted] participants for Group A dose escalation, [redacted] participants each for Groups B and B2 (if evaluated), and [redacted] participants for Group C PD cohorts. The total sample size in Part 2 is approximately [redacted] participants, with sample sizes of approximately [redacted] participants each for Groups D and E, [redacted] participants in Group F, and [redacted] participants in Group G. The total sample size in Part 3 is approximately [redacted] participants with approximately [redacted] participants for each dose level (up to [redacted] per indication (up to [redacted]. In Part 3, an additional [redacted] participants may be enrolled in a cohort pending the totality of the data available including safety and efficacy. The sample sizes for the study are determined based on the number of anticipated dose levels and the number of participants per dose level. Specifically, it is assumed that Group A has [redacted] dose levels of titration with [redacted] participant per dose level and [redacted] dose levels with [redacted] per dose level. Additionally, it is assumed that Group B and B2 have [redacted] dose levels with [redacted] participants per dose level. Finally, it is assumed that Group C, D, E, and F have [redacted] dose levels with [redacted] participants per dose level.

10.3 Analysis Sets

For the purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign informed consent (and are registered into the IRT)
Treated	All participants who received at least 1 dose of study intervention
Response-Evaluable	All participants who receive at least one dose of study intervention, have a baseline tumor assessment with measurable disease, and 1 of the following: 1) at least 1 evaluable on-treatment tumor assessment, 2) clinical progression, or 3) death prior to the first on-treatment tumor evaluation

Population	Description
Pharmacokinetic	All treated participants who have any available concentration-time data
Evaluable Pharmacokinetic	All participants who have adequate PK profiles or have at least 1 evaluable PK parameter
Immunogenicity	All participants who receive nivolumab or ipilimumab who have baseline and at least 1 post baseline measurement
Biomarker	All participants who take at least one dose of study treatment and have at least one non-missing biomarker assessment, excluding the disqualified assessments.

Abbreviations: IRT, interactive response technology; PK, pharmacokinetic.

Unless otherwise specified, the safety analyses will include all treated participants.

10.4 Statistical Analyses

10.4.1 General Considerations

The dose escalation decisions in Part 1 and Part 2 will be guided by [redacted] method. The study will start with an accelerated titration approach to limit the number of participants treated with sub-therapeutic doses in Part 1, Group A. Compared with standard designs, accelerated titration design can greatly reduce the number of undertreated participants without sacrificing safety. Once accelerated titration stops, at least [redacted] participants will be enrolled per dose level and dose escalation decisions will be guided by the [redacted] design to identify the MTD. The [redacted] design takes a very simple form, rendering it easy to implement in practice. The dose escalation and de-escalation in the [redacted] design is determined by comparing the observed DLT rate at the current dose with a pair of fixed dose escalation and de-escalation boundaries, which allows generation of a decision table that guides dose selection depending on the number of participants treated and observed DLTs. As an extension to the standard [redacted] further allows real-time dose assignment decisions while some participants' toxicity data are still pending, thus provides a practical design to accelerate early phase drug development. When there is no pending data, the [redacted] will seamlessly reduce to the [redacted] design. A [redacted] dose-escalation decision table with a selected target DLT rate of [redacted], an escalation boundary of [redacted], and de-escalation boundary of [redacted] is presented in [redacted]

Dose escalation may be stopped prior to reaching an MTD based on review of available safety, PK, and pharmacodynamic data and discussions between Sponsor and Investigators. While the [redacted] will use DLT and safety information only, clinical assessment will take into consideration of the totality of available data including PK/pharmacodynamics from all treated participants, in assigning the next dose level. The final recommended MTD/maximum administered dose/recommended Phase 2 dose will be based on the recommendation from the [redacted] and overall clinical assessment of all available safety, PK, PD, and efficacy data.

10.4.2 Primary Endpoint(s)

Primary endpoints are described in Table 10.4.2-1.

Table 10.4.2-1: Primary Endpoints

Primary Endpoint	Description	Timeframe
Incidence of DLTs, AEs, SAEs, AEs leading to discontinuation, and death.	DLT rate by dose level, frequency distribution of treated participants with AE using the worst CTC grade. Participants will only be counted (1) once at the preferred term level, (2) once at the system organ class level, and (3) once in the 'total participant' row at their worst CTC grade, regardless of system organ class or PT. Select safety summaries will be presented separately for the monotherapy treatment combination treatment.	For DLTs, until end of DLT assessment period; Others, until end of safety follow-up period.

Abbreviations: AE, adverse event; CTC, Common Terminology Criteria; DLT, dose limiting toxicity; PT, preferred term; SAE, serious adverse event.

10.4.3 Secondary Endpoint(s)

Secondary endpoints are described in Table 10.4.3-1.

Table 10.4.3-1: Secondary Endpoints

Secondary Endpoint	Description	Timeframe
Summary measures of BMS-986408 PK parameters in plasma, such as but not limited to, Cmax, Tmax, AUC(0-T) from concentration-time data during BMS-986408 monotherapy and combination treatment with nivolumab or nivolumab and ipilimumab.	Summary statistics tabulations by dose: geometric means and coefficients of variation (medians and ranges for Tmax). Scatter plots vs dose for each cycle measured; dose proportionality based on a power model and a CI around the power coefficient.	Up to the last PK sampling timepoint.
ORR and DOR per RECIST v1.1	The ORR and its corresponding 95% exact CI will be calculated by Clopper-Pearson method. Median DOR and its corresponding 95% CI will be estimated using KM product-limit method.	Up to last tumor assessments until disease progression or death.

Abbreviations: AUC(0-T), area under the concentration-time curve from time 0 to the time of the last quantifiable concentration; CI, confidence interval; Cmax, maximum concentration; DOR, duration of response; KM, Kaplan-Meier; ORR, objective response rate; PK, pharmacokinetic; RECIST, Response Evaluation Criteria in Solid Tumors; Tmax, time of maximum observed concentration.

10.4.4 Exploratory Endpoint(s)

Exploratory PK, biomarker, and efficacy analyses will be described in the statistical analysis plan finalized before final database lock.

Unless specified otherwise, all safety analyses will be performed on all treated participants.

10.4.5 Other Analyses

The PK analysis and PD analyses, if performed, will be presented separately from the main clinical study report. Frequency and percentage of participants reporting each [redacted] will be summarized by timepoint.

10.5 Interim Analyses

Interim analyses may be performed for administrative purposes or publications. No formal inferences requiring any adjustment to statistical significance level will be performed.

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12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
1L	first-line
ADA	anti-drug antibody
AE	adverse event
AIDS	acquired immune deficiency syndrome
[redacted]	[redacted]
ALP	alkaline phosphatase
ALT	alanine aminotransferase
anti-mCTLA-4 mAb	mouse anti- cytotoxic T-lymphocyte-associated protein 4 monoclonal antibody
anti-mPD-1 mAb	mouse anti-programmed cell death-1 monoclonal antibody
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC(0-T)	area under the concentration-time curve from time 0 to time of last quantifiable concentration
AUC(TAU)	area under the concentration-time curve in 1 dosing interval
AxMP	auxiliary medicinal product
BID	twice daily
BMS	Bristol-Myers Squibb
BRAF	B-type Raf proto-oncogene
BSEP	bile salt export pump
C	cycle
Cavg	average serum/plasma concentration
Cavg28	average serum/plasma concentration at Day 28
Cavgss	average serum/plasma concentration at steady-state
CD	cluster of differentiation
Ceoi	observed concentration at the end of infusion
CI	confidence interval
CL	clearance
CLss	steady-state clearance
Cmax	maximum concentration

Term	Definition
Cmin28	trough concentration at Day 28
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CPI	checkpoint inhibitor
CR	complete response
CRF	case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
[redacted]	[redacted]
CV%	% coefficient of variation
[redacted]	[redacted]
D	day
DAG	diacylglycerol
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
DGK	diacylglycerol kinase
DLT	dose-limiting toxicity
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DOR	duration of response
DRESS	drug reaction with eosinophilia and systemic symptoms
[redacted]	[redacted]
[redacted]	[redacted]
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eGFR	estimated glomerular filtration rate
[redacted]	[redacted]

Term	Definition
EOI	end of infusion
EOT	end of treatment
E-R	exposure-response
EU	European Union
FDA	Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
FIH	first-in-human
FSH	follicle-stimulating hormone
fT3	free triiodothyronine
fT4	free thyroxine
[redacted]	[redacted]
GLP	Good Laboratory Practice
[redacted]	[redacted]
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HED	human equivalent dose
HIV	human immunodeficiency virus
[redacted]	[redacted]
HNSCC	squamous cell carcinoma of the head and neck
[redacted]	[redacted]
[redacted]	[redacted]
HR	hazard ratio
IB	Investigator's Brochure
IC	inclusion criteria
ICF	informed consent form
IEC	Independent Ethics Committee
IF	interferon

Term	Definition
IgG	immunoglobulin G
IgG4	immunoglobulin G4
IHC	immunohistochemistry
IL	interleukin
IM	intramuscular
IMAE	immune-mediated adverse event
IMP	investigational medicinal product
IO	immuno-oncology
IP	investigational product
IRB	Institutional Review Board
IRT	interactive response technology
IV	intravenous
IVIG	Intravenous immune globulin
K-M	Kaplan-Meier
[redacted]	[redacted]
LDH	lactate dehydrogenase
MAP	mean arterial blood pressure
MATE	multidrug and toxin extrusion protein
[redacted]	[redacted]
[redacted]	[redacted]
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MRP	multidrug resistance-associated protein
[redacted]	[redacted]
MSS	microsatellite stable
MTD	maximum tolerated dose
[redacted]	[redacted]
NCI	National Cancer Institute
NIMP	non-investigational medicinal product
nivo	nivolumab

Term	Definition
[redacted]	[redacted]
NOEL	no-observed-effect level
NRAS	neuroblastoma ras viral oncogene homolog
NSCLC	non-small cell lung cancer
NSQ	non-squamous
NTCP	sodium taurocholate cotransporting polypeptide
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
ORR	objective response rate
OS	overall survival
[redacted]	[redacted]
PCR	polymerase chain reaction
PD	pharmacodynamic
PD-1	programmed death protein-1
PDCT	platinum-doublet chemotherapy
p-DILI	potential drug-induced liver injury
PD-L1	programmed death ligand 1
PD-L2	programmed death ligand 2
PE	physical examination
[redacted]	[redacted]
PET	positron emission tomography
PFS	progression-free survival
[redacted]	[redacted]
PK	pharmacokinetic(s)
PPI	proton pump inhibitor
PPK	population PK
Q3D	every 3 days
QD	once daily
QTc	corrected QT interval

Term	Definition
[redacted]	[redacted]
QxW	once every x weeks
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
[redacted]	[redacted]
RP2D	recommended Phase 2 dose(s)
RT-PCR	reverse transcription polymerase chain reaction,
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
[redacted]	[redacted]
SD	stable disease
SJS	Stevens-Johnson syndrome
SmPC	Summary of Product Characteristics
SMT	Safety Management Team
SOC	standard of care
STD10	severely toxic dose in 10%
SUSAR	suspected, unexpected serious adverse reaction
T. bili	total bilirubin
T3	triiodothyronine
T4	thyroxine
TCR	T cell receptor
[redacted]	[redacted]
TEN	toxic epidermal necrolysis
T-Halfeff	effective terminal half life
[redacted]	[redacted]
[redacted]	[redacted]
Tmax	time of maximum observed concentration
[redacted]	[redacted]
TSH	thyroid-stimulating hormone

Term	Definition
[redacted]	[redacted]
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information
Vss	steady-state volume of distribution
WOCBP	women of childbearing potential
WWPS	Worldwide Patient Safety

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

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

REGULATORY AND ETHICAL CONSIDERATIONS

This study will be conducted in accordance with:

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

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

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

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

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

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

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

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

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

- ICH guidelines
- United States (US) Code of Federal Regulations, Title 21, Part 50 (21CFR50)
- European Regulation 536/2014 for clinical studies
- European Medical Device Regulation 2017/745 for clinical device research
- the IRB/IEC
- all other applicable local regulations

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

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

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

- IRB/IEC
- Regulatory authority(ies), if applicable according to 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, by the local Health Authority must be sent to Bristol-Myers Squibb Company (BMS).

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

FINANCIAL DISCLOSURE

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

INFORMED CONSENT PROCESS

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

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

The investigator or his/her representative must:

- Obtain IRB/IEC written approval/favorable opinion of the written ICF and any other information to be provided to the participant prior to the beginning of the study and after any revisions are completed for new information.
- Provide a copy of the ICF and written information about the study in the language in which the participant is proficient prior to clinical study participation. The language must be nontechnical and easily understood.
- Explain the nature of the study to the participant and answer all questions regarding the study.
- Inform participant that his/her participation is voluntary. The participant will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- Allow time necessary for participant to inquire about the details of the study.
- Obtain an ICF signed and personally dated by participant and by the person who conducted the informed consent discussion.
- Include a statement in the participant's medical record that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Re-consent the participant to the most current version of the ICF(s) during his/her participation.
- Revise the ICF whenever important new information becomes available that is relevant to the participant's consent. The investigator, or a person designated by the investigator, should fully inform the participant of all pertinent aspects of the study and of any new information relevant to the participant's willingness to continue participation in the study. This communication should be documented.

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

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

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

BMS COMMITMENT TO DIVERSITY IN CLINICAL TRIALS

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

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

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

DATA PROTECTION, DATA PRIVACY, AND DATA SECURITY

BMS collects and processes personal data of study participants, patients, health care providers, and researchers for biopharmaceutical research and development to advance innovative, high-quality medicines that address the medical needs of patients. BMS ensures the privacy, protection, and confidentiality of such personal data to comply with applicable laws. To achieve these goals, BMS has internal policies that indicate measures and controls for processing personal data. BMS adheres to these standards to ensure that collection and processing of personal data are limited and proportionate to the purpose for which BMS collects such personal data. This purpose is clearly and unambiguously notified to the individual at the time of collection of personal data. In the true spirit of science, BMS is dedicated to sharing clinical trial information and data with participants, medical/research communities, the media, policy makers, and the general public. This is done in a manner that safeguards participant privacy and informed consent while respecting the integrity of national regulatory systems. Clinical trial data, health-related research, and pharmacovigilance activities on key-coded health data transferred by BMS across national borders is done in compliance with the relevant data protection laws in the country and GCP requirements.

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

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

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

- Responsibilities of IT Personnel
- Securing the BMS Digital Infrastructure
- Identity and Access Management
- External Partner Connections
- Cyber Threat Detection and Response

- Internal Cyber Incident Investigation

SOURCE DOCUMENTS

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

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

1) The investigator may need to request previous medical records or transfer records depending on the study. Also, current medical records must be available.
2) Definition of what constitutes source data and its origin can be found in the source data location list/map or equivalent document.

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

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

STUDY INTERVENTION RECORDS

Records for study intervention BMS-986408, nivolumab, and ipilimumab (whether supplied by BMS, its vendors, or the site) must substantiate study intervention integrity and traceability from receipt, preparation, administration, and through destruction or return. Records must be made available for review at the request of BMS/designee or a Health Authority.

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

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

CASE REPORT FORMS

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

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

pregnancy, which will be reported on the electronic SAE form and Pregnancy Surveillance Form, respectively. If the electronic SAE form is not available, a paper SAE form can be used.

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

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

The completed CRF and SAE/pregnancy CRFs must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a sub-investigator and who is delegated this task on the Delegation of Authority Form. Sub-investigators in Japan may not be delegated the CRF approval task. The investigator must retain a copy of the CRFs, including records of the changes and corrections.

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

MONITORING

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

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

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

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

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

RECORDS RETENTION

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

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

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

RETURN OF STUDY INTERVENTION

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

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

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

- On-site disposal practices must not expose humans to risks from the drug.

- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's standard operating procedures and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal (eg, incinerator, licensed sanitary landfill, or licensed waste-disposal vendor) must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Study Monitor to review throughout the clinical trial period.

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

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

STUDY AND SITE CLOSURE

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

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

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

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local Health Authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable

regulatory requirements. The investigator shall promptly inform the participant and should ensure appropriate participant therapy and/or follow-up.

DISSEMINATION OF CLINICAL STUDY DATA

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

In the European Union (EU), the summary of results and summary for laypersons will be submitted within 1 year of the end of trial in EU/European Economic Area and third countries.

CLINICAL STUDY REPORT

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

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

- Participant recruitment (eg, among the top quartile of enrollers)

SCIENTIFIC PUBLICATIONS

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

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

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

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

3) Final approval of the version to be published

4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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

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

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

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

ADVERSE EVENTS

Adverse Event Definition:
An adverse event (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a clinical investigation participant administered study treatment that does not necessarily have a causal relationship with this treatment.
An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study treatment, whether or not considered related to the study treatment.
Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or results from other safety assessments (eg, electrocardiograms, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Note that abnormal lab tests or other safety assessments should only be reported as AEs if the final diagnosis is not available. Once the final diagnosis is known, the reported term should be updated to be the diagnosis. • Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration, even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose, as a verbatim term (as reported by the investigator), should not be reported as an AE/serious adverse event (SAE) unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae and should specify "intentional overdose" as the verbatim term.
Events <u>NOT</u> Meeting the AE Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy); the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

DEFINITION OF SAE

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

SERIOUS ADVERSE EVENTS

A serious adverse event (SAE) is defined as any untoward medical occurrence that, at any dose:
Results in death.
Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
Requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below). NOTE: The following hospitalizations are not considered SAEs in Bristol-Myers Squibb (BMS) clinical studies: • A visit to the emergency room or other hospital department < 24 hours that does not result in admission (unless considered an important medical or life-threatening event). • Elective surgery, planned prior to signing consent. • Admissions as per protocol for a planned medical/surgical procedure. • Routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy). • Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases. • Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason). • Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols).
Results in persistent or significant disability/incapacity.
Is a congenital anomaly/birth defect.

Is an important medical event (defined as a medical event[s] that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm and blood dyscrasias or convulsions that do not result in hospitalization. Potential drug-induced liver injury (DILI) is also considered an important medical event. (See Section 9.2.7 for the definition of potential DILI.)

Pregnancy and DILI must follow the same transmission timing and processes to BMS as used for SAEs. (See Section 9.2.5 for reporting pregnancies.)

EVALUATING AES AND SAES

Assessment of Causality

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

- **Assessment of Intensity**

The investigator will make an assessment of intensity for each AE and SAE reported during the study using National Cancer Institute Common Terminology Criteria for Adverse Events v 5.0 (NCI-CTCAE v 5.0)

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

Follow-up of AEs and SAEs

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

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

All SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

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

SAE Email Address: [redacted]

SAE Facsimile Number: *Will be provided by local site monitor.*

SAE Telephone Contact (required for SAE and pregnancy reporting): *Will be provided by local site monitor.*

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

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

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP:

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

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

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

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

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

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

End of Relevant Systemic Exposure

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

METHODS OF CONTRACEPTION

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

Highly Effective Contraceptive Methods That Are <u>User Dependent</u> *Failure rate of < 1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation and/or implantation. (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol.)[b] – Oral (birth control pills) – Intravaginal (rings) – Transdermal • Combined (estrogen-and progestogen-containing) hormonal contraception must begin at least 30 days prior to initiation of study therapy.
• Progestogen-only hormonal contraception associated with inhibition of ovulation. (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol.)[b] – Oral – Injectable • Progestogen-only hormonal contraception must begin at least 30 days prior to initiation of study therapy.
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation and/or implantation. (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol.)[b] • Intrauterine device.

- Intrauterine hormone-releasing system (IUS). (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol.)[b,c]
- Bilateral tubal occlusion.

- Vasectomized partner

Having a vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

Male participants will be required to always use a latex or other synthetic condom during any sexual activity (eg, vaginal, anal, oral) with WOCBP, even if the participants have undergone a successful vasectomy or if their partner is already pregnant or breastfeeding.

- Sexual abstinence.

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

- Continuous abstinence must begin at least 30 days prior to initiation of study therapy.
- It is not necessary to use any other method of contraception when complete abstinence is elected.
- WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2.
- Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participant chooses to forego complete abstinence.
- Periodic abstinence (including, but not limited to, calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception for this study.

NOTES:

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

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

[c] IUSs are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness. For information specific to this

study regarding permissibility of hormonal contraception, refer to .Sections 6.1 INCLUSION CRITERIA and 7.7.1 PROHIBITED AND/OR RESTRICTED TREATMENTS of the protocol..

Less Than Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of > 1% per year when used consistently and correctly.*
• Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously. • Diaphragm with spermicide. • Cervical cap with spermicide. • Vaginal sponge with spermicide. • Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action. (This method of contraception cannot be used by WOCBP participants in studies where hormonal contraception is prohibited.)
Unacceptable Methods of Contraception
• Periodic abstinence (calendar, symptothermal, postovulation methods). • Withdrawal (coitus interruptus). • Spermicide only. • LAM.

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of pregnancy information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 9.2.5 and Appendix 3.

APPENDIX 5 RESPONSE EVALUATION CRITERIA IN SOLID TUMORS GUIDELINES (VERSION 1.1) WITH BMS MODIFICATIONS

1 EVALUATION OF LESIONS

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

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

2 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.

3 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.

3.1 Special considerations regarding lesion measurability

3.1.1 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.

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').

5 RESPONSE CRITERIA

5.1 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.

5.1.1 Special Notes on the Assessment of Target Lesions

5.1.1.1 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.

5.1.1.2 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.

5.1.1.3 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'.

5.2 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.

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

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

5.2.1.1 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.

5.2.1.2 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.

5.2.2 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.

5.3 Response Assessment

5.3.1 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.

5.3.2 Time Point Response

At each protocol specified time point, a response assessment occurs. Table 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 is to be used.

Table 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: 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
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.

5.3.3 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 3. 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 3: 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

Table 3: Best Overall Response (Confirmation of CR and PR Required)		
Overall Response First Time Point	**Overall Response Subsequent Time Point**	**Best Overall Response**
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE
CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, 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.

5.3.4 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.

REFERENCES

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

APPENDIX 6 EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMACE STATUS

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

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

APPENDIX 7 MANAGEMENT ALGORITHMS FOR STUDIES UNDER CTCAE VERSION 5.0

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.

Grade of Diarrhea/ Colitis (NCI CTCAE v5)	Management	Follow-up
Grade 1 Diarrhea: < 4 stools/day over baseline Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms • Educate patient to report worsening immediately If worsens: • Treat as Grade 2 or Grade 3-4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated < 24 hrs; Limiting instrumental ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to Grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recurs: • 0.5-1 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to Grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as Grade 3-4
Grade 3-4 Diarrhea (G3): ≥ 7 stools per day over baseline; IV fluids ≥24 hrs; limiting self care ADL Colitis (G3): severe abdominal pain, peritoneal signs G4: life-threatening, perforation	• Discontinue or delay I-O therapy per protocol* • 1 to 2 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication) or other immunosuppressants. • Consider testing CMV for steroid refractory colitis Note: Infliximab should not be used in cases of perforation or sepsis

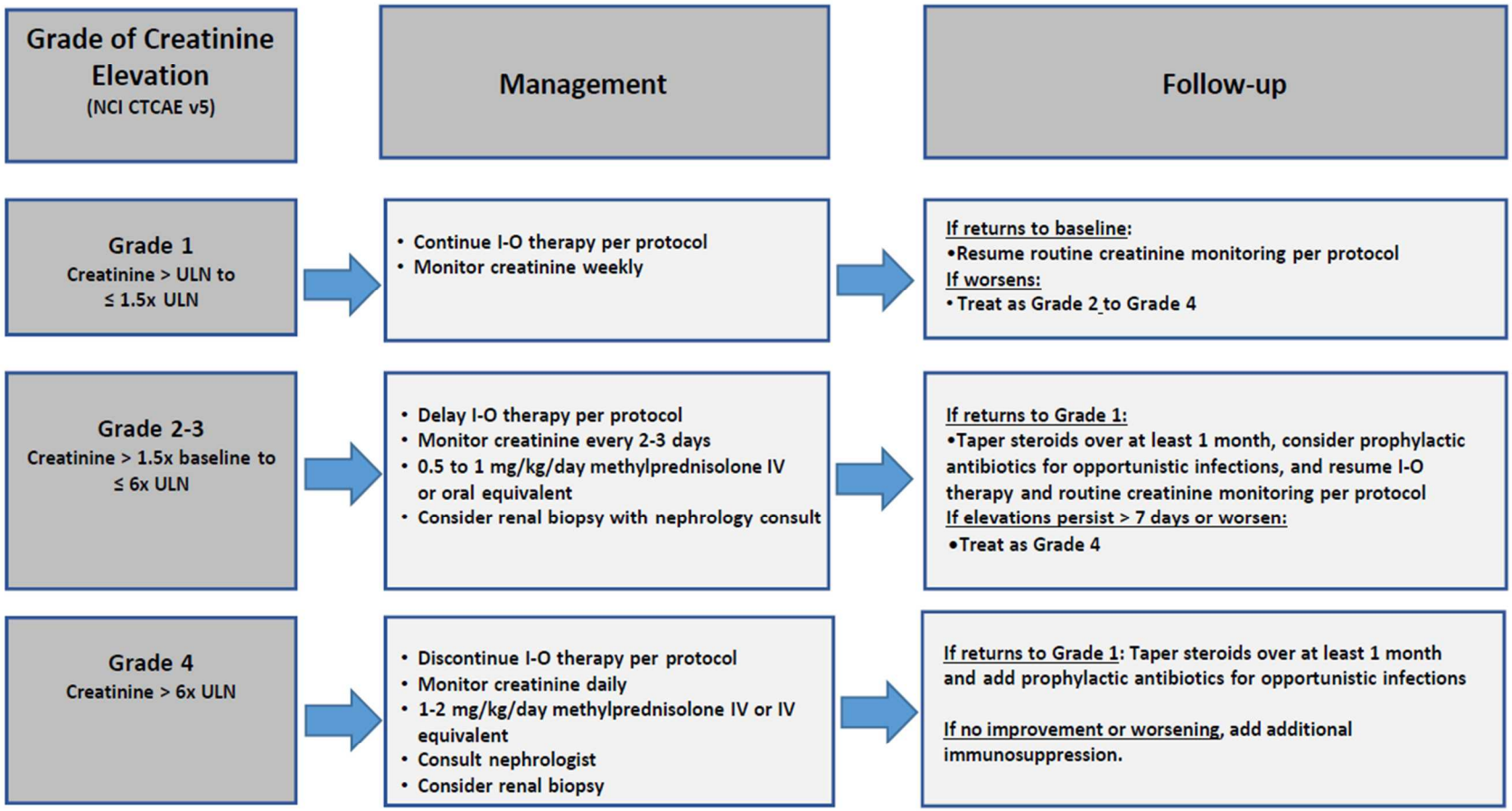
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

28-Sep-2020

Renal Adverse Event Management Algorithm

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

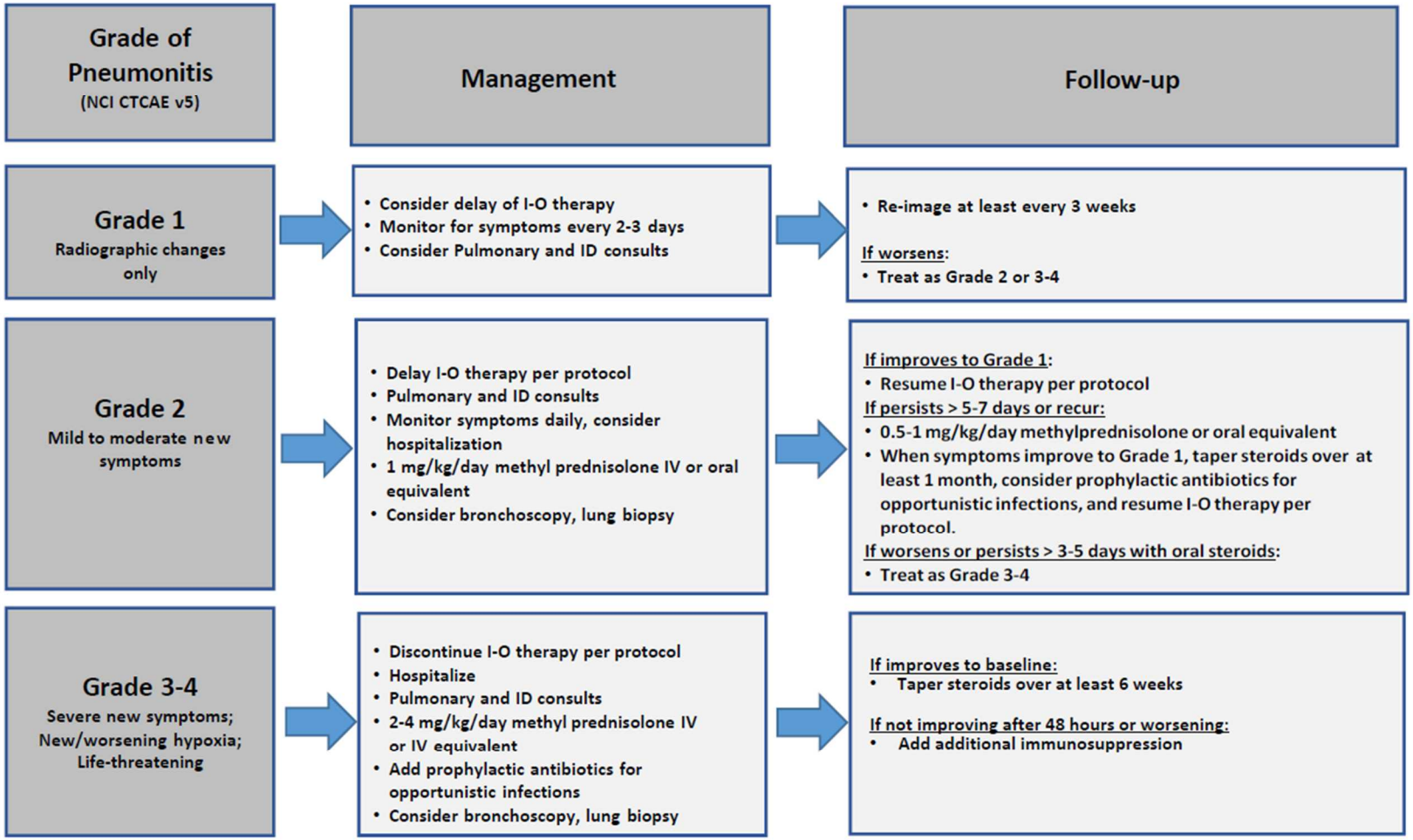


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

28-Sep-2020

Pulmonary Adverse Event Management Algorithm

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

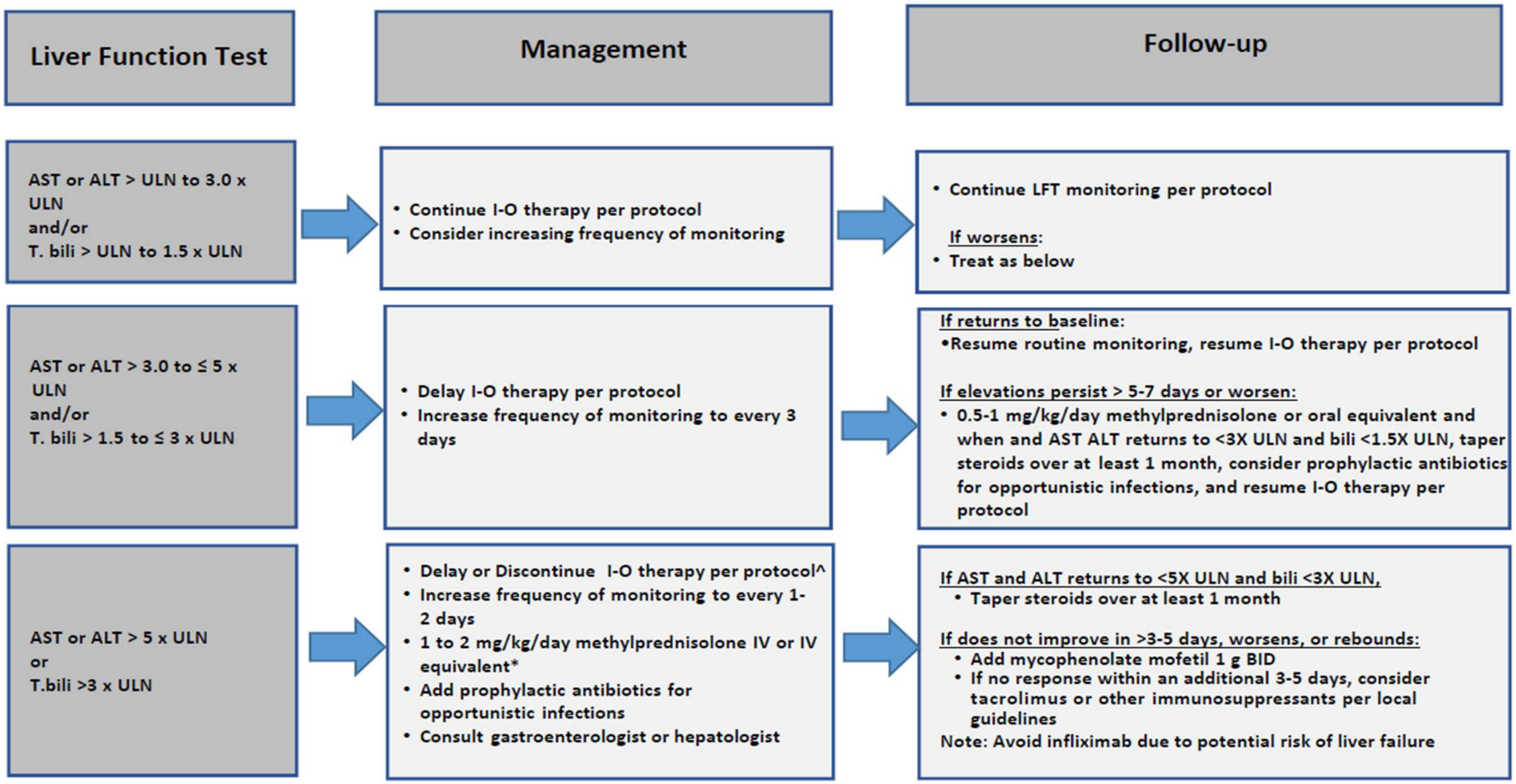


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

28-Sep-2020

Hepatic Adverse Event Management Algorithm

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

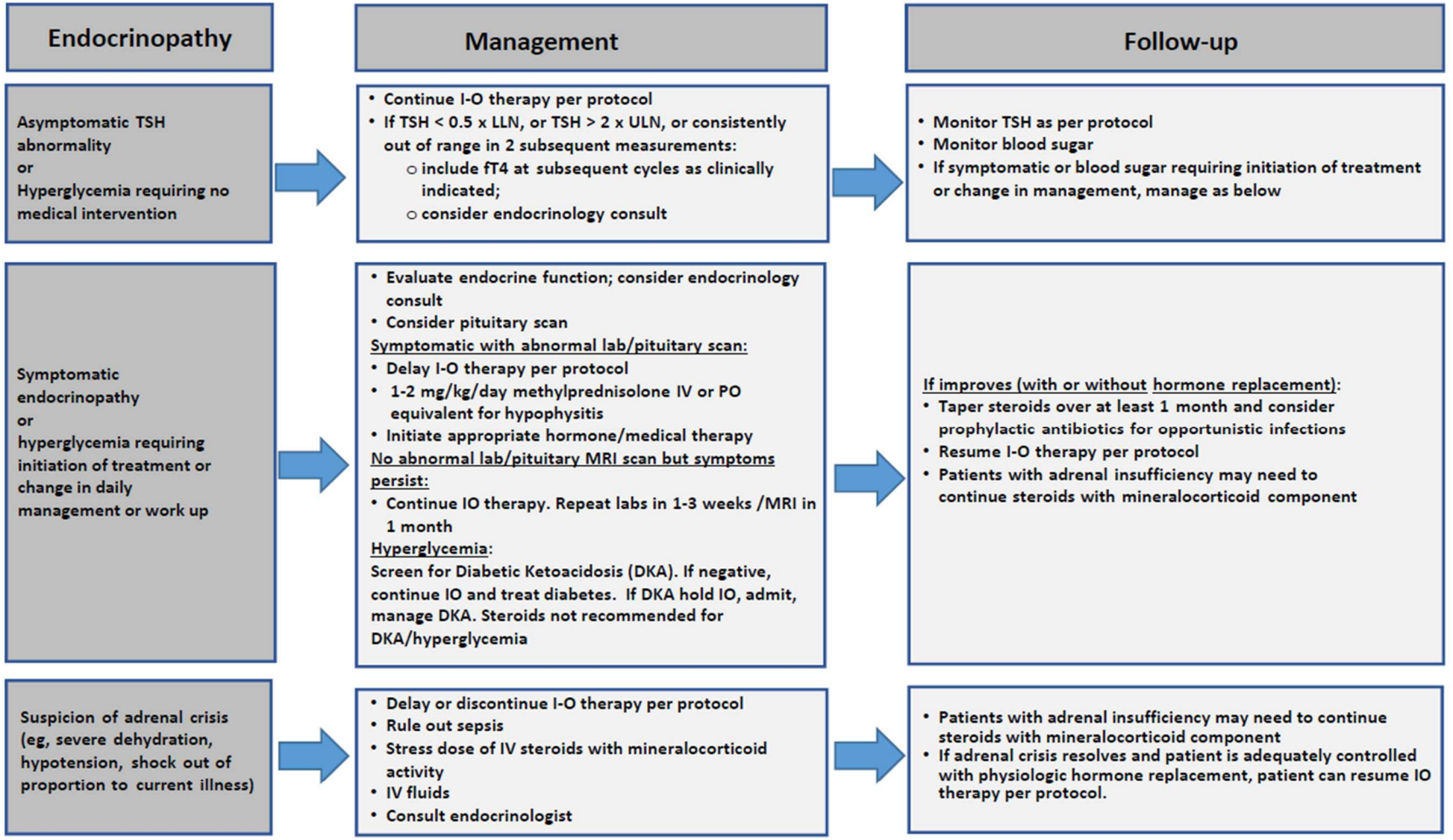


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

28-Sep-2020

Endocrinopathy Adverse Event Management Algorithm

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

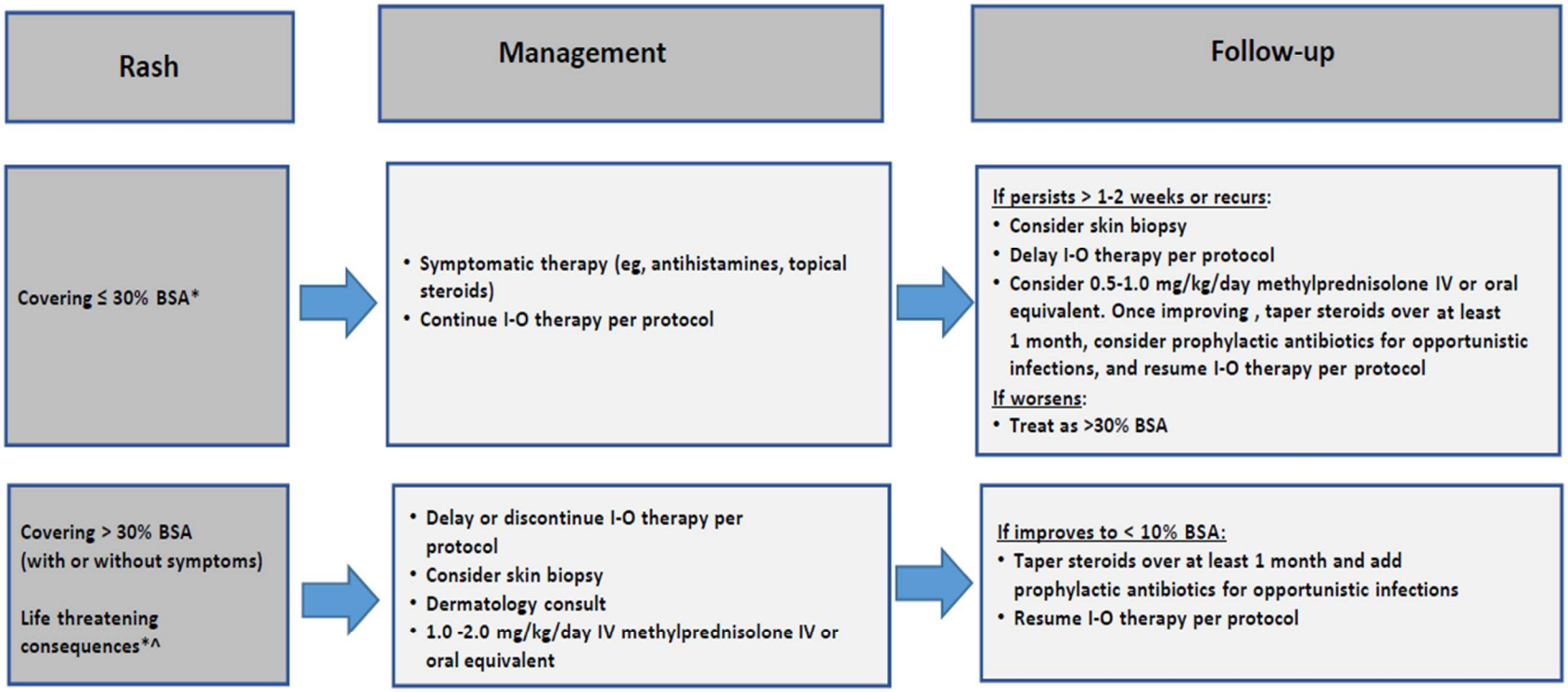


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

28-Sep-2020

Skin Adverse Event Management Algorithm

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



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

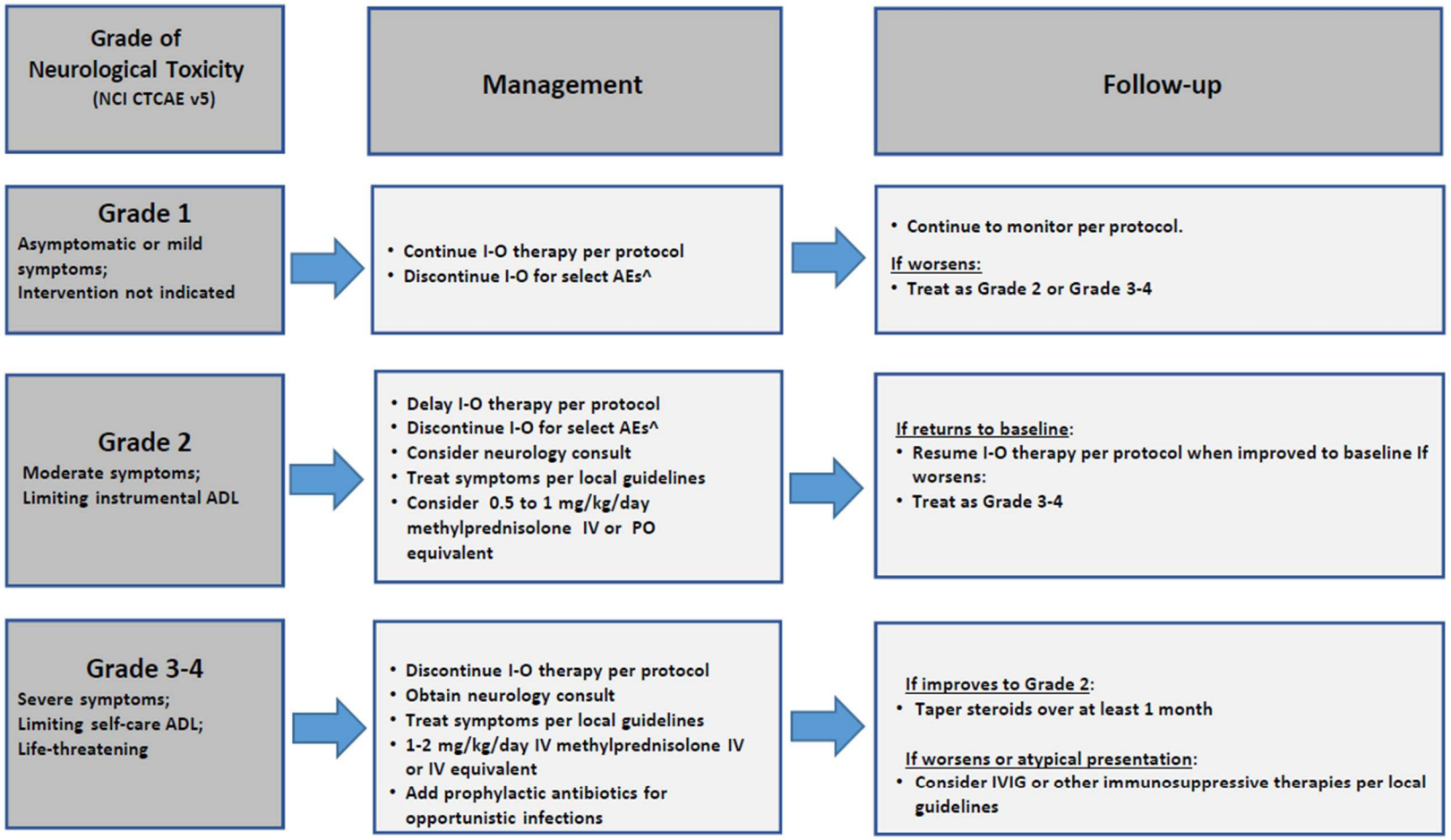
*Refer to NCI CTCAE v5 for term-specific grading criteria.

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

28-Sep-2020

Neurological Adverse Event Management Algorithm

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



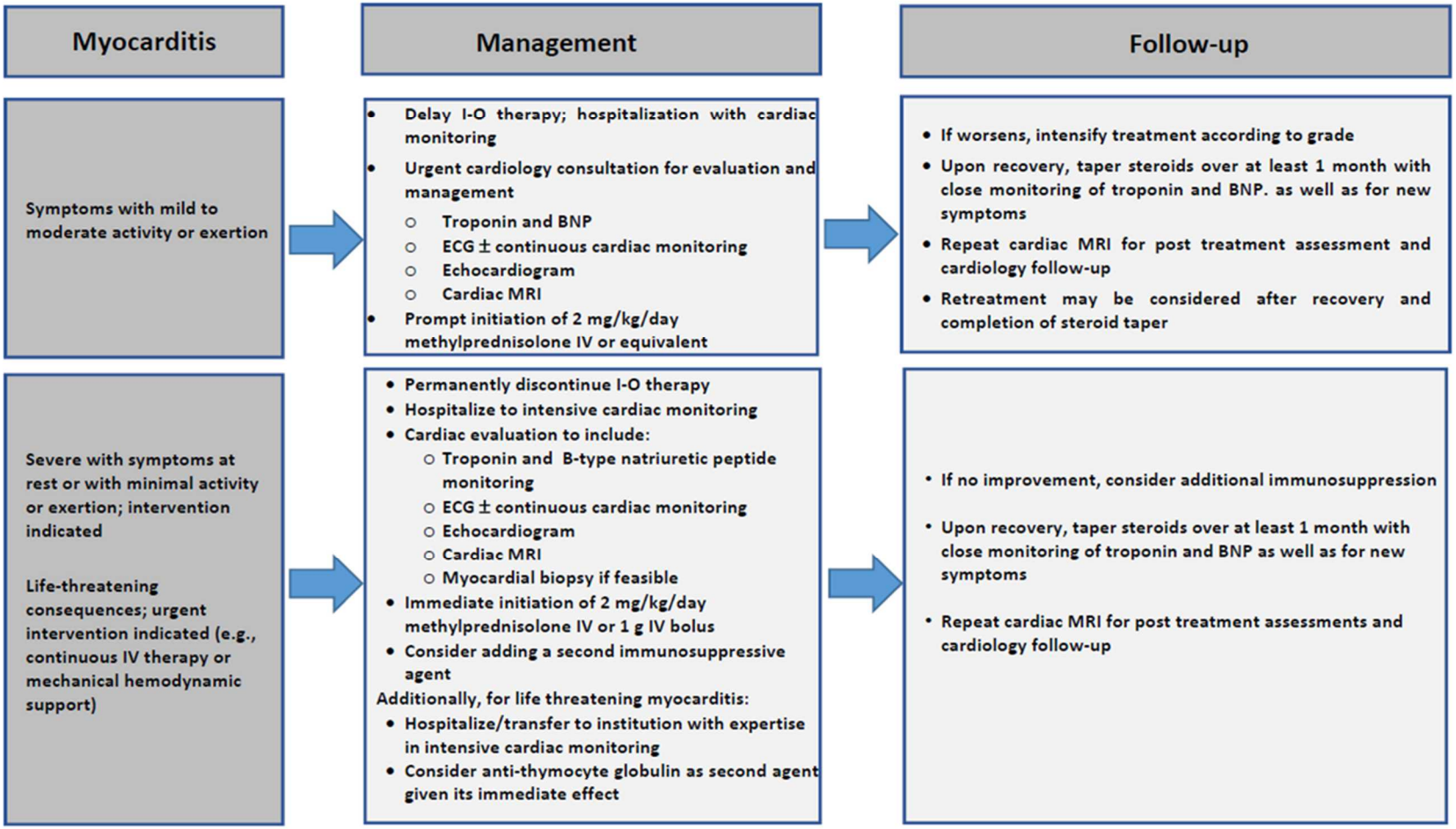
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

28-Sep-2020

Myocarditis Adverse Event Management Algorithm

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

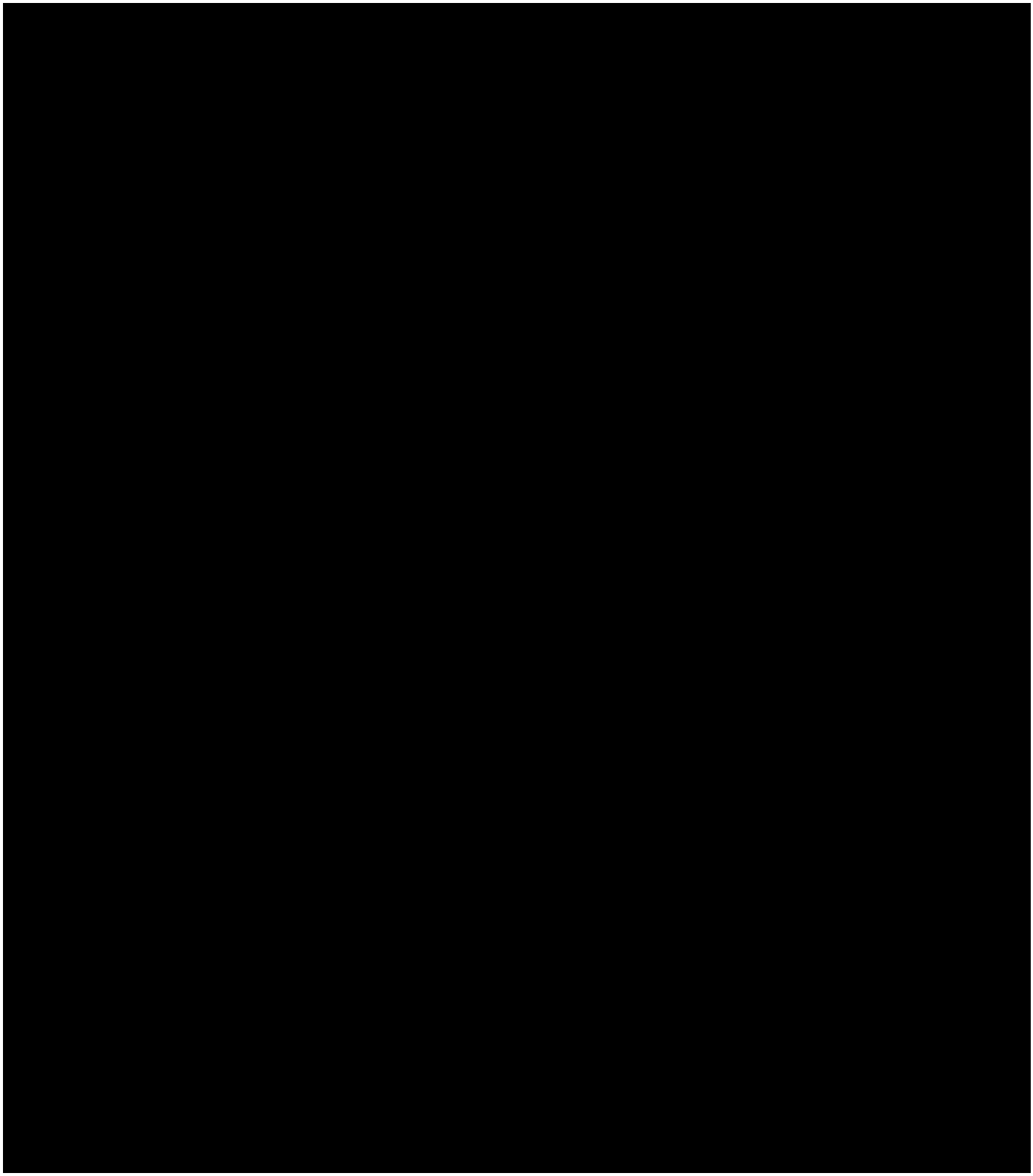


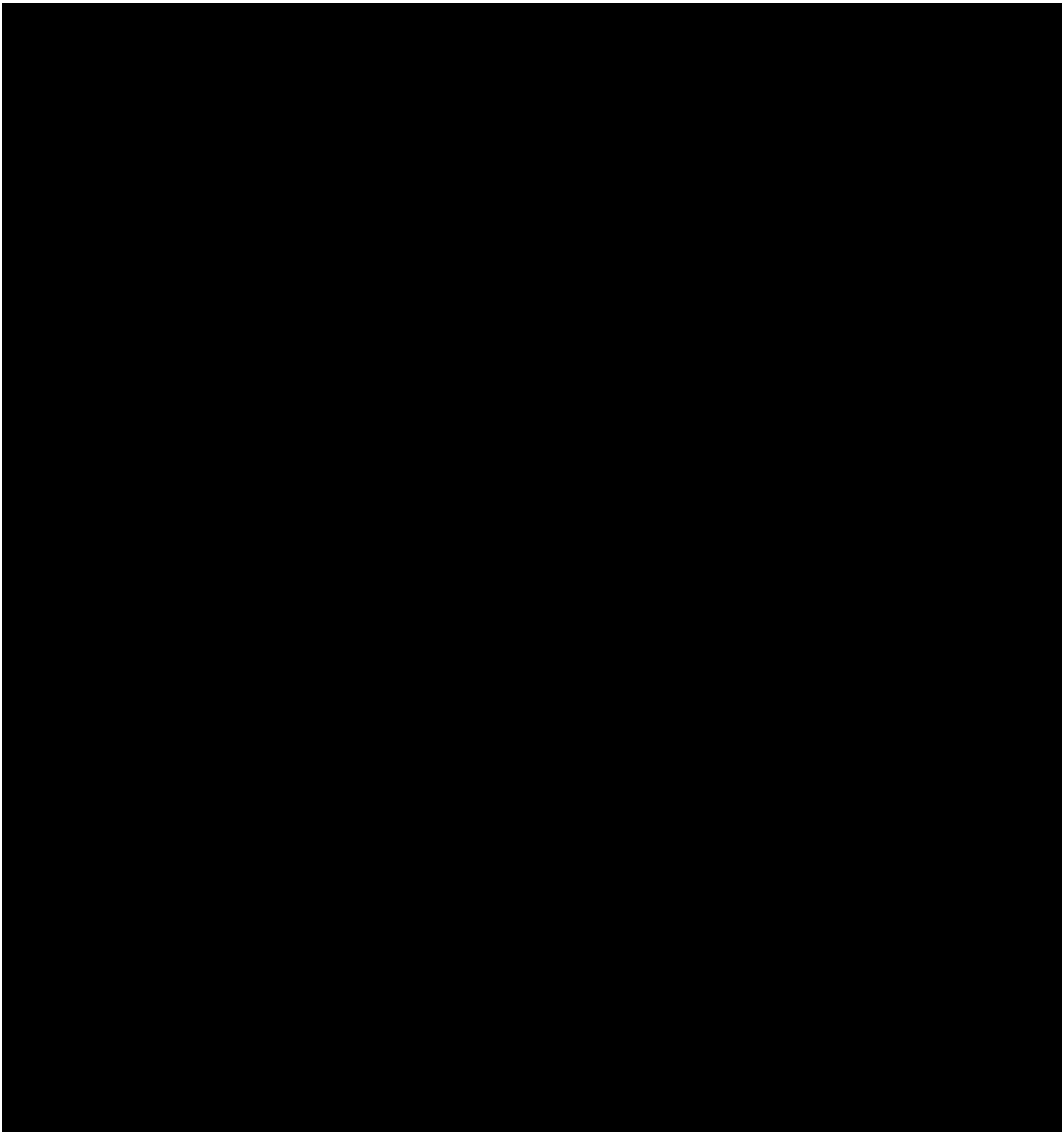
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

28-Sep-2020

[redacted]

[redacted]





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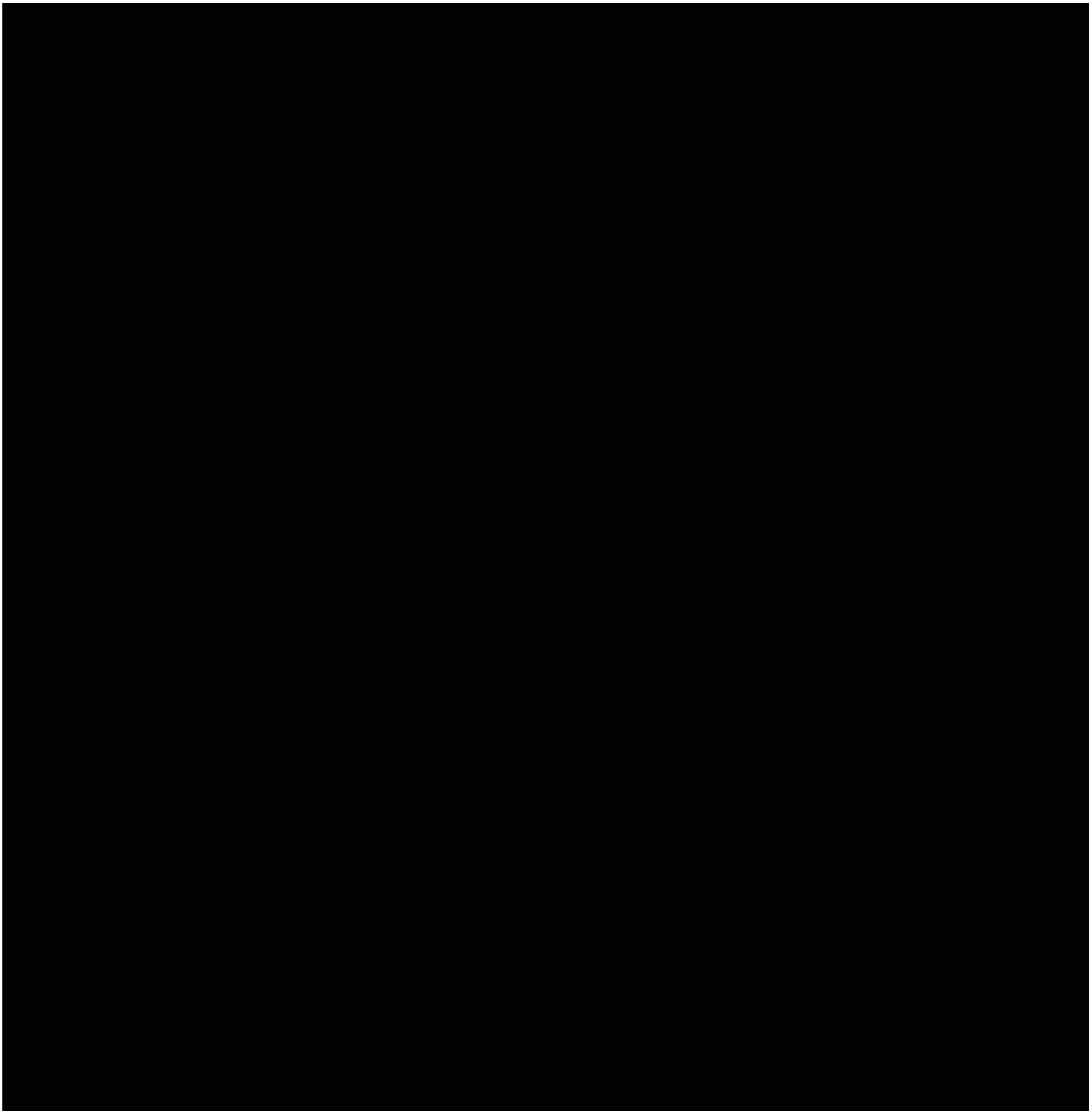

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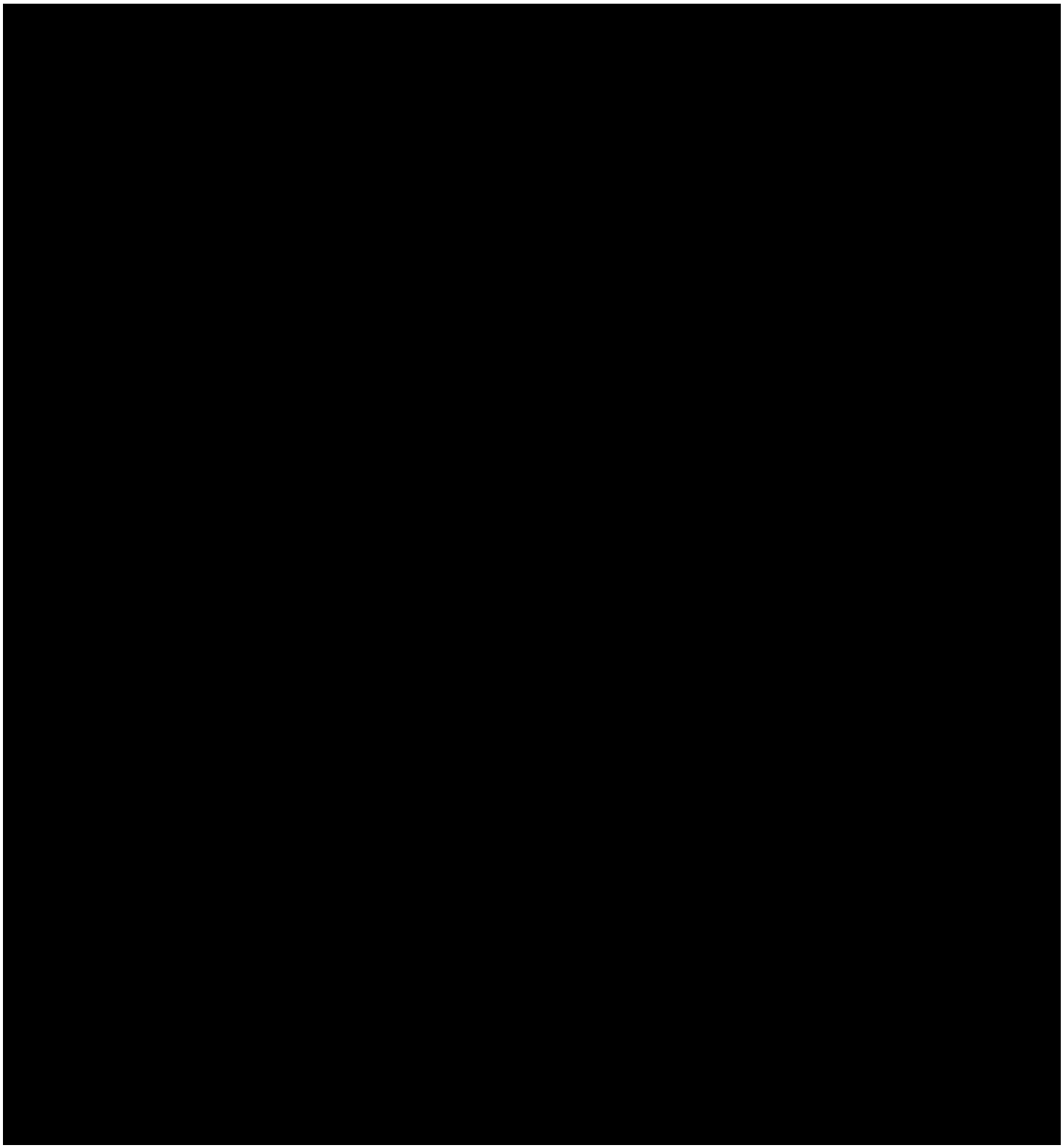
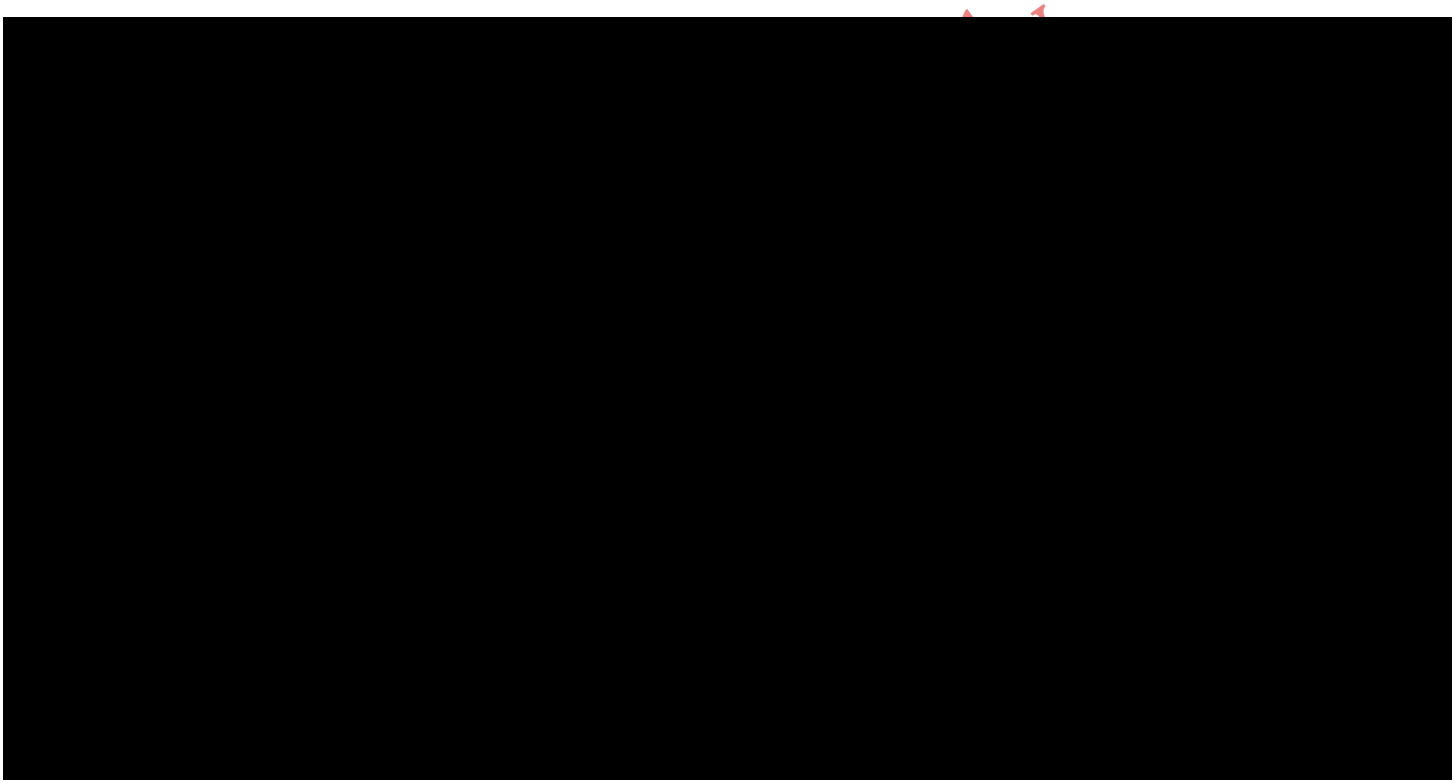




APPENDIX 13 COUNTRY- AND REGION-SPECIFIC REQUIRMENTS

Country/Region	Requirement
All countries within the European Union or European Economic Area	Persons under legal protection who require a legally authorized representative are prohibited (See Section 6.1)
France	Only persons affiliated to social security can be included (see Section 6.1)

APPENDIX 14 PROTOCOL AMENDMENT SUMMARY OF CHANGE HISTORY

Overall Rationale for Protocol Amendment 03, 21-Apr-2023

The main purpose of this amendment is to add clarification around [redacted] exclusionary criteria, update [redacted] exclusionary criteria, add guidance regarding [redacted] management, and to update the duration of contraception for males and females.

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

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 03

Section Number & Title	Description of Change	Brief Rationale
Table 2-2 On Treatment Procedural Outline (Part 1, Groups A, B, and C) Table 2-3: On Treatment Procedural Outline (Part 2, Groups D and E) Section 6.2: Exclusion Criteria	• Specified that electrocardiograms (ECGs) should be predose and prior to blood draws. • For Part 2, added ECG timepoint on Cycle 1 Day 1 at 6 hours after dosing BMS-986408. [redacted]	Updated monitoring, exclusion criteria and dose modification based on potential [redacted] prolongation.
[redacted]		
Section 6.1: Inclusion Criteria	Added cross-reference to new Appendix 13, for country- and region-specific requirements (#1a).	Clarification added that persons under legal protection in EU are prohibited.
Appendix 13: Country- and Region-specific Requirements	Added requirement for countries within the European Union or European Economic Area to prohibit inclusion of persons requiring a legally authorized representative and added requirement for France that only persons affiliated with social security can be included.	France-specific inclusion criteria regarding social security was added per [redacted] request.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 6.1: Inclusion Criteria Section 9.2.5 Pregnancy	• For female participants receiving BMS-986408, extended length of time during which donation of eggs is not allowed (#4a). • For male participants receiving BMS-986408, extended length of time for: use of condoms, refraining from sperm donation, abstaining or using a condom with pregnant/breastfeeding partners, and use of effective contraception by their female partners (#4b). • In Pregnancy section, extended the length of time for notifying BMS of pregnancy at the time of study exposure or of penile intercourse without a condom.	The current non-GLP genotoxicity package indicates that BMS-986408 is not genotoxic; however, given the potential for genotoxicity without a GLP genotoxicity package, the duration of contraception was aligned for potential genotoxicity.
Section 6.2: Exclusion Criteria	• Added details for uncontrolled hypertension (#1j[x] deleted and marked as Not Applicable; new #1j[xii] added). • Added laboratory test findings for electrolyte imbalances (#4[l]).	Clarifications.
Section 6.2: Exclusion Criteria Section 7.4.3: [redacted]	• Added exclusions for history of [redacted] (#1s) and for chronic active [redacted] • Added management of effective treatment of [redacted].	Given potential for [redacted] with immunotherapy, updated the exclusion criteria and added management guidelines.
[redacted]		
Section 7.4.4: [redacted]	For Grade 3 non-hematological toxicity, clarified “radiographic” manifestations of pancreatitis.	Clarification of dose-limiting toxicity criteria regarding increases in amylase or lipase.

Overall Rationale for Protocol Amendment 02, 02-Dec-2022

The purpose of this amendment is to remove severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) serology requirements, add language to indicate the use of 2 BMS-986408 [redacted] add an exploratory biomarker collection to be correlated with clinical outcomes, add a [redacted] for BMS-986408 when administered [redacted]. Several other changes, as noted below, were made to improve clarity and readability.

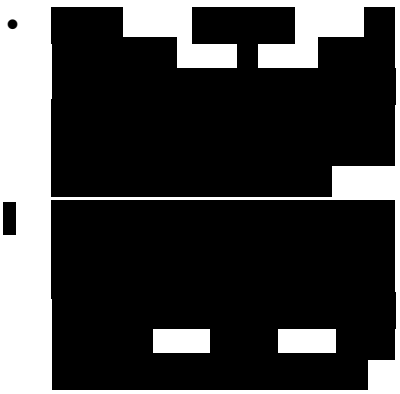
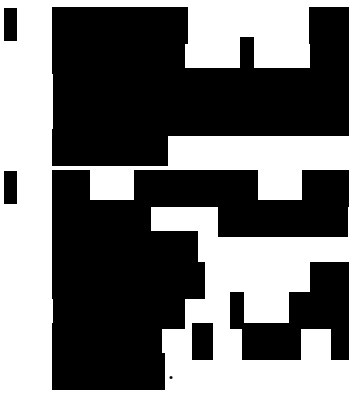
Revisions apply to future participants enrolled in the study and, where applicable, to all participants currently enrolled.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	• Updated the name and contact information for the clinical scientist. • Added EU CTR study number.	• Updated due to administrative changes.
Protocol Summary	• Updated the protocol summary to match the relevant protocol revisions.	• Updated to reflect changes in the protocol body as summarized below.
Table 2-1: Screening Procedural Outline (CA099003) Table 2-2: On Treatment Procedural Outline (Part 1, Groups A, B, and C) Table 2-3: On Treatment Procedural Outline (Part 2, Groups D and E) (Renamed) Table 2-4: Follow-up Procedural Outline (CA099003) (Renumbered) Section 3.3: Benefit/Risk Assessment Table 4-1: Objectives and Endpoints Table 9.4.4-1: Clinical Laboratory Assessments Table 9.8-1: Biomarker Sampling Schedule for Part 1, Groups A and B (Monotherapy Cohorts) Table 9.8-2: Biomarker Sampling Schedule for Part 1, Group C (Monotherapy Cohort) and Part 2, Groups D (Combination Cohort with Nivolumab) and E (Combination Cohort with Nivolumab and Ipilimumab) (Renamed) Section 9.10: Other Assessments	• Removed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) serology language.	• Based on the significant advancements in understanding SARS-CoV-2, available treatment options, including monoclonal antibodies, and effective vaccination, the collection of SARS-CoV-2 serologies are no longer warranted.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-1: Screening Procedural Outline (CA099003)	• Added [redacted] to screening visit procedures. • [redacted] • Combined all adverse events to one cell within table.	• Updated to align with the rest of the document. • [redacted] • Combined for improved clarity.
Table 2-2: On Treatment Procedural Outline (Part 1, Groups A, B, and C)	• Combined all adverse events to one cell within table. • Added collection window for clinical laboratory assessments. • Added "includes plasma and urine samples" to PK collection notes in schedule of activities for Part 1, Groups A, B, and C.	• Combined for improved clarity. • Collection window added for clinical laboratory assessments to allow for flexibility given lab turnaround time. • Added language to clarify that Part 1 monotherapy PK collections will include both plasma and urine samples.
	[redacted]	
	• Added BMS-986408 [redacted] and Cycle 3 Day 1, under new table subsection Other Assessments.	• The palatability of BMS-986408 administered [redacted] will be assessed. Results will be summarized by timepoint.
Table 2-2: On Treatment Procedural Outline (Part 1, Groups A, B, and C) Table 2-3: On Treatment Procedural Outline (Part 2, Groups D and E) (Renamed) Section 5.1: Overall Design [redacted] Table 7.1-1: Study Intervention(s) Administered (Renamed)	• Added language regarding BMS-986408 Formulation 1 and Formulation 2.	• Clarification that this study will include 2 BMS-986408 tablet formulations (Formulation 1 and Formulation 2) to be used throughout study conduct.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-3: On Treatment Procedural Outline (Part 2, Groups D and E) (Renamed)	• Table 2-3: On Treatment Procedural Outline (Part 2, Group D) was modified to incorporate the schedule for Part 2 Group E from Table 2-4: On Treatment Procedural Outline (Part 2, Group E). • Added Cycle 1 Day 2 visit for Part 2, Groups D and E. • Combined all adverse events to one cell within table. • Indicated that EOT biopsy is optional at the discretion of the Investigator and/or participant. [redacted] • Added collection window for clinical laboratory assessments. • Added BMS-986408 [redacted] for Cycle 1 Day 1, and Cycle 3 Day 1, under new table subsection Other Assessments.	• Tables were combined for conciseness and to increase readability. • Cycle 1 Day 2 visit was inadvertently excluded. • Updated for improved clarity. • [redacted] • Collection window added for clinical laboratory assessments to allow for flexibility given lab turnaround time. • The palatability of BMS-986408 administered [redacted] will be assessed. Results will be summarized by timepoint.
Table 4-1: Objectives and Endpoints	[redacted]	

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
	[redacted]	
Table 4-1: Objectives and Endpoints Table 9.8-2: Biomarker Sampling Schedule for Part 1, Group C (Monotherapy Cohort) and Part 2, Groups D (Combination Cohort with Nivolumab) and E (Combination Cohort with Nivolumab and Ipilimumab (Renamed) Section 9.8.1: Peripheral Biomarkers	• Added exploratory biomarker, collection of soluble analytes, for Part 1, Group C, and Part 2, Groups D and E at the following timepoints: C1D1 predose, C3D1, C5D1, and on complete response.	• Soluble analytes will be measured in Part 1, Group C, and Part 2, Groups D and E; changes in soluble analytes will be correlated with clinical outcomes and used to investigate pharmacodynamic effects.
Section 5.1: Overall Design	[redacted]	

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 5.1.2: Treatment Period	• Study treatment start language was moved from Section 7.1.2 to Section 5.1.2. • Modified language for elements captured in the participant diary via the removal of 'symptoms, concomitant medications taken for the symptoms as well as daily'.	• Language was inadvertently placed in Section 7.1.2. • Updated to align with elements captured on participant diary intake form.
Section 6.1: Inclusion Criteria	• Removed language referring to legally acceptable representative in Inclusion Criterion (IC) 1) a). • Added "CPI therapy does not have to be the most recent prior line therapy" to IC 2) e). • Added a new IC: Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1, IC 2) g).	• Legally acceptable representatives will not be utilized in this study; this language was inadvertently included. • Added for clarification. • To ensure participants' ECOG status is acceptable for enrollment into the trial.
Section 6.2: Exclusion Criteria	• Exclusion Criterion 1) j) ix) for hypertension was revised to be "not applicable per Protocol Amendment 02" and a new criterion for uncontrolled hypertension was added as exclusion criteria 1) j) x)	• Revised to align with target patient population for enrollment purposes.
Section 7.1.1: BMS-986408 Dosing	• 	

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 7.1: Study Intervention(s) for CA099003 (Renamed) Table 7.1-1: Study Intervention(s) Administered (Renamed) Appendix 2: Return of Study Intervention (Renamed) Appendix 2: Study and Site Closure (Renamed)	• Renamed table titles. • Renamed section titles.	• Renamed to be consistent with section name and protocol model document.
[redacted]		
Section 7.7.2.2: Palliative Local Therapy (New Section)	• Added language/guidance for palliative local therapy as a new section.	• Added to provide guidance for concomitant palliative local therapy.
Section 8.1.1: Treatment Beyond Disease Progression	• Updated section to refer to all study interventions.	• Language inadvertently referred to nivolumab only.
Section 9.2.3: Follow-up of AEs and SAEs	• Updated statement for following SAEs until resolution.	• Updated to align with rest of protocol language.
Table 9.4.4-1: Clinical Laboratory Assessments	• Removed hepatitis B virus "HBV" from serology assessments. • Updated thyroid-stimulating hormone (TSH) language to include “Day 1 of each cycle on treatment and EOT”. • Updated Urinalysis language to include “ per Section 2”	• Hepatitis B surface antigen (HBsAG) is a marker of HBV; HBV language was inadvertently included. • Updated for improved clarity. • Updated for improved clarity.
Section 9.5: Pharmacokinetics	• Indicated details for [redacted] to be assessed on specific day and time periods. Assessment will include concentration of BMS-986408 [redacted] within the collected [redacted] samples.	• Language added to align with rest of protocol.
Table 9.5-4: Pharmacokinetic and Immunogenicity Sampling Schedule for Part 2, Group E (Combination Cohort with Nivolumab and Ipilimumab)	• Removed ipilimumab Cycle 2 Day 1 (C2D1) end of infusion (EOI) timepoint.	• Ipilimumab should not have an EOI time point on C2D1 as dosing schedule is once every 8 weeks (Q8W).
Section 9.8: Biomarkers	• Removed “peripheral blood and tumor” specific language from collection statement.	• Removed, since tumor samples are not collected for Groups A and B.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 9.8-1: Biomarker Sampling Schedule for Part 1, Groups A and B (Monotherapy Cohorts)	• Added archival tumor tissue collection at screening within the table, and details of providing archival tumor tissue as optional, was denoted in footnote a.	• Added to align with language in Section 2 schedule of activities.
Section 9.8.1: Peripheral Biomarkers	• Indicated that blood samples may be assessed for presence or absence of soluble analytes.	• Updated to align with addition of exploratory biomarker.
Section 9.8.1.4: [redacted]	• Updated technique used for preserving [redacted] from "cryopreserved" to "flash frozen".	• Updated to align with laboratory manual.
Section 9.8.1.5: Measurement of Soluble Analytes (New Section)	• Added new section for measurement of soluble analytes in plasma.	• Soluble analytes will be measured in Part 1, Group C, and Part 2, Groups D and E; changes in soluble analytes will be correlated with clinical outcomes and used to investigate pharmacodynamic effects.
Section 9.8.2: Tumor-based Biomarkers	• Fresh biopsy collection is now optional for Part 1, Groups A and B.	• Language added to allow for flexibility regarding biopsy collection.
Table 9.8-2: Biomarker Sampling Schedule for Part 1, Group C (Monotherapy Cohort) and Part 2, Groups D (Combination Cohort with Nivolumab) and E (Combination Cohort with Nivolumab and Ipilimumab) (Renamed)	• Table 9.8.2: Biomarker Sampling Schedule for Part 1, Group C (Monotherapy cohort) and Part 2, Group D (Combination Cohort with Nivolumab) was modified to incorporate the schedule for Part 2 Group E from Table 9.8.3: Biomarker Sampling Schedule for Part 2, Group E (Combination Cohort with Nivolumab and Ipilimumab). • Renamed Table to include the Group E Combination Cohort with Nivolumab and Ipilimumab).	• Tables were combined for conciseness and to increase readability.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 9.10: Other Assessments	• Updated language to mention tissue collections in Part 1, Group C, and Part 2, Groups D and E. • Included details for [redacted] to be completed within 2 minutes and 20 minutes upon dosing on Cycle1 Day 1 and Cycle 3 Day 1 with [redacted] BMS-986408 [redacted].	• Updated for clarification. • The palatability of BMS-986408 administered [redacted] will be assessed. Results will be summarized by timepoint.
Section 10.4.1: General Considerations	• Updated details for dose escalation decisions in Part 1 and Part 2 of the study.	• Sentence revised for improved clarity.
Section 10.4.5: Other Analyses	• Added assessment technique details for participant's [redacted] reporting.	• The palatability of BMS-986408 administered [redacted] will be assessed. Results will be summarized by timepoint.
[redacted]		
All	• Minor formatting and typographical corrections.	• Minor; therefore, they have not been summarized.

Overall Rationale for Protocol Amendment 01: 25-Mar-2022

The purpose of this amendment is, [redacted] to modify dose-limiting toxicity criteria, to align the discontinuation criteria for subjects with elevations in liver function laboratory values with current FDA guidance, [redacted]. In addition, minor edits were made to the Schedule of Activities and pharmacokinetics (PK) section to more accurately reflect the planned analysis.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	Updated name and contact information for clinical trial physician.	Administrative
Section 2: Schedule of Activities	Removed pharmacodynamic blood, serum, and plasma sampling from Table 2-1 (Screening)	To align with sampling schedules in Section 9.8 Biomarkers
	[redacted]	
	Added optional biopsy collection at end of treatment in Table 2-2 (Part C), Table 2-3 (Part D), and Table 2-4 (Part E)	To align with Table 9.8-2 9 (Parts C and D) and Table 9.8-3 (Part E)
	Reversed the order in which PK sampling and ECGs should occur if multiple procedures are required at the same time point.	For operational efficiency.
Section 6.1: Inclusion Criteria	Modified IC 4 a) v) (2) first sub-bullet as follows: Original: *At least 14 days (or 5 half lives, once established, whichever is shorter)* Revised: *At least 14 days (or 5 half lives, once established)*	For consistency with language in the rest of the document.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 6.1: Inclusion Criteria	Removed 4 b) i) Modified 4 b) ii) [renumbered 4 b i)] as follows: Original: *Male participants will be required...* Revised: *Male participants, including azoospermic males, will be required...*	To remove redundancy.

[redacted]

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
	[redacted]	
[redacted]		To align with FDA guidance on evaluation [redacted]
Section 7.4.2: Criteria to Resume Treatment	Added instruction for Part 2 Group E that decisions to eliminate any component of the assigned study regiment must be discussed with and approved by the medical monitor.	To ensure appropriate discontinuation of combination study therapy.
[redacted]		

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 9.5: Pharmaco-kinetics	Made the following changes to Table 9.5-1: • Removed AUC (INF) • Replaced T-Half with T-Halfeff • Removed Vss/F • Modified definition of %UR • Added Total UR • Added footnote	Sample collection at 24 h post dose does not permit calculation of AUC (INF), T-Half, or Vss/F. Modified definition of UR and added footnote for clarity. Added Total UR for completeness of analysis.
Section 9.8: Biomarkers	Created separate columns in Table 9.8-2 and Table 9.8-3 for collection of whole blood for RNASeq and whole blood for TCRSeq	For clarity, as 2 separate samples are required.
Section 10.3: Analysis Sets	Added Evaluable PK population	For completeness of analysis.
Appendix 2: Study Governance Considerations	Added new sections on BMS Commitment to Diversity in Clinical Trials and Data Protection, Data Privacy, and Data Security	To align with BMS commitment to diversity in clinical trials and to comply with EU-CTR requirements on data protection.
All	Minor typographical or editorial corrections	Minor and therefore have not been summarized.