Official Title of Study:

A Phase 1/2 Study of BMS-986253 in Combination With Nivolumab or Nivolumab Plus Ipilimumab in Advanced Cancers

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CLINICAL PROTOCOL CA027002

A Phase 1/2 Study of BMS-986253 in Combination with Nivolumab or Nivolumab plus Ipilimumab in Advanced Cancers

Protocol Amendment Number: 07

Incorporates Administrative Letter 06

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DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Protocol Amendment 07 Global	17-May-2024	This amendment updates the primary analysis for Part 2. The population was changed from those with [redacted] to all randomized participants, given additional analysis on baseline sIL-8 data suggesting an association with tumor burden, thus decreasing the relevance of using sIL-8 as a selection biomarker. Further, to facilitate a timelier analysis, the primary endpoint was revised to objective response rate (from PFS). With these updates, the sample size was also updated. Approximately [redacted] participants ([redacted] in each treatment arm) currently enrolled in Part 2 will provide a sufficient sample size to analyze the new primary endpoint of objective response rate under a statistical framework. Additional changes to simplify assessments are included to reduce participant burden following the final analysis.
Administrative Letter 06	06-Nov-2023	Study personnel updated.
Protocol Amendment 06 Global	17-May-2023	• Adds safety information about hemophagocytic lymphohistiocytosis. • Opens enrollment in Part [redacted] to participants with mismatch repair proficient colorectal cancer. • [redacted] • Identifies recommended Phase 2 dose for Part 2 as 3600 mg every 2 weeks.
Protocol Amendment 05 Global	17-Feb-2022	Protocol Amendment 5 [redacted] Although there have been no such events to date, management guidelines for potential cytokine release syndrome (CRS) is added [redacted] Inclusion criteria were updated to clarify prior therapies required for several indications [redacted] Criteria regarding prior use of targeted therapy in participants with [redacted] melanoma is also updated to accommodate prioritization of combination immunotherapy when appropriate. Incorporates Administrative Letter 05. Appendix 6, Management Algorithms for Studies Under CTCAE Version 4.0, [redacted]
Administrative Letter 05	08-Feb-2021	The purpose of this administrative letter is to communicate the change of the Study Director/Medical Monitor and to clarify language regarding SARS-CoV-2 vaccines.
Protocol Amendment 04 Global	23-Nov-2020	Based on interim analysis of data from Part 1 (as described in BMS-986253 IB version 05, March 2020), the following study design revisions to the protocol were made: Part 1: In Part 1B, the maximum administered dose of BMS-986253 was increased from 2400 mg Q2W to 3600 mg Q2W, [redacted] Part 1C was added to assess the triplet combination of BMS-986253 plus nivolumab plus ipilumumab. Part 2: The study design was changed to a randomized, double-blind investigation of BMS-986253 plus nivolumab plus ipilimumab versus placebo plus nivolumab plus ipilimumab in advanced melanoma.

Document	Date of Issue	Summary of Change
		The treatment period was also extended from 2 years to 3 years.
Administrative Letter 04	15-Oct-2019	The purpose of this administrative letter is to clarify observation periods after BMS-986253 and nivolumab infusions.
Revised Protocol 03 Global	10-Jul-2019	The purpose of this revised protocol is to expand enrollment in Part 1 to allow further assessment of pharmacodynamic changes in the tumor microenvironment at a specific dosing regimen, if warranted. The maximum number of treated participants in Part 1 was increased from approximately [redacted] The presentation of the objectives and endpoints have been changed [redacted] Lastly, inclusion criteria for participants within Part 1 have been modified. The tumor types in Part 1 have not changed; however, modifications of the inclusion criteria define a more homogeneous population within those tumor types (restricted to participants who progressed on or within 3 months of anti-PD(L)1-based therapy) to aid in additional pharmacodynamic analysis.
Administrative Letter 03	25-Feb-2019	The purpose of this administrative letter is to clarify acceptable methods for establishing HPV status in participants with oropharyngeal squamous cell carcinoma of the head and neck (SCCHN) and clarify instructions for PK time matched ECGs.
Revised Protocol 02 Global	02-Nov-2018	The study design is being modified for participants enrolling in Part 1B to provide flexibility to explore additional dosing regimens. In addition, revision is made to clarify and amend procedures related to collection of SAEs during the Pre-Screen Period. All participants will be entered into IRT and receive a unique subject ID after signing the Pre-Screen ICF. SAEs related to the pre-screen blood draw will be collected and followed until resolution or stabilization. The inclusion criteria are also being modified to allow certain PD-(L)1 naive participants with NSCLC, RCC, SCCHN, and UCC into the study. Lastly, this revised protocol includes guidance on palliative treatments that occur during the study period.
Revised Protocol 01 Global	13-Mar-2018	Incorporates Administrative Letters 01 and 02 and the following changes: 1) expands enrollment in Part 1 to include advanced Squamous cell carcinoma of the head and Neck (SCCHN) and Urothelial cancer (UCC) participants, 2) modifies eligibility criteria for participants with NSCLC, RCC, TNBC, HCC, CRC, and 3) modifies the sampling schedule for pharmacodynamic assessment.
Administrative Letter 02	07-Feb-2018	Correction to section 6.2, exclusion criteria numbering
Administrative Letter 01	29-Jan-2018	Correction to section 6.1, inclusion criteria numbering
Original Protocol	27-Oct-2017	Not applicable

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 07

This protocol amendment updates the primary analysis for the randomized assessment in Part 2. Additional analysis on baseline serum IL-8 (sIL-8) data suggested an association with tumor burden, decreasing the relevance of using sIL-8 as a selection biomarker. Thus, the primary analysis population was changed from [redacted] to all randomized participants. To facilitate a timely analysis, the primary endpoint was further revised to objective response rate (ORR). Approximately [redacted] participants ([redacted] in each treatment arm) currently enrolled in Part 2 will provide a sufficient sample size to analyze the new primary endpoint of ORR under a statistical framework [redacted] Additionally, for Part 2, objectives and endpoints no longer considered essential for the study analysis have been reclassified as exploratory.

Additional changes are made to simplify study procedures for participants following the final analysis. These changes aim to alleviate participant and site burden and remove sample collections and study procedures that are no longer considered necessary. Assessments and procedures deemed necessary for monitoring the safety of the subjects remain unchanged.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 07

Section Number & Title	Description of Change	Brief Rationale
Title Page	Updated the clinical scientist and clinical trial physician/medical monitor information. Removed the EudraCT identifier and updated the European Union trial number.	Administrative change. The term "EudraCT" is obsolete, as it refers to the previous European legislation.
Section 1: Protocol Summary	Updated to reflect changes made in the body of the protocol.	To align with protocol updates.
Table 2-4: On-treatment Procedural Outline (Cohorts 1B4 through 1B6 - BMS-986253 Q2W and Nivolumab Q4W) Table 2-6: On-treatment Procedural Outline (Part 1C and Part 2 - BMS-986253 Q2W and Nivolumab and Ipilimumab Q3W) Table 2-7: Safety Follow-up Procedural Outline Section 5.1.5.2: Response Follow-up Period [redacted] Section 7.11: Treatment After the End of the Study	• Updated the body imaging requirements for on-treatment and follow-up visits to follow the standard of care and can stop when final analysis is completed. • Updated the electrocardiogram (ECG) requirements for Parts 1A, 1B, and 1C cohorts to be assessed by independent core laboratory until the final analysis. • Updated the requirement for treatment after the end of the study. • Updated the criteria for discontinuation from the study treatment. • Noted that images will no longer be submitted to blinded independent central review (BICR) for evaluation and pharmacokinetic (PK),	To remove unnecessary sample collections and study procedures after the final analysis is completed.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 07		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 8.1: Discontinuation from Study Treatment Section 9.1.3: Electrocardiograms Section 9.4: Efficacy Assessments Section 9.4.1: Imaging Assessment for the Study Section 9.4.2: BICR Confirmation of Progression (Part 2) Section 9.5: Pharmacokinetics and Immunogenicity Assessments Section 9.8: Biomarkers	immunogenicity, and biomarker samples will no longer be collected following final analysis.	
Table 2-6: On-treatment Procedural Outline (Part 1C and Part 2 - BMS-986253 Q2W and Nivolumab and Ipilimumab Q3W)	Added that participants with no relevant changes to ECGs at 6 months of treatment may stop subsequent routine ECGs.	To reduce participant and site burden.
Table 2-7: Safety Follow-up Procedural Outline Section 5.1.5.1: Safety Follow-up Period Section 5.1.5.2: Response Follow-up Period Section 5.1.5.3: Survival Follow-up Period Section 8.1.2: Post Treatment Follow-up [redacted]	• Removed survival follow-up visits throughout the protocol. • Removed the 60-day safety follow-up visit. • Removed the assessment of participant survival status.	To simplify the procedures to reduce participant and site burden after the final analysis.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 07

Section Number & Title	Description of Change	Brief Rationale
[redacted]		
Table 4-1: Objectives and Endpoints - Part 1	The secondary endpoint for median duration of response per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 was changed to duration of response per RECIST v1.1 per investigator.	Editorial change.
Table 4-2: Objectives and Endpoints - Part 2	Updated the primary objective for Part 2: • To compare ORR of BMS-986253 plus nivolumab plus ipilimumab with placebo plus nivolumab and ipilimumab using RECIST v1.1. The primary endpoint for Part 2 was updated to ORR based on BICR assessments per RECIST v1.1 in all randomized participants. [redacted]	The primary endpoint of Part 2 was revised to ORR in all randomized participants regardless of baseline sIL-8 level. The primary, secondary, [redacted] were updated to align with the revised endpoints of Part 2, [redacted]

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 07		
Section Number & Title	**Description of Change**	**Brief Rationale**
	[redacted]	
Section 5.1: Overall Design Figure 5.1-3: Study Design Part 2 Section 5.2: Number of Participants Section 5.4.3: Rationale for Selecting Participants Based on Serum IL-8 Section 7.4: Method of Treatment Assignment and Stratification Section 7.5.2: Part 2 Section 10.1.3: Part 2 [redacted] Table 10.3.1-2: Part 2 Efficacy Analysis Former Section 10.3.8.2: Part 2 Interim Analysis for Efficacy	Reduced the number of participants in Part 2 from approximately [redacted] updated the total number of participants and statistical considerations and analyses, and removed the requirement to enroll at least 51 participants with baseline [redacted] in Part 2. Updated the analysis plan according to the change in the primary endpoint for Part 2.	Reduced the number of participants to plan for a final analysis with the currently enrolled participants. Removed the requirement for [redacted] to allow all participants to be included for further analysis irrespective of their sIL-8 levels. The statistical considerations for Part 2 were modified per updated objectives and endpoints.
Section 7.5.2: Part 2	Added a paragraph that Sponsor and Investigators will be unblinded to treatment assignments once database lock for the final analysis is completed.	To simplify the procedures and reduce participant burden after the final analysis.
Section 9.2.4: Regulatory Reporting Requirements for SAEs Appendix 2: Study Governance Considerations	The legal framework has been updated from the European Directive 2001/20/EC to the European Regulation 536/2014.	To align with new European Union regulations.
All	Formatting and editorial corrections.	Minor; therefore, have not been summarized.

TABLE OF CONTENTS

1 PROTOCOL SUMMARY

Protocol Title: A Phase 1/2 Study of BMS-986253 in Combination with Nivolumab or Nivolumab plus Ipilimumab in Advanced Cancers

Study Phase: 1/2

Rationale:

BMS-986253 is a fully human-sequence immunoglobulin G1 kappa (IgG1κ) monoclonal antibody (mAb) directed against human interleukin-8 (IL-8). Development of BMS-986253 in cancer is supported by pre-clinical findings showing anti-IL-8 disruption of the IL-8: C-X-C chemokine receptor type 1/2 (CXCR1/2) signaling axis, which inhibits the recruitment of immunosuppressive myeloid derived suppressor cells (MDSC) to the tumor microenvironment, reduces cancer stem cell (CSC) renewal, reverses epithelial mesenchymal transition (EMT), and inhibits angiogenesis. These are all important mechanisms for cancer induced immunosuppression, recurrence, and metastasis. Moreover, emerging literature suggests a strong association between high IL-8 levels and both resistance to anti-programmed cell death (ligand) 1 (PD-[L]1) agents and overall poor survival. The present study will support the clinical development strategy for BMS-986253 as an anti-cancer agent in combination with nivolumab, or in combination with nivolumab and ipilimumab. It is hypothesized that inhibition of MDSC tumor infiltration, reduction of CSC renewal, and reversal of cancer cell EMT driven by BMS-986253 disruption of the IL-8: CXCR1/2 signaling axis will further sensitize IL-8-producing tumors to immune checkpoint blockade.

Study Population:

Participants must be at least 18 years of age and have histologic or cytologic confirmation of a solid tumor that is advanced (metastatic, recurrent, and/or unresectable) with radiographically measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, [redacted] For Parts 1A and 1B, participants must have [redacted] at baseline. For Parts 1C and 2, participants may have any baseline serum IL-8 level.

Objectives and Endpoints:

Table 1: Objectives and Endpoints - Part 1

Objectives	Endpoints
Primary	
• To characterize safety, tolerability, and DLTs, and to determine the RP2D of BMS-986253 administered in combination with nivolumab, or in combination with nivolumab and ipilimumab in participants with advanced solid tumors.	• Incidence of AEs, SAEs, AEs meeting protocol-defined DLT criteria, and AEs leading to discontinuation, death, and laboratory abnormalities.
Secondary	
• To evaluate the preliminary efficacy of BMS-986253 in combination with nivolumab in participants with advanced solid tumors using RECIST v1.1.	• ORR and DOR per RECIST v1.1 per investigator.

Table 1: Objectives and Endpoints - Part 1

Objectives	Endpoints
• To characterize the PK and immunogenicity of BMS-986253 when administered in combination with nivolumab, or in combination with nivolumab and ipilimumab in participants with advanced solid tumors.	• Summary measures of PK parameters and incidence of ADA to BMS-986253
• To assess serum IL-8 levels at baseline (ie, screening) and changes in IL-8 levels on treatment.	• Summary measures of IL-8 and change (or percent change) from baseline in IL-8 on treatment

Abbreviations: ADA, anti-drug antibody; AE, adverse event; BICR, blinded independent central review; DLT, dose-limiting toxicity; DOR, duration of response; ORR, objective response rate; PK, pharmacokinetic(s); RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended Phase 2 dose; SAE, serious adverse event.

Table 2: Objectives and Endpoints - Part 2

Objectives	Endpoints
Primary	
• To compare the ORR of BMS-986253 plus nivolumab plus ipilimumab with placebo plus nivolumab and ipilimumab using RECIST v1.1.	• ORR based on BICR assessments per RECIST v1.1 in all randomized participants.
Secondary	
• To estimate the PFS of BMS-986253 plus nivolumab plus ipilimumab and placebo plus nivolumab and ipilimumab in participants with advanced melanoma using RECIST v1.1 (regardless of baseline serum IL-8 levels).	• mPFS and PFS hazard ratio based on BICR assessments per RECIST v1.1.
• To compare the safety of BMS-986253 plus nivolumab plus ipilimumab with placebo plus nivolumab plus ipilimumab in participants with advanced melanoma.	• Incidence of AEs, SAEs, and AEs leading to discontinuation, death, and laboratory abnormalities.

Abbreviations: AE, adverse event; BICR, blinded independent central review; ORR, objective response rate; mPFS, median progression-free survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event.

Overall Design:

This is a Phase 1/2 study of BMS-986253 administered in combination with nivolumab or in combination with nivolumab and ipilimumab in participants with advanced solid tumors. The study is comprised of 2 Parts.

In Part 1, the safety of BMS-986253 in combination with nivolumab or in combination with nivolumab and ipilimumab will be evaluated in participants with advanced solid tumors. Part 1 is divided into 3 subsections: Part 1A (BMS-986253 plus nivolumab safety evaluation lead-in), Part 1B (BMS-986253 plus nivolumab dose finding), and Part 1C (safety evaluation of BMS-986253 in combination with nivolumab and ipilimumab). Parts 1A and 1B evaluate the doublet

combination of BMS-986253 and nivolumab in participants with [redacted]. Part 1C is a safety evaluation of the triplet combination of BMS-986253, nivolumab, and ipilimumab in participants with any baseline level of serum IL-8. Safety, pharmacokinetics (PK), and pharmacodynamics will be continuously evaluated throughout the study. The recommended Phase 2 dose (RP2D) will be determined based on the totality of the data in Part 1, to define the safe and most biologically active dose.

Part 2 is a randomized, double-blind evaluation of BMS-986253 plus nivolumab plus ipilimumab versus placebo plus nivolumab plus ipilimumab in participants with melanoma who have progressed on anti-PD-(L)1 therapy.

The following tumor types will be enrolled as described in the inclusion criteria:

- Parts 1A and 1B (must have [redacted]): melanoma, renal cell carcinoma (RCC), urothelial cancer (UCC), squamous cell carcinoma of the head and neck (SCCHN), and non-small cell lung cancer (NSCLC) (NSCLC cannot enroll in 1B6 [redacted])
- Part 1C: melanoma, UCC, hepatocellular carcinoma (HCC), and colorectal cancer (CRC)
- Part 2: melanoma

Part 1A: Safety Evaluation Lead-in (already enrolled, [redacted] participants, per BMS-986253 IB)

The safety evaluation lead-in (Part 1A) will begin with a cohort of participants who will receive a 2400 mg flat dose of BMS-986253 Q4W combined with 480 mg flat dose of nivolumab Q4W. A slightly higher dose (32 mg/kg or 2560 mg administered Q2W; yielding an overall dose of 64 mg/kg or 5120 mg per month) of BMS-986253 monotherapy has been shown to be safe and well tolerated in BMS Study CA027001 (see BMS-986253 IB). [redacted] After review of the clinical safety, including dose-limiting toxicities (DLTs) for the first 4 participants, the dose-finding phase (Part 1B) will open.

Part 1B: Dose-finding (participants enrolled in each cohort are per BMS-986253 IB)

In Part 1B, participants will be randomly assigned to receive 1 of 3 dosing regimens:

- Cohort 1B1: 2400 mg of BMS-986253 Q4W and 480 mg of nivolumab Q4W [redacted]
- Cohort 1B2: 1200 mg of BMS-986253 Q4W and 480 mg of nivolumab Q4W [redacted]
- Cohort 1B3: 600 mg of BMS-986253 Q4W and 480 mg of nivolumab Q4W [redacted]

Assignment into any dosing regimen arm may be suspended [redacted] In addition, up to 4 new dosing regimens assessing the combination of BMS-986253 and nivolumab may be initiated [redacted]
Additional cohorts for alternate dosing regimens may include:

- Cohort 1B4: 2400 mg of BMS-986253 Q2W and 480 mg of nivolumab Q4W [redacted]
- Cohort 1B5: 1200 mg of BMS-986253 Q2W and 480 mg of nivolumab Q4W [redacted]
- Cohort 1B6: 3600 mg of BMS-986253 Q2W and 480 mg of nivolumab Q4W [redacted]

[redacted]

If analyses indicate further assessment of a dosing regimen is not warranted and/or assessment of an additional dosing regimen is indicated, then randomization will be stopped, and subsequent participants will be assigned sequentially to ongoing dosing regimens available at that time.

[redacted]

Part 1C: Safety Evaluation of BMS-986253 in Combination with Nivolumab and Ipilimumab

Part 1C is a safety evaluation of BMS-986253 in combination with nivolumab and ipilimumab. Part 1C will begin once the DLT period is completed for Cohort 1B6 (BMS-986253 3600 mg Q2W + nivolumab 480 mg Q4W), and will enroll simultaneously with Part 1 Cohort 1B6. [redacted]

The higher-dose triplet combination Cohort 1C1 will enroll first. The safety and tolerability of this part will be evaluated [redacted] design to guide dose escalation decisions and the overall assessment [redacted]

In Part 1C, participants will initially be enrolled onto Cohort 1C1. For the first 12 weeks, participants will receive BMS-986253 3600 mg Q2W from Part 1B + nivolumab 1 mg/kg Q3W + ipilimumab 3 mg/kg Q3W. After 12 weeks, participants will receive BMS-986253 3600 mg Q2W from Part 1B and nivolumab 480 mg Q4W. [redacted]

[redacted]

Part 2: Double-blind Randomized Evaluation of BMS-986253 plus Nivolumab plus Ipilimumab versus Placebo plus Nivolumab plus Ipilimumab in Advanced Melanoma

Part 2 will begin after determination of the RP2D of BMS-986253 based on Part 1A and 1B data and generation of safety data on the triplet combination of BMS-986253 plus nivolumab plus ipilimumab in Part 1C.

Part 2 is a double-blind randomized evaluation of BMS-986253 plus nivolumab plus ipilimumab (2A) versus placebo plus nivolumab plus ipilimumab (2B) to evaluate the efficacy of BMS-986253 in participants with advanced melanoma who are refractory to anti-PD-(L)1 therapy.

This portion of the study will include participants with unresectable or metastatic melanoma (non-ocular), who had progression on or after anti-PD-(L)1 therapy, but have not been treated with prior anti-cytotoxic T-lymphocyte-associated protein 4 (anti-CTLA-4) therapy. Participants will be randomly assigned in a 1:1 ratio to 1 of 2 treatment arms:

- 2A: BMS-986253 + nivolumab + ipilimumab
- 2B: placebo + nivolumab + ipilimumab

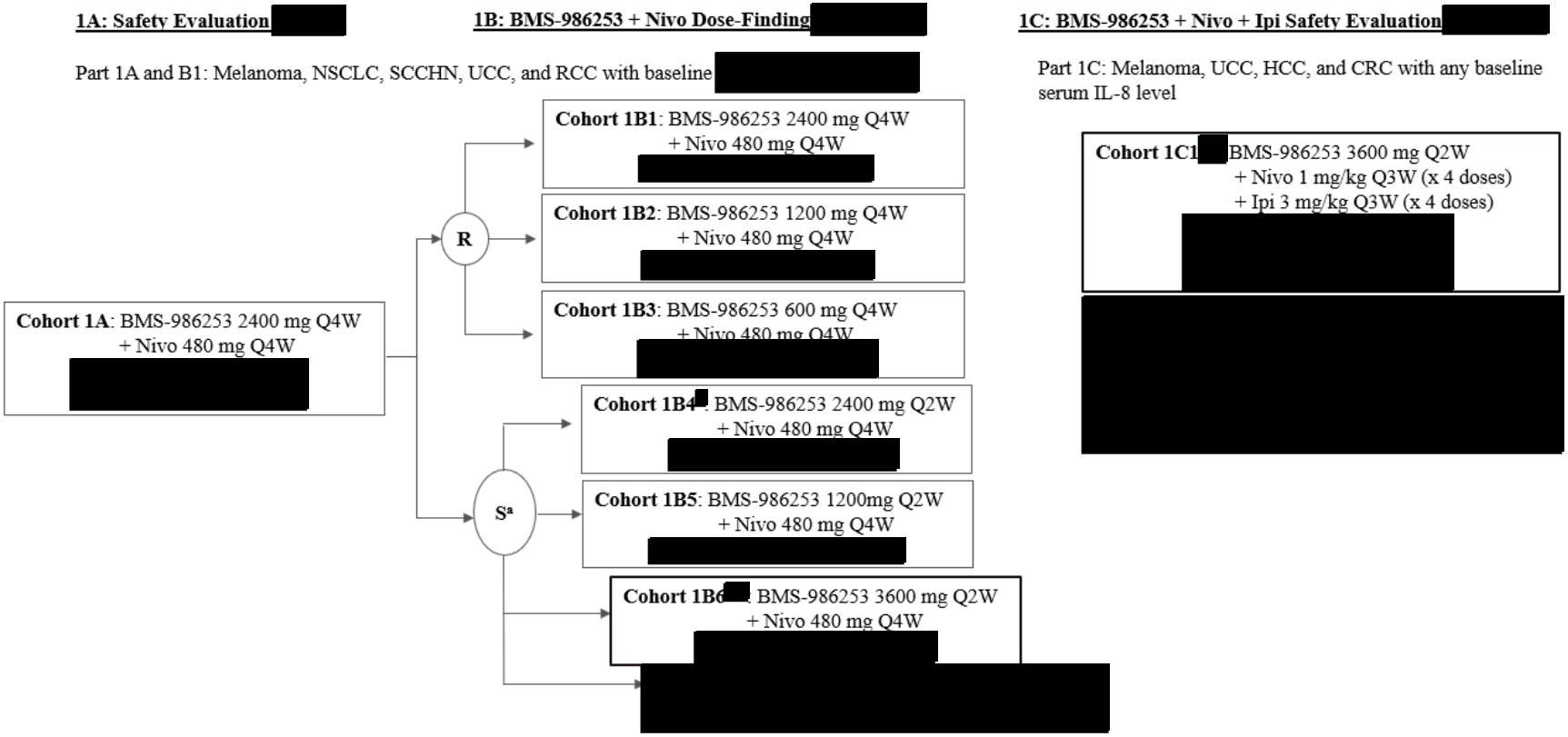
During randomization, participants will be stratified by the following factors: screening serum IL-8 level, [redacted] and lactate dehydrogenase (LDH) levels.

The dose of nivolumab and ipilimumab will be determined by safety data from Part 1C, and the dose of BMS-986253 will be determined by the totality of Part 1 data. If safety is confirmed in Cohort 1C1, for the first 12 weeks, participants will receive ipilimumab 3 mg/kg Q3W intravenously (IV) (4 doses), nivolumab 1 mg/kg Q3W IV (4 doses), and BMS-986253 3600 mg Q2W or placebo IV (given at Q2W frequency for 6 doses). After 12 weeks, participants will be maintained on BMS-986253 3600 mg Q2W or placebo IV (Q2W) and nivolumab IV (480 mg Q4W). [redacted]

Approximately [redacted] participants will be included in Part 2 and randomized in a 1:1 ratio to each arm.

The study design schemes are presented in Figures 1 and 2.

Figure 1: Study Design: Part 1

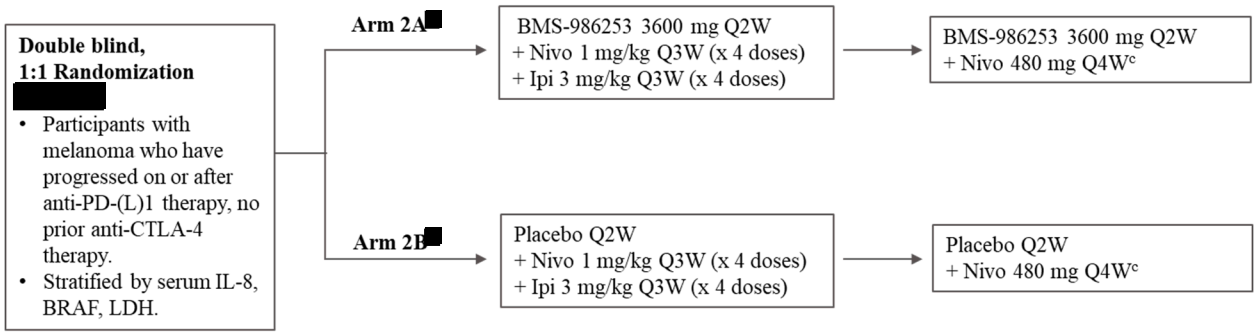


Abbreviations: CRC, colorectal cancer; HCC, hepatocellular carcinoma; IL, interleukin; Ipi, ipilimumab; max, maximum; Nivo, nivolumab; NSCLC, non-small cell lung cancer; QXW, every X weeks; R, randomized; RCC, renal cell carcinoma; S, sequential assignment; SCCHN, squamous cell carcinoma of the head and neck; UCC, urothelial cancer.

[a] Once sequential enrollment begins, up to 4 additional cohorts may be evaluated in Part 1B.

[redacted]

Figure 2: Study Design: Part 2



Abbreviations: BRAF, proto-oncogene B-Raf; CTLA, cytotoxic T-lymphocyte-associated protein; IL, interleukin, Ipi, ipilimumab; LDH, lactate dehydrogenase; Nivo, nivolumab; PD-(L)1, programmed cell death (ligand) 1; QXW, every X weeks.

[redacted]

[c] After 12 weeks, nivolumab will be administered at 480 mg Q4W.

The study will be divided into 4 periods: Pre-Screening, Screening, Treatment, and Follow-up.

Pre-Screening Period (applicable for Part 1 only):

Participants will provide consent for pre-screening to obtain a serum IL-8 level; further screening procedures will not be completed until the IL-8 level is resulted (except for participants with HCC and CRC). Depending on availability of cohorts at the time of enrollment, serum IL-8 results may determine eligibility and cohort assignment.

- Enrollment into Part 1B requires [redacted]
- Enrollment into Part 1C does NOT require a minimum serum IL-8 level.
- For participants with HCC and CRC: results of screening IL-8 are NOT required prior to signing the Main Informed Consent, since all HCC and CRC participants will be assigned to Part 1C (Part 1C does not require a minimum serum IL-8 level). Participants with HCC and CRC may enroll only when Part 1C is open.
- For participants with melanoma or UCC only being considered for Part 1C (for example, if Part 1B is not actively enrolling participants), results of screening IL-8 are NOT required prior to signing the Main Informed Consent.

Screening:

The screening period will be up to 28 days and begins by establishing the participant's initial eligibility and signing of the informed consent form (ICF). In order to establish eligibility for this study, participants will undergo baseline physical examinations, vital signs and oxygen saturation

measurements, 12-lead electrocardiogram (ECG), [redacted] and clinical laboratory evaluations.

If a participant exceeds the 28-day screening period (eg, [redacted] waiting for a laboratory value), the participant must be reconsented, but does not require a new participant identification number. The fewest number of procedures from the initial screening should be repeated to qualify the participant, while maintaining participant safety and eligibility. Repeat serum IL-8 testing will not be required if the previous sample was obtained within 42 days of study treatment initiation.

Assignment to a Study Part 1 (1A, 1B, or 1C) must be designated in the IRT system prior to the participant's assignment to a dosing regimen. In Part 2, all participants will be randomly assigned to Arm 2A (BMS-986253 + nivolumab + ipilimumab) or 2B (placebo + nivolumab + ipilimumab). Prior to randomization in Part 2, screening laboratory test results for serum IL-8 and LDH must be received, and [redacted] must be entered in the electronic case report form (eCRF). Part 2 of the study is double-blind; the participant, Sponsor, and site staff (except as indicated) will not be aware of treatment/cohort assignment.

Treatment:

Table 3: Dose, Frequency, Infusion Time, and Sequence of Ips

Cohort	BMS-986253 Dose and Frequency	BMS-986253 Infusion Time (min)	Nivolumab Dose and Frequency	Nivolumab Infusion Time (min)	Ipilimumab Dose and Frequency	Ipilimumab Infusion Time (min)	Order of Drug Administration
Part 1							
1A [a]	2400 mg Q4W		480 mg Q4W		NA		
1B1 [a]	2400 mg Q4W		480 mg Q4W		NA		
1B2 [a]	1200 mg Q4W		480 mg Q4W		NA		
1B3 [a]	600 mg Q4W		480 mg Q4W		NA		
1B4	2400 mg Q2W		480 mg Q4W		NA		
1B5	1200 mg Q2W		480 mg Q4W		NA		
1B6	3600 mg Q2W		480 mg Q4W		NA		
[redacted]							
1C1	3600 mg Q2W		1 mg/kg Q3W (x 4 doses), followed by 480 mg Q4W		3 mg/kg Q3W (x 4 doses)		
[redacted]							
Part 2							
2A	3600 mg Q2W		1 mg/kg Q3W [g] (x 4 doses), followed by 480 mg Q4W		3 mg/kg Q3W (x 4 doses)		
2B	Placebo Q2W		1 mg/kg Q3W [g] (x 4 doses), followed by 480 mg Q4W		3 mg/kg Q3W (x 4 doses)		

Abbreviations: [redacted] C, Cycle; D, Day; Ipi, ipilimumab; Nivo, nivolumab; QXW, every X weeks.

a [redacted]

Follow-up:

- Safety Follow-up Period: Upon completion of study therapy (or up to a maximum of 156 weeks if applicable), or once the decision is made to discontinue the participant from treatment, ie, at end of treatment (EOT), all participants will enter a safety follow-up period. For participants who complete all scheduled cycles of therapy, the EOT visit will be the same visit as the last scheduled and completed on-treatment visit, and will be 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 next visit following the last study dose. If the EOT visit occurs 30 days or more after receipt of the last dose, then the EOT visit and Follow-up 1 visit can be completed at the same time. All participants will be evaluated for any new AEs for a minimum of 100 days after discontinuing study treatment. Follow-up visits should occur at Days 30 and 100 (± 7 days for all study visits) after the last dose. All participants will be required to complete the clinical safety follow-up visits, regardless of whether new anti-cancer therapy is started, except those participants who withdraw consent for study participation.
- Response Follow-up Period: At the time of study treatment discontinuation, participants in Part 1 will continue to have radiologic and clinical tumor assessments on the same schedule, every 8 weeks (± 7 days), for the first 48 weeks after the first dose. After 48 weeks, radiological and clinical tumor assessments will occur every 12 weeks (± 7 days), until withdrawal of consent, death, final analysis, or initiation of another anti-cancer treatment, whichever occurs first, for up to 2 years after EOT. Participants in Part 2 will continue to have radiologic and clinical tumor assessments on the same schedule, every 8 weeks (± 7 days), starting from first dose for the first 48 weeks, then every 12 weeks (± 7 days), until blinded independent central review (BICR)-confirmed disease progression, final analysis, or treatment discontinuation (including treatment beyond progression), whichever occurs later. After the final analysis, radiological assessments will be done per standard of care, at the discretion of the treating physician.

Number of Participants:

The maximum total number of participants will be approximately [redacted] Specifically, up to approximately [redacted] of these participants will be treated in Part 1, and approximately [redacted] participants will be treated in Part 2.

Study treatment:

The study treatment is presented in Table 4.

Table 4: Study Treatment

Product Description/ Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Packaging/ Appearance	Storage Conditions (per label)
BMS-986253 Injection	[redacted]	IP	Open label[a]	Vial	Refer to the label on container and/or pharmacy manual

Table 4: Study Treatment

Product Description/ Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Packaging/ Appearance	Storage Conditions (per label)
BMS-986253 Injection	[redacted]	IP	Open label[a]	Vial	Refer to the label on container and/or pharmacy manual
Nivolumab (BMS-936558) solution for injection		IP	Open label[a]	Vial	Refer to the label on container and/or pharmacy manual
Ipilimumab solution for injection		IP	Open label[a]	Vial	Refer to the label on container and/or pharmacy manual
Ipilimumab solution for injection		IP	Open label[a]	Vial	Refer to the label on container and/or pharmacy manual
Normal saline solution for injection[b]		IP	Open label	Various (local commercial product)	Refer to the label on container
Dextrose solution for injection[b]		IP	Open label	Various (local commercial product)	Refer to the label on container

Abbreviation: IP, Investigational Product.

[a] The term "open label" refers to the medication as it is upon receipt at the pharmacy. In Part 2 of this trial, BMS-986253/placebo will be prepared, dispensed, and administered in a double-blinded fashion.

[b] This will be sourced by the investigative sites if permitted by local regulations.

Study Assessments and Analyses:

Safety Assessments: Safety assessments will be based on AE reports and the results of vital signs including oxygen saturation, ECGs, physical examinations, and clinical laboratory tests. AEs will be coded using the most current version of Medical Dictionary for Regulatory Activities and the incidence of observed AEs will be tabulated and reviewed for potential significance and clinical importance. AEs will be assessed continuously during the study and for a minimum of 100 days after the last dose of study treatment. A 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 v4.03.

PK and Immunogenicity Assessments: *Following the final analysis, PK and IMG samples will no longer be collected.*

PK and immunogenicity (IMG) assessment data for BMS-986253, nivolumab, and ipilimumab will be collected from study participants. All time points are relative to the start of the first drug

administration on that day. All on-treatment time points are intended to align with days on which study drug is administered; if dosing occurs on a different day, the PK and IMG sampling should be adjusted accordingly. If it is known that a dose is going to be delayed, then the predose sample should be collected just prior to the delayed dose. However, if a predose sample is collected but the dose is subsequently delayed, an additional predose sample should not be collected. All pre-dose samples should be taken within 30 minutes before the start of any dose infusion. EOI samples should be taken immediately prior to completion of the infusion, preferably within 2 minutes. Blood samples should be drawn from a site other than the infusion site (ie, contralateral arm) on days of infusion.

PK of BMS-986253 will be derived, if feasible, from serum concentration versus time data following administration of BMS-986253 on Cycle 1 Day 1. Individual participant PK parameter values will be derived by non-compartmental methods using a validated PK analysis program (Part 1 only). Actual times will be used for all formal analyses.

Sparse nivolumab and ipilimumab concentration-time data will be collected and may be used in an integrated PPK or exposure response analysis along with data from other studies, which will be the subject of a separate report. Separate samples will be collected for PK and IMG assessments.

Further details of sample collection, processing, and shipment will be provided in the laboratory procedures manual. Serum PK samples will be analyzed for BMS-986253, nivolumab, and ipilimumab by validated ligand-binding assays. In addition, serum samples will be archived for potential metabolite analysis, if the need arises and to the extent possible.

Immunogenicity samples will be analyzed for anti-nivolumab/anti-ipilimumab/anti-BMS-986253 antibodies by validated IMG assays. IMG samples positive for anti-nivolumab, anti-ipilimumab, and anti-BMS-986253 may be analyzed for neutralizing antibodies by a validated method. [redacted]

For all PK and IMG plasma/serum samples, the date and actual time collected must be recorded. For participants whose only peripheral access is via a venous access device or peripherally inserted central catheter, refer to the Laboratory Manual for the proper technique to ensure undiluted whole blood for PK assessments.

Biomarker Assessments: *Following the final analysis, biomarker samples will no longer be collected.*

Biomarker measures of baseline, on treatment, and upon disease progression [redacted]

Efficacy Assessments: *Following the database lock for the final analysis, efficacy will no longer be assessed. Imaging should be performed per standard of care at the discretion of the treating physician.*

Efficacy assessments for the anti-tumor activity of BMS-986253, in combination with nivolumab or in combination with nivolumab and ipilimumab, will use investigator assessed tumor measurements per RECIST v1.1.

Assessment of partial response and complete response must be confirmed at least 4 weeks after initial response. Changes in tumor measurements and tumor responses will be assessed by the investigator per study design using RECIST v1.1 criteria. Investigators will also report the number and size of new lesions that appear while on study. The timepoint of tumor assessments will be reported on the eCRF based on the investigator's assessment.

A BICR will be utilized in this study for determination of BICR-assessed endpoints. The BICR will review all available tumor assessment scans for all treated participants until the final analysis. Details of BICR responsibilities and procedures will be specified in the BICR charter.

A best overall response of SD requires a minimum of 49 days on study from the date of first dose to the date of the first imaging assessment.

[redacted]

Data Monitoring Committee: Yes, only for Part 2.

2 SCHEDULE OF ACTIVITIES

Table 2-1: Prescreening Procedural Outline (applicable for Part 1 only)

Procedure	Prescreening Visit	Notes
Eligibility Assessments		
Prescreen Informed Consent for Serum IL-8	X	Participants must sign the Pre-Screen Informed Consent prior to testing the screening serum IL-8 level. The pre-screen testing for serum IL-8 will occur before the 28-day screening window. Participants may not receive any systemic therapy after screening serum IL-8 is drawn. Depending on availability of cohorts at the time of enrollment, serum IL-8 results may determine eligibility and cohort assignment. For participants with CRC and HCC: results of screening IL-8 are not required prior to signing the Main Informed Consent. For participants with melanoma or UCC only being considered for Part 1C (for example, if Part 1B is not actively enrolling participants), results of screening IL-8 are NOT required prior to signing the Main Informed Consent.
IRT Assignment	X	To obtain participant identification number. This must be done prior to testing screening serum IL-8.
Laboratory Test for Serum IL-8	X	
Adverse Event Reporting		
Monitor for Serious Adverse Events	X	All SAEs related to the blood draw must be collected from the date of participant's written consent (Pre-screen ICF) and followed until resolution or stabilization of the SAE.

Abbreviations: CRC, colorectal cancer; HCC, hepatocellular cancer; IL-8, interleukin-8; IRT, Interactive Response Technologies; SAE, serious adverse event.

Table 2-2: Screening Procedural Outline (All Study Phases)

Procedure	Screening Visit Day -28 to Day -1	Notes
Eligibility Assessments		
Main Informed Consent	X	For participants in Part 1: eligible participants (as determined by serum IL-8 prescreen results and cohort availability) must sign the main informed consent within 1 week of serum IL-8 positive result by the central laboratory. For Part 1 participants with CRC and HCC: results of screening IL-8 are not required prior to signing the Main Informed Consent. All CRC and HCC participants will be assigned to Part 1C, and may enroll only when Part 1C is open.
ECOG Performance Status	X	Appendix 5
Inclusion/Exclusion Criteria	X	
Medical History	X	All medical history relevant to the disease under study, and COVID-19 vaccines more than 30 days prior to first study treatment. Include any toxicities or allergy related to previous treatments.
Prior Cancer Therapies	X	Including all prior cancer treatment regimens and medications administered.
[redacted]		

Table 2-2: Screening Procedural Outline (All Study Phases)

Procedure	Screening Visit Day -28 to Day -1	Notes
IRT Assignment	X	After completing all screening procedures, utilize IRT to either screen fail or obtain assignment information, as applicable. Assignment can occur up to 3 days prior to first dose.
Tumor Type Assessment		
Body Imaging	X	Contrast enhanced CT/MRI of the chest, abdomen, pelvis, and all other known/suspected sites of disease. Images will be acquired within 28 days prior to the first treatment dose. Images acquired as part of care prior to signing the ICF, but within the 28-day limit, will be acceptable if there is no intervening treatment, and all required scanning acquisition parameters are met (if feasible per local regulations). For participants with SCCHN, a CT or MRI of the neck is required. For participants with HCC, imaging of the abdomen should include multi-phasic (at least three of the following four phases: precontrast, arterial, venous, delayed) CT or MRI of the liver. See Section 9.4.1 for further details.
Brain Imaging	X	Part 1: At screening, MRI of the brain without and with contrast is required for participants with known or suspected brain metastases who have not had brain imaging within 28 days of anticipated first study drug administration. Part 2: MRI of the brain (without and with contrast) is required for ALL participants during screening to rule out evidence of progression for brain metastases within the 28 days prior to treatment. CT of the Brain (without and with contrast) can be performed if MRI is contraindicated. See Section 9.4.1 for further details. Images will be acquired within 28 days prior to the first treatment dose. Images acquired as part of care prior to signing the ICF, but within the 28-day limit, will be acceptable if there is no intervening treatment, and all required scanning acquisition parameters are met (if feasible per local regulations).
Other Bone Scan	X	As clinically indicated per local standards. See Section 9.4.1 for further details.

Table 2-2: Screening Procedural Outline (All Study Phases)

Procedure	Screening Visit Day -28 to Day -1	Notes
Safety Assessments		
Concomitant Medication Assessment	X	Collect and record concomitant medication up to 4 weeks prior to screening. Collect and record vaccine use within 30 days prior to first study treatment.
ECG	X	ECGs should be recorded after the participant has been supine for at least 5 minutes.
PE	X	If the screening PE is performed within 24 hours prior to dosing on Day 1 then a single exam may count as both the Screening and pre-dose evaluation.
Clinical Complaints	X	Clinical complaints related to the disease under study present 14 days prior to the first dose of study treatment must be collected.
Physical Measurements	X	Includes height, weight, and body mass index.
Vital Signs/Oxygen Saturation	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. Consider alternate position(s) for vital sign collection. Obtain oxygen saturation at rest and exertion.
Laboratory Tests	X	Includes blood and urine samples.
FSH	X	Post-menopausal women < 55 years old. Refer to Appendix 4.
Pregnancy Test	X	For women of child-bearing potential only. Refer to Appendix 4.
Serology	X	Includes hepatitis B surface antigen, hepatitis C antibody, or a more complete panel for participants with hepatocellular carcinoma (see Table 9.1.4-1 for panel information).
Hematology	X	See Table 9.1.4-1 for panel information.
Serum chemistry	X	See Table 9.1.4-1 for panel information.
Other laboratory tests	X	Includes thyroid panel, amylase, lipase, etc (see Table 9.1.4-1 for panel information). For HCC participants: AFP
IL-8 [redacted]	X	Only for Part 2.
Urinalysis	X	See Table 9.1.4-1 for panel information.

Table 2-2: Screening Procedural Outline (All Study Phases)

Procedure	Screening Visit Day -28 to Day -1	Notes
HPV status of tumor for SCCHN of the oropharynx	X	HPV status for oropharyngeal cancers must be determined locally using p16 IHC or HPV PCR as described in Section 9.8.5. If HPV status was previously determined using an acceptable method listed in Section 9.8.5, re-testing is not necessary.
Stool Sample	X	A screening stool sample must be collected as per the supplemental laboratory manual.
Adverse Event Reporting		
Monitor for Adverse Events		All SAEs must be collected from the time of signing the consent and for a minimum of 100 days after discontinuing study treatment.

Abbreviations: AFP, alpha fetoprotein; C, cycle; CRC, colorectal cancer; CT, computed tomography; D, day; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; FSH, follicle stimulating hormone; HCC, hepatocellular carcinoma; HPV, human papillomavirus; ICF, informed consent form; IHC, immunohistochemistry; IL-8, interleukin-8; IRT, Interactive Response Technologies; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; PE, physical examination; SAE, serious adverse event; SCCHN, squamous cell carcinoma of the head and neck.

Table 2-3: On-treatment Procedural Outline (Part 1A and Cohorts 1B1 through 1B3 - BMS-986253 Q4W and Nivolumab Q4W)

Procedure	Cycle 1 (28 d)					Cycle 2 (28 d)				Cycle 3 (28 d)	Cycle 4 (28 d)					Cycle 5+ (28 d)	EOT [a,b]	Notes
	D1	D2	D8[c]	D15[c]	D22[c]	D1[c]	D2[c]	D8	D15[c]	D1[c]	D1[c]	D2[c]	D8[c]	D15[c]	D22[c]	D1[c]		
Safety Assessments[d]																		
ECOG Performance Status	X					X				X	X					X		Appendix 5
Concomitant Medication Assessments	X		X	X	X	X		X	X	X	X					X	X	Assess concomitant treatment during the study duration.
[redacted]																		

Table 2-3: On-treatment Procedural Outline (Part 1A and Cohorts 1B1 through 1B3 - BMS-986253 Q4W and Nivolumab Q4W)

Procedure	Cycle 1 (28 d)					Cycle 2 (28 d)				Cycle 3 (28 d)	Cycle 4 (28 d)					Cycle 5+ (28 d)	EOT [a,b]	Notes
	D1	D2	D8[c]	D15[c]	D22[c]	D1[c]	D2[c]	D8	D15[c]	D1[c]	D1[c]	D2[c]	D8[c]	D15[c]	D22[c]	D1[c]		
[redacted]																		
ECG	X					X				X	X					X	X	12-lead ECGs should be recorded after participant has been supine for at least 5 minutes. [redacted]

Table 2-3: On-treatment Procedural Outline (Part 1A and Cohorts 1B1 through 1B3 - BMS-986253 Q4W and Nivolumab Q4W)

Procedure	Cycle 1 (28 d)					Cycle 2 (28 d)				Cycle 3 (28 d)	Cycle 4 (28 d)					Cycle 5+ (28 d)	EOT [a,b]	Notes
	D1	D2	D8[c]	D15[c]	D22[c]	D1[c]	D2[c]	D8	D15[c]	D1[c]	D1[c]	D2[c]	D8[c]	D15[c]	D22[c]	D1[c]		
																		[redacted]
Laboratory Testing	X[e]			X		X			X	X	X					X	X	See Section 9.1.4.
Physical Examination (Complete)	X		X	X	X	X			X	X	X					X	X	Physical Examination (Complete)
Pregnancy Test (WOCBP)	X					X				X	X					X	X	Serum or urine pregnancy test must be performed (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG) within 24 hours prior to administration of study drug.

Table 2-3: On-treatment Procedural Outline (Part 1A and Cohorts 1B1 through 1B3 - BMS-986253 Q4W and Nivolumab Q4W)

Procedure	Cycle 1 (28 d)					Cycle 2 (28 d)				Cycle 3 (28 d)	Cycle 4 (28 d)					Cycle 5+ (28 d)	EOT [a,b]	Notes
	D1	D2	D8[c]	D15[c]	D22[c]	D1[c]	D2[c]	D8	D15[c]	D1[c]	D1[c]	D2[c]	D8[c]	D15[c]	D22[c]	D1[c]		
Thyroid Function Tests (TSH)	X										X					X*	X	*TSH to be done every 3rd cycle starting at Cycle 7. If TSH is abnormal. Free T3 and Free T4 should be collected. Results should be examined by the investigator or appropriate designee within 48 hours of dose administration.
Weight	X					X				X	X					X	X	
Vital Signs and Oxygen Saturations	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. Consider alternate position(s) for vital sign collection. Obtain oxygen saturation at rest. *Pre- and post-dose vital signs on Day 1 of each cycle.

Table 2-3: On-treatment Procedural Outline (Part 1A and Cohorts 1B1 through 1B3 - BMS-986253 Q4W and Nivolumab Q4W)

Procedure	Cycle 1 (28 d)					Cycle 2 (28 d)				Cycle 3 (28 d)	Cycle 4 (28 d)					Cycle 5+ (28 d)	EOT [a,b]	Notes
	D1	D2	D8[c]	D15[c]	D22[c]	D1[c]	D2[c]	D8	D15[c]	D1[c]	D1[c]	D2[c]	D8[c]	D15[c]	D22[c]	D1[c]		
																		Note: post dose vital signs are to be taken after BMS-986253 infusion AND after Nivolumab infusion.
Adverse Event Reporting																		
Monitor for Nonserious Adverse Events	Nonserious AEs must be collected starting with the first dose of study drug and for a minimum of 100 days after discontinuing study treatment.																	
Monitor for Serious Adverse Events	All SAEs must be collected from the time of signing the consent and for a minimum of 100 days after discontinuing study treatment. Death due to disease progression within 100 days of discontinuation of study treatment must be reported as an SAE.																	
PK Assessments	See Section 9.5 for further details																	
Immunogenicity Assessments	See Section 9.5 for further details																	
Biomarker Assessments	See Section 9.8																	
Additional Research Sampling	See Section 9.8.4																	
Efficacy Assessments	See Section 9.4																	

Table 2-3: On-treatment Procedural Outline (Part 1A and Cohorts 1B1 through 1B3 - BMS-986253 Q4W and Nivolumab Q4W)

Procedure	Cycle 1 (28 d)					Cycle 2 (28 d)				Cycle 3 (28 d)	Cycle 4 (28 d)					Cycle 5+ (28 d)	EOT [a,b]	Notes
	D1	D2	D8[c]	D15[c]	D22[c]	D1[c]	D2[c]	D8	D15[c]	D1[c]	D1[c]	D2[c]	D8[c]	D15[c]	D22[c]	D1[c]		
Body Imaging	Contrast enhanced CT/MRI of the chest, abdomen, pelvis, and all other known/suspected sites of disease should occur every 8 weeks (± 7 days), starting from first dose for the first 48 weeks, then every 12 weeks (± 7 days) until withdrawal of consent, death, or initiation of another anti-cancer treatment, whichever occurs first. See Section 9.4.1																	
	For participants with SCCHN, a CT or MRI of the neck is required.																	
	For HCC participants, contrast-enhanced triphasic CT of the liver is required. See Section 9.4.1 for further details.																	
Brain Imaging	Participants with a history of brain metastasis should have surveillance MRI as clinically indicated at the discretion of the investigator. See Section 9.4.1.																	
Other: Bone Scan	As clinically indicated per local standards. See Section 9.4.1																	
Clinical Supplies																		
IRT Assignment	X																	Once eligibility has been confirmed, IRT assignment may be performed up to 3 days prior to study drug administration.

Table 2-3: On-treatment Procedural Outline (Part 1A and Cohorts 1B1 through 1B3 - BMS-986253 Q4W and Nivolumab Q4W)

Procedure	Cycle 1 (28 d)					Cycle 2 (28 d)				Cycle 3 (28 d)	Cycle 4 (28 d)					Cycle 5+ (28 d)	EOT [a,b]	Notes
	D1	D2	D8[c]	D15[c]	D22[c]	D1[c]	D2[c]	D8	D15[c]	D1[c]	D1[c]	D2[c]	D8[c]	D15[c]	D22[c]	D1[c]		
Study Drug Administration																		Details regarding preparation and administration are provided in the pharmacy manual or training materials.
BMS-986253 Administration	X					X				X	X					X		See Section 7.1 for BMS-986253 dose administration.
Nivolumab Administration	X					X				X	X					X		See Section 7.1 for nivolumab dose administration.

Abbreviations: AE, adverse event, BMS, Bristol Myers Squibb; CBC, complete blood count; C, Cycle; CT, computed tomography; d, days; D, Day; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EDC, Electronic Data Capture; EOI, end of infusion; EOT, end of treatment; HCC, hepatocellular carcinoma; hCG, human chorionic gonadotropin; IL-8, interleukin-8; IRT, Interactive Response Technologies; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; [redacted] PK, pharmacokinetic(s); Q4W, every 4 weeks; SAE, serious adverse event; SCCHN, squamous cell carcinoma of the head and neck; T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone; WOCBP, women of childbearing potential.

[a] For participants who complete all scheduled cycles of therapy, the EOT visit will be the same visit as last scheduled and completed on-treatment visit and the start of the Week 1 Clinical/Safety Follow-up visit.

[b] For participants who do not complete all scheduled cycles of therapy, the EOT visit will be the next visit following the last study dose. If the EOT visit occurs 30 days or more after receipt of the last dose, then the EOT visit and Follow-up 1 visit can be completed at the same time.

[c] ± 3-day window

[d] If multiple procedures are required at a single timepoint, safety assessments (ECGs, vital signs, and pulse oximetry) are a higher priority than PK/Immunogenicity sampling.

[e] In addition to pre-treatment laboratory tests, CBC with differential will be collected with the last PK laboratory draw on C1D1 [redacted]

Table 2-4: On-treatment Procedural Outline (Cohorts 1B4 through 1B6 - BMS-986253 Q2W and Nivolumab Q4W)

Procedure	Cycle 1 (28 d)					Cycle 2 (28 d)				Cycle 3 (28 d)		Cycle 4 (28 d)					Cycle 5 + (28 d)		EOT[a,b]	Notes
	D1	D2	D8[c]	D15[c]	D22[c]	D1[c]	D2[c]	D8	D15[c]	D1[c]	D15[c]	D1[c]	D2[c]	D8[c]	D15[c]	D22[c]	D1[c]	D15		
Safety Assessments[d]																				
ECOG Performance Status	X			X		X			X	X		X					X			Appendix 5
Concomitant Medication Assessments	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Assess concomitant treatment during the study duration.
[redacted]																				

Table 2-4: On-treatment Procedural Outline (Cohorts 1B4 through 1B6 - BMS-986253 Q2W and Nivolumab Q4W)

Procedure	Cycle 1 (28 d)					Cycle 2 (28 d)				Cycle 3 (28 d)		Cycle 4 (28 d)					Cycle 5 + (28 d)		EOT[a,b]	Notes
	D1	D2	D8[c]	D15[c]	D22[c]	D1[c]	D2[c]	D8	D15[c]	D1[c]	D15[c]	D1[c]	D2[c]	D8[c]	D15[c]	D22[c]	D1[c]	D15		
[redacted]																				
ECG	X			X		X			X	X		X					X		X	12-lead ECGs should be recorded after participant has been supine for at least 5 minutes. [redacted]

Table 2-4: On-treatment Procedural Outline (Cohorts 1B4 through 1B6 - BMS-986253 Q2W and Nivolumab Q4W)

Procedure	Cycle 1 (28 d)					Cycle 2 (28 d)				Cycle 3 (28 d)		Cycle 4 (28 d)					Cycle 5 + (28 d)		EOT[a,b]	Notes
	D1	D2	D8[c]	D15[c]	D22[c]	D1[c]	D2[c]	D8	D15[c]	D1[c]	D15[c]	D1[c]	D2[c]	D8[c]	D15[c]	D22[c]	D1[c]	D15		
																				[redacted]
Laboratory Testing	X[e]			X		X			X	X		X					X		X	See Section 9.1.4
Physical Examination (Complete)	X		X	X	X	X			X	X		X					X		X	Physical Examination (Complete)
Pregnancy Test (WOCBP)	X					X				X		X					X			Serum or urine pregnancy test must be performed (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG) within 24 hours prior to administration of study drug.
Thyroid Function Tests (TSH)	X*											X*					X*		X	*TSH to be done every 3rd cycle, ie, C1D1, C4D1, C7D1, etc. If TSH is abnormal, T3 and free T4 should be collected. Results should be examined by the investigator or appropriate designee within 48 hours of dose administration.

Table 2-4: On-treatment Procedural Outline (Cohorts 1B4 through 1B6 - BMS-986253 Q2W and Nivolumab Q4W)

Procedure	Cycle 1 (28 d)					Cycle 2 (28 d)				Cycle 3 (28 d)		Cycle 4 (28 d)					Cycle 5 + (28 d)		EOT[a,b]	Notes
	D1	D2	D8[c]	D15[c]	D22[c]	D1[c]	D2[c]	D8	D15[c]	D1[c]	D15[c]	D1[c]	D2[c]	D8[c]	D15[c]	D22[c]	D1[c]	D15		
Weight	X					X				X		X					X		X	
Vital Signs and Oxygen Saturations	X*	X	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. Consider alternate position(s) for vital sign collection. Obtain oxygen saturation at rest. *Pre- and post-dose vital signs on Day 1 of each cycle. Note: post dose vital signs are to be taken after BMS-986253 infusion AND after Nivolumab infusion.
Adverse Event Reporting																				
Monitor for Nonserious Adverse Events	Nonserious AEs must be collected starting with the first dose of study drug and for a minimum of 100 days after discontinuing study treatment.																			

Table 2-4: On-treatment Procedural Outline (Cohorts 1B4 through 1B6 - BMS-986253 Q2W and Nivolumab Q4W)

Procedure	Cycle 1 (28 d)					Cycle 2 (28 d)				Cycle 3 (28 d)		Cycle 4 (28 d)					Cycle 5 + (28 d)		EOT[a,b]	Notes
	D1	D2	D8[c]	D15[c]	D22[c]	D1[c]	D2[c]	D8	D15[c]	D1[c]	D15[c]	D1[c]	D2[c]	D8[c]	D15[c]	D22[c]	D1[c]	D15		
Monitor for Serious Adverse Events	All SAEs must be collected from the date of participant's written consent and for a minimum of 100 days after discontinuing study treatment. Death due to disease progression within 100 days of discontinuation of study treatment must be reported as an SAE.																			
PK Assessments	See Section 9.5 for further details																			
Immunogenicity Assessments	See Section 9.5 for further details																			
Biomarker Assessments	See Section 9.8																			
Additional Research Sampling	See Section 9.8.4																			
Efficacy Assessments	See Section 9.4																			
Body Imaging	Contrast enhanced CT/MRI of the chest, abdomen, pelvis, and all other known/suspected sites of disease should occur every 8 weeks (± 7 days), starting from first dose for the first 48 weeks, then every 12 weeks (± 7 days) until withdrawal of consent, death, initiation of another anti-cancer treatment, or final analysis, whichever occurs first. See Section 9.4.1. For participants with SCCHN, a CT or MRI of the neck is required.																			
Brain Imaging	Participants with a history of brain metastasis should have surveillance MRI as clinically indicated at the discretion of the investigator. See Section 9.4.1.																			
Other: Bone Scan	As clinically indicated per local standards. See Section 9.4.1																			
Clinical Supplies																				
IRT Assignment	X																			Once eligibility has been confirmed, IRT assignment may be performed up to 3 days prior to study drug administration.

Table 2-4: On-treatment Procedural Outline (Cohorts 1B4 through 1B6 - BMS-986253 Q2W and Nivolumab Q4W)

Procedure	Cycle 1 (28 d)					Cycle 2 (28 d)				Cycle 3 (28 d)		Cycle 4 (28 d)					Cycle 5 + (28 d)		EOT[a,b]	Notes
	D1	D2	D8[c]	D15[c]	D22[c]	D1[c]	D2[c]	D8	D15[c]	D1[c]	D15[c]	D1[c]	D2[c]	D8[c]	D15[c]	D22[c]	D1[c]	D15		
Study Drug Administration																				Details regarding preparation and administration are provided in the pharmacy manual or training materials.
BMS-986253 Administration	X			X		X			X	X	X	X			X		X	X		BMS-986253 will be administered on day 1 and 15 of ALL cycles. See Section 7.1 for BMS-986253 dose administration.
Nivolumab Administration	X					X				X		X					X			See Section 7.1 for Nivolumab dose administration.

Abbreviations: AE, adverse event; BMS, Bristol Myers Squibb; C, Cycle; CBC, complete blood count; CT, computed tomography; d, days; D, Day; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EDC, Electronic Data Capture; EOI, end of infusion; EOT, end of treatment; HCC, hepatocellular carcinoma; hCG, human chorionic gonadotropin; IL-8, interleukin-8; IRT, Interactive Response Technologies; MRI, magnetic resonance imaging; [redacted]; PK, pharmacokinetic(s); Q2W, every 2 weeks; Q4W, every 4 weeks; SAE, serious adverse event; SCCHN, squamous cell carcinoma of the head and neck; T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone; WOCBP, women of childbearing potential.

[a] For participants who complete all scheduled cycles of therapy, the EOT visit will be the same visit as the last scheduled and completed on-treatment visit and the start of the Week 1 Clinical/Safety Follow-up visit.

[b] For participants who do not complete all scheduled cycles of therapy, the EOT visit will be the next visit following the last study dose. If the EOT visit occurs 30 days or more after receipt of the last dose, then the EOT visit and Follow-up 1 visit can be completed at the same time.

[c] ± 3-day window

[d] If multiple procedures are required at a single timepoint, safety assessments (ECGs, vital signs, and pulse oximetry) are a higher priority than PK/Immunogenicity sampling.

[e] In addition to pre-treatment laboratory tests, CBC with differential will be collected with the last PK laboratory draw on C1D1 [redacted]

Table 2-5: On-treatment Procedural Outline [redacted]

Procedure	Cycle 1 [redacted]		Cycle 2 [redacted] and Beyond	EOT[a,b]	Notes
	D1	D1	D8		
Safety Assessments[c]					
Vital Signs and Oxygen Saturations	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. Consider alternate position(s) for vital sign collection. Obtain oxygen saturation at rest. *Pre- and post-dose vital signs on Day 1 of each cycle. Note: Post dose vital signs are to be taken after BMS-986253 infusion AND after nivolumab infusion.
Weight	X	X		X	
Physical Examination (Complete)	X	X		X	Physical Examination (Complete)
ECOG Performance Status	X	X			Appendix 5
Concomitant Medication Assessments	X	X		X	Assess concomitant treatment during the study duration.
ECG	X	X		X	12-lead ECGs should be recorded after participant has been supine for at least 5 minutes. [redacted] Table 9.5-5 for timing.
Procedures					
Laboratory Testing	X	X		X	See Section **9.1.4**

Table 2-5: On-treatment Procedural Outline [redacted]

Procedure	Cycle 1 [redacted]		Cycle 2 [redacted] and Beyond		EOT[a,b]	Notes
	D1		D1	D8		
Pregnancy Test (WOCBP)	X		X		X	Serum or urine pregnancy test must be performed (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG) within 24 hours prior to administration of study drug.
Thyroid Function Tests (TSH)	X*		X*		X	*TSH to be done every 4 cycles, ie, C1D1, C5D1, C9D1, etc. If TSH is abnormal, T3 and free T4 should be collected. Results should be examined by the investigator or appropriate designee within 48 hours of dose administration.
[redacted]						
Adverse Event Reporting						
Monitor for Nonserious Adverse Events	All nonserious adverse events must be collected starting with the first dose of study drug and for a minimum of 100 days after discontinuing study treatment					
Monitor for Serious Adverse Events	All SAEs must be collected from the time of signing the consent and for a minimum of 100 days after discontinuing study treatment. Death due to disease progression within 100 days of discontinuation of study treatment must be reported as an SAE.					
Additional Assessments						
PK Assessments	See Section **9.5** for further details					
Immunogenicity Assessments	See Section **9.5** for further details					
Biomarker Assessments	See Section **9.8**					
Additional Research Sampling	See Section **9.8.5**					

Table 2-5: On-treatment Procedural Outline [redacted]

Procedure	Cycle 1 [redacted]		Cycle 2 [redacted] and Beyond		EOT[a,b]	Notes
	D1		D1	D8		
Efficacy Assessments	See Section **9.4**					
Body Imaging	Contrast-enhanced CT/MRI of the chest, abdomen, pelvis, and all other known/suspected sites of disease should occur every 8 weeks (± 7 days), starting from first dose for the first 48 weeks, then every 12 weeks (± 7 days) until withdrawal of consent, death, or initiation of another anti-cancer treatment, whichever occurs first. See Section **9.4.1.** For participants with SCCHN, a CT or MRI of the neck is required.					
Brain Imaging	Participants with a history of brain metastasis should have surveillance MRI as clinically indicated at the discretion of the investigator. See Section **9.4.1**.					
Other: Bone Scan	As clinically indicated per local standards. See Section **9.4.1.**					
Clinical Supplies						
IRT Assignment	X					Once eligibility has been confirmed, IRT assignment may be performed up to 3 days prior to study drug administration.
Study Drug Administration						Details regarding preparation and administration are provided in the pharmacy manual or training materials.
[redacted]						

Abbreviations: C, Cycle; CT, computed tomography; d, days; D, Day; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EDC, Electronic Data Capture; EOI, end of infusion; EOT, end of treatment; hCG, human chorionic gonadotropin; IRT, Interactive Response Technologies; MRI, magnetic resonance imaging; PK, pharmacokinetic(s); [redacted] SAE, serious adverse event; T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone; WOCBP, women of childbearing potential.

[a] For participants who complete all scheduled cycles of therapy, the EOT visit will be the same visit as the last scheduled and completed on-treatment visit and the start of the Week 1 Clinical/Safety Follow-up visit.

[b] For participants who do not complete all scheduled cycles of therapy, the EOT visit will be the next visit following the last study dose. If the EOT visit occurs 30 days or more after receipt of the last dose, then the EOT visit and Follow-up 1 visit can be completed at the same time.

[c] If multiple procedures are required at a single timepoint, safety assessments (ECGs, vital signs, and pulse oximetry) are a higher priority than PK/immunogenicity sampling.

Table 2-6: On-treatment Procedural Outline (Part 1C and Part 2 - BMS-986253 Q2W and Nivolumab and Ipilimumab Q3W)

Procedure	Cycle 1 and 2 (42 d)					Cycle 3 and Beyond (28 d)		EOT[a,b]	Notes
	D1	D15	D22	D29	D36	D1	D15		
Safety Assessments[c]									
Vital Signs and Oxygen Saturations	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. Consider alternate position(s) for vital sign collection. Obtain oxygen saturation at rest. *Pre- and post-dose vital signs on Day 1 of each cycle. Note: Post dose vital signs are to be taken after nivolumab infusion, ipilimumab infusion and BMS-986253 or placebo infusion.
Weight	X		X			X		X	
Physical Examination (Complete)	X		X			X		X	Physical Examination (Complete)
ECOG Performance Status	X		X			X			Appendix 5
Concomitant Medication Assessments	X	X	X	X		X		X	Assess concomitant treatment during the study duration.

Table 2-6: On-treatment Procedural Outline (Part 1C and Part 2 - BMS-986253 Q2W and Nivolumab and Ipilimumab Q3W)

Procedure	Cycle 1 and 2 (42 d)					Cycle 3 and Beyond (28 d)		EOT[a,b]	Notes
	D1	D15	D22	D29	D36	D1	D15		
ECG	X		X*			X		X	12-lead ECGs should be recorded after participant has been supine for at least 5 minutes. [redacted] Participants with no clinically relevant changes on ECGs at 6 months on treatment may discontinue routine ECGs. See [redacted] of ECGs. * Required for Part 1C only.
Laboratory Testing	X		X			X		X	See Section 9.1.4 **Only applicable for Part 1C:** For HCC participants AFP
Pregnancy Test (WOCBP)	X					X		X	Serum or urine pregnancy test must be performed (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of hCG) within 24 hours prior to administration of study drug.
Thyroid Function Tests (TSH)	X		X			X*			*TSH to be done on C3D1, C4D1, C5D1, and C6D1. TSH to be done every other cycle, after C6D1 (ie, C8D1, C10D1, etc). If TSH is abnormal, T3 and free T4 should be collected. Results should be examined by the investigator or appropriate designee within 48 hours of dose administration.
[redacted]									

Table 2-6: On-treatment Procedural Outline (Part 1C and Part 2 - BMS-986253 Q2W and Nivolumab and Ipilimumab Q3W)

Procedure	Cycle 1 and 2 (42 d)					Cycle 3 and Beyond (28 d)		EOT[a,b]	Notes
	D1	D15	D22	D29	D36	D1	D15		
Adverse Event Reporting									
Monitor for Nonserious Adverse Events	All nonserious adverse events must be collected starting with the first dose of study drug and for a minimum of 100 days after discontinuing study treatment.								
Monitor for Serious Adverse Events	All SAEs must be collected from the date of participant's written consent and for a minimum of 100 days after discontinuing study treatment. Death due to disease progression within 100 days of discontinuation of study treatment must be reported as an SAE.								
Other Assessments									
PK Assessments	See Section 9.5 for further details								
Immunogenicity Assessments	See Section 9.5 for further details								
Biomarker Assessments	See Section 9.8								
Additional Research Sampling	See Section 9.8.4								
Efficacy Assessments	See Section 9.4								
Body Imaging	**For Part 1C:** Contrast-enhanced CT/MRI of the chest, abdomen, pelvis, and all other known/suspected sites of disease should occur every 8 weeks (± 7 days), starting from first dose for the first 48 weeks, then every 12 weeks (± 7 days) until withdrawal of consent, death, or								

Table 2-6: On-treatment Procedural Outline (Part 1C and Part 2 - BMS-986253 Q2W and Nivolumab and Ipilimumab Q3W)

Procedure	Cycle 1 and 2 (42 d)					Cycle 3 and Beyond (28 d)		EOT[a,b]	Notes
	D1	D15	D22	D29	D36	D1	D15		
	initiation of another anti-cancer treatment, whichever occurs first. For HCC participants, contrast-enhanced triphasic CT of the liver is required. See Section 9.4.1. **For Part 2:** Timing of scans should be based on date of first treatment, which is considered Week 1. Contrast-enhanced CT/MRI of the chest, abdomen, pelvis, and all other known/suspected sites of disease should occur every 8 weeks (± 7 days), starting from first dose for the first 48 weeks, then every 12 weeks (± 7 days). Tumor assessments should continue until BICR-confirmed disease progression, final analysis, or treatment discontinuation (including treatment beyond progression), whichever occurs later. See Section 9.4.1.								
Brain Imaging	Participants with a history of brain metastasis should have surveillance MRI as clinically indicated at the discretion of the investigator. See Section 9.4.1.								
Other: Bone Scan	As clinically indicated per local standards. See Section 9.4.1.								
Clinical Supplies									
IRT Assignment	X								Once eligibility has been confirmed, IRT assignment may be performed up to 3 days prior to study drug administration.
Study Drug Administration									
[redacted]									
Nivolumab Administration	X		X			X			Nivolumab will be administered every 3 weeks for the first 2 cycles (4 doses) and then every 4 weeks for Cycle 3 and beyond. See Section 7.1 for nivolumab dose administration.
Ipilimumab Administration	X		X						Ipilimumab will be administered every 3 weeks on Cycles 1 and 2 (4 doses) ONLY. See Section 7.1 for ipilimumab dose administration.

Abbreviations: AFP, alpha fetoprotein; BICR, blinded independent central review; C, Cycle; CT, computed tomography; d, days; D, day; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EDC, Electronic Data Capture; EOT, end of treatment; HCC, hepatocellular carcinoma; hCG, human chorionic gonadotropin; IRT, Interactive Response Technologies; MRI, magnetic resonance imaging; PK, pharmacokinetic(s); QXW, every X weeks; SAE, serious adverse event; T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone; WOCBP, women of childbearing potential.

[a] For participants who complete all scheduled cycles of therapy, the EOT visit will be the same visit as the last scheduled and completed on-treatment visit and the start of the Week 1 Clinical/Safety Follow-up visit.

[b] For participants who do not complete all scheduled cycles of therapy, the EOT visit will be the next visit following the last study dose. If the EOT visit occurs 30 days or more after receipt of the last dose, then the EOT visit and Follow-up 1 visit can be completed at the same time.

[c] If multiple procedures are required at a single timepoint, safety assessments (ECGs, vital signs, and pulse oximetry) are a higher priority than PK/immunogenicity sampling.

Table 2-7: Safety Follow-up Procedural Outline

Procedure	FU 1 30 Days (± 7 Days)	FU 3 100 Days (± 7 Days)	Response Follow-up (Q12W)	Notes
Safety Assessments				
Concomitant Medications	X	X		
ECOG Performance Status	X	X		Appendix 5
Physical Examination	X	X		
Vital Signs/Oxygen Saturation and Weight	X	X		Including weight, body temperature, respiratory rate, pulse oximetry, seated BP, and heart rate.
Laboratory Tests				
Hematology and Serum Chemistry	X	X		See Section 9.1.4 **Only applicable for Part 1C:** For HCC participants: AFP
Pregnancy testing (WOCBP)	X	X		
Pharmacokinetic Assessment				
PK / Immunogenicity Sampling	See Section 9.5 for further details			
Adverse Event Reporting				AEs reported during this time period should be followed until resolved to baseline, stabilized, or deemed irreversible.
Monitor for Nonserious AEs	All nonserious adverse events must be collected starting with the first dose of the study and for a minimum of 100 days after discontinuing study treatment.			
Monitor for SAEs	All SAEs must be collected from the time of signing the consent and for a minimum of 100 days after discontinuing study treatment. Death due to disease progression within 100 days of discontinuation of dosing must be reported as an SAE.			

Table 2-7: Safety Follow-up Procedural Outline

Procedure	FU 1 30 Days (± 7 Days)	FU 3 100 Days (± 7 Days)	Response Follow-up (Q12W)	Notes
Efficacy Assessments				
New and Subsequent Anti-cancer Therapy	X	X		New anti-cancer therapy including radiotherapy, surgery, and systemic therapy
Tumor Type Assessment				
Body Imaging	**Part 1:** See Section 9.4.1. After EOT, participants should continue tumor assessment on the same schedule, every 8 weeks (± 7 days), starting from first dose for the first 48 weeks, then every 12 weeks (± 7 days), until withdrawal of consent, death, initiation of another anti-cancer treatment, final analysis, or for up to a maximum of 2 years, whichever occurs first. **Part 2:** Timing of scans should be based on date of first treatment, which is considered Week 1. See Section 9.4.1. After EOT, participants in Part 2 will continue to have radiologic and clinical tumor assessments on the same schedule, every 8 weeks (± 7 days), starting from the first dose for the first 48 weeks, then every 12 weeks (± 7 days), until BICR-confirmed disease progression, final analysis, or treatment discontinuation (including treatment beyond progression), whichever occurs later. For participants with SCCHN, a CT or MRI of the neck is required. For HCC participants, contrast-enhanced triphasic CT of the liver is required. See Section 9.4.1 for further details.			
Brain Imaging	See Section 9.4.1. Participants with a history of brain metastasis should have surveillance MRI as clinically indicated at the discretion of the investigator.			
Other Bone Scan	See Section 9.4.1. As clinical indicated per local standards.			

Abbreviations: AE, adverse event; AFP, alpha fetoprotein; BICR, blinded independent central review; BP, blood pressure; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; EOT, end of treatment; FU, follow-up; HCC, hepatocellular carcinoma; IgG, immunoglobulin G; MRI, magnetic resonance imaging; PK, pharmacokinetic(s); Q12W, every 12 weeks; SAE, serious adverse event; SCCHN, squamous cell carcinoma of the head and neck; WOCBP, women of childbearing potential.

3 INTRODUCTION

This is a study of BMS-986253, a monoclonal antibody (mAb) against human interleukin-8 (IL-8), conducted in humans with advanced solid tumors. This study will evaluate the safety profile, tolerability, pharmacokinetics (PK), pharmacodynamics, and preliminary efficacy of BMS-986253 in combination with nivolumab (Parts 1A and 1B) or in combination with nivolumab and ipilimumab (Parts 1C and 2) in participants with advanced solid tumors.

Parts 1A and 1B will evaluate the safety, tolerability, PK, and pharmacodynamics of different doses of BMS-986253 in combination with nivolumab in participants with non-small cell lung cancer (NSCLC), melanoma, squamous cell carcinoma of the head and neck (SCCHN), urothelial cancer (UCC) and renal cell carcinoma (RCC), who have [redacted] Part 1C will evaluate the safety and tolerability of BMS-986253 in combination with nivolumab and ipilimumab in participants with melanoma, colorectal cancer (CRC), hepatocellular cancer (HCC), and UCC, who may have any serum IL-8 level. Part 2 is a randomized, double-blind evaluation to assess efficacy of BMS-986253 in combination with nivolumab and ipilimumab versus placebo plus nivolumab and ipilimumab in participants with unresectable or metastatic melanoma.

3.1 Study Rationale

Immuno-oncology (I-O) drugs, which harness the immune system to fight cancer, have emerged as a major advancement in cancer treatment.[1] Current approaches include blocking immunosuppressive signals, such as programmed cell death 1 (PD-1) or cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) with antagonistic antibodies and stimulating immunity with agonistic antibodies. Despite recent progress, in many cases resistance to the immunotherapy occurs due to the interplay of various mechanisms of immune suppression.[2] Thus, new combination strategies are needed to target these multiple mechanisms of immune suppression to overcome the resistance and to extend the breadth of current immune therapies.

There is growing evidence that IL-8 (also called CXCL8) plays an important role in immunosuppression.[3] IL-8 belongs to the CXC chemokine subfamily that includes several molecules involved in the activation and chemoattraction of various leukocytes.[4] IL-8 expression is highly regulated in healthy individuals with serum IL-8 concentrations at very low or undetectable levels [redacted][5,6] However, IL-8 serum concentrations are often elevated in cancer patients.[3,7,8,9,10] IL-8 may be produced by a variety of cells, including cancer cells, leukocytes, endothelial cells, and fibroblasts. IL-8 binds to two receptors, CXCR1 and CXCR2,[11] and promotes recruitment of myeloid derived suppressor cells (MDSCs) to the tumor microenvironment (TME), and suppress T-cell function. [12,13] IL-8 has also been shown to play a pro-tumoral role in the TME, and promote the epithelial mesenchymal transition (EMT),[14] cancer stem cell (CSC) renewal,[15,16] and angiogenesis.[17,18]

In many types of advanced cancer, high levels of IL-8 correlate with worse prognosis as well as resistance to therapeutic approaches, including anti PD-1 and anti-CTLA-4 therapy.[3,19,20,21,25] One

hypothesis that can explain this resistance is IL-8-dependent recruitment of immunosuppressive MDSC into the tumor.[22] Preliminary analysis of several clinical trials containing nivolumab-based therapy confirm recent observations made by other groups, that high levels of IL-8 are associated with resistance to anti-PD-L1-based therapy in advanced NSCLC, melanoma, and RCC (see Section 5.4.3).[21,23] Thus, blocking IL-8 with an antagonist antibody in combination with nivolumab or nivolumab plus ipilimumab represents an approach with the potential to extend I-O benefits to patients not adequately served by existing anti-PD-(L)1 therapies alone. Pharmacological inhibition of IL-8 is a rational approach to disrupt not only immunosuppression associated with MDSCs, but also pro-tumorigenic mechanisms of CSC maintenance, EMT, and angiogenesis.

3.2 Background

3.2.1 BMS-986253

BMS-986253 is a fully human-sequence IgG1κ mAb directed against IL-8. [redacted] The antibody will thus antagonize the IL-8 mediated signals and may increase the anti-tumor response through distinct mechanisms of action:

- blocking the recruitment of immunosuppressive MDSC to the tumor
- disrupting angiogenesis
- inhibition of invasive EMT
- affecting the CSC phenotype

Furthermore, relieving the immunosuppression by reducing MDSCs in the tumor microenvironment has the potential to increase the activation of Effector CD8 T cells in synergy with PD-1 blockade by nivolumab. This study will, in part, evaluate this hypothesis in participants with NSCLC, melanoma, RCC, UCC, or SCCHN that progress on or after anti-PD-(L)1 therapy and which have a detectable level of IL-8 in the serum.

Previous data on treatment with BMS-986253 monotherapy in humans, demonstrated a safe and tolerable profile (see BMS-986253 Investigator's Brochure [IB]).[24] The highest dose tested in humans was administered in the CA027001 Study, in which multiple ascending doses of BMS-986253 were found to be safe and well tolerated across the dose range of 4 to 32 mg/kg every 2 weeks (Q2W) in 15 participants with advanced tumors.[25] This was equivalent to a 2560 mg flat dose for 80 kg body weight Q2W or a 5120 mg total accumulative dose Q4W. No serious adverse events (SAEs) were considered related to BMS-986253 monotherapy. There was no increase in the frequency of adverse events (AEs) with increased doses. There were no deaths or discontinuations due to AEs in this study. The maximum tolerated dose (MTD) was not reached.

The current study will evaluate the safety, tolerability, and preliminary efficacy of intravenous (IV) doses of BMS-986253, administered in combination with nivolumab or in combination with nivolumab and ipilimumab in participants with advanced solid tumors, and is expected to

determine the recommended Phase 2 dose(s) (RP2D) of the combination to be used in future studies.

It is anticipated that anti-IL-8 mAb (BMS-986253) administered in combination with anti-PD-1 mAb (nivolumab) or in combination with nivolumab and anti-CTLA-4 mAb (ipilimumab), will demonstrate adequate safety and tolerability, as well as a favorable risk/benefit profile to support further clinical testing.

The scientific rationale for the study design is discussed in greater detail in Section 5.3. Additional details such as BMS-986253 Nonclinical/Clinical Pharmacology, Nonclinical/Clinical PK/ pharmacodynamics, Nonclinical Toxicology and clinical safety are summarized in the BMS-986253 IB.[24]

3.2.2 Nivolumab

Nivolumab is a fully human, IgG4 (kappa) isotype mAb that binds to PD-1 with nanomolar affinity (dissociation constant, 3.06 nM) and a high degree of specificity. Nivolumab blocks binding of PD-1 to its ligands programmed death ligand 1 (PD-L1) and programmed death ligand 2 (PD-L2). Nonclinical in vitro testing of nivolumab demonstrated that binding to PD-1 results in enhanced T-cell proliferation and release of interferon gamma in vitro in mixed lymphocyte reaction and cytomegalovirus assays.

The nonclinical safety of nivolumab was evaluated in a comprehensive toxicology program in mice and monkeys and was submitted as part of Biologics License Application 125554. Details of the in vitro and in vivo nonclinical pharmacology studies conducted to support the development of nivolumab can be found in Section 4.1 of the nivolumab IB.

While nivolumab was well tolerated in cynomolgus monkeys, there is a potential for enhanced toxicity when combined with other immunostimulatory agents. However, nonclinical studies with nivolumab did not predict clinically relevant adverse effects (eg, no evidence of immune-mediated adverse effects was observed in nonclinical toxicology studies with nivolumab). Therefore, combination nonclinical toxicology studies with BMS-986253 and nivolumab have not been conducted and are not required by the International Conference on Harmonisation S9 Note for Guidance on Nonclinical Evaluation for Anticancer Pharmaceuticals. The safety of the combination will be carefully monitored in the planned clinical trial.

The overall safety experience with nivolumab, as either monotherapy or in combination with other therapeutics, is based on experience in approximately 26,400 subjects (see nivolumab IB).[26] Nivolumab has been approved by the United States (US) Food and Drug Administration (FDA) for various indications, including unresectable or metastatic melanoma (as a single agent and in combination with ipilimumab), metastatic NSCLC (as a single agent and in combination with ipilimumab), advanced RCC (as a single agent and in combination with ipilimumab), recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after a platinum-based therapy, advanced or metastatic urothelial carcinoma with disease progression on or after a platinum-based therapy, and MSI-H CRC (as a single agent or in combination with ipilimumab).

For nivolumab monotherapy, the safety profile is similar across tumor types. The only exception is pulmonary inflammation AEs, which may be numerically greater in participants with NSCLC. In participants with NSCLC, it can be difficult to distinguish between nivolumab-related and unrelated causes of pulmonary symptoms and radiographic changes. There is no relationship between the incidence, severity, or causality of AEs and the nivolumab dose level. The safety of nivolumab in combination with other therapeutics such as ipilimumab, cytotoxic chemotherapy, anti-angiogenics, and targeted therapies is being explored in several ongoing clinical trials. The safety profile of nivolumab combination therapy varies with the agent combined with nivolumab, but is generally consistent with the safety profiles observed with either agent alone and, in some cases, both frequency and severity of AEs were greater than that observed with either agent alone. Additional details on the safety profile of nivolumab, including results from other clinical studies, are summarized in the nivolumab IB.[26]

3.2.3 Ipilimumab

Ipilimumab is a fully human IgG1 (kappa) monoclonal antibody that binds to human cytotoxic T-lymphocyte antigen 4 (CTLA-4) with nanomolar affinity (dissociation constant 5.25 nM) and a high degree of specificity. CTLA-4 is expressed on a subset of activated T-cells on which it acts as a negative regulator of T-cell activity. Ipilimumab is a mAb 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 Treg function, which may contribute to a general increase in T-cell responsiveness, including the anti-tumor response.

The overall safety experience of ipilimumab as either monotherapy or in combination with other therapeutics is based on experience in over 30,000 subjects. Additional details on the safety profile of ipilimumab, including results from other clinical studies, are summarized in the ipilimumab IB.[27]

Ipilimumab has been approved by the US FDA for the treatment of several cancers, including unresectable or metastatic melanoma (single agent or combined with nivolumab), intermediate- or poor-risk RCC (in combination with nivolumab), MSI-H CRC that has progressed after chemotherapy (in combination with nivolumab), HCC that has previously been treated with sorafenib (in combination with nivolumab), and first-line NSCLC with PD-L1 $\geq 1\%$ (in combination with nivolumab).

3.2.4 Nivolumab plus Ipilimumab

The combination of nivolumab and ipilimumab has been approved by the US FDA for the treatment of patients across a variety of cancers, including melanoma, intermediate-/poor-risk-RCC, NSCLC, MSI-H CRC, and HCC (as indicated in Section 3.2.3). The safety profile of nivolumab plus ipilimumab is characterized by immune-related toxicities, such as diarrhea, rash, pneumonitis, liver toxicity, and endocrinopathies. The frequencies and intensities of these events in the combination are variable and depend on the specific doses and schedule used. Additional details on the safety profile on the combination of nivolumab and ipilimumab, are summarized in the nivolumab IB.[26]

[redacted]

3.3 Benefit/Risk Assessment

Patients who have advanced solid tumors including metastatic/unresectable melanoma, NSCLC, SCCHN, RCC, UCC, HCC, or CRC, that progress after at least 1 line of standard systemic therapy have a poor prognosis and no curative options.

The safety of BMS-986253 as monotherapy has been established in earlier studies in healthy volunteers, participants with inflammatory skin disease (Palmoplantar Pustulosis), and in participants with advanced malignancies. BMS-986253 monotherapy has been administered to participants with advanced malignancies [redacted] and was demonstrated to be safe and tolerable.

The safety profile of nivolumab monotherapy is well defined and is based on experience with greater than 15,000 participants evaluated in clinical trials. The frequency and types of immune-mediated adverse reactions (IMARs) are similar across multiple types of tumors and are described in the Reference Safety Information (RSI) in the current nivolumab IB. Management algorithms for nivolumab-induced AEs involving gastrointestinal, renal, pulmonary, hepatic, endocrinopathy, skin, and neurologic systems are included in the protocol (Appendix 5).

The safety profile of ipilimumab monotherapy is well defined and is based on experience with greater than 7,300 participants evaluated in clinical trials. The frequency and types of IMARs are similar across multiple types of tumors and are described in the RSI in the current ipilimumab IB.[27] Management algorithms for ipilimumab-induced AEs involving myocarditis, gastrointestinal, renal, pulmonary, hepatic, endocrinopathy, skin, and neurologic systems are included in the protocol (Appendix 6).

In combination with nivolumab, the risk that BMS-986253 may potentiate immune-mediated adverse reactions should be low as blocking IL-8 does not directly activate T-cells. Blocking IL-8 may, in fact, reduce the inflammatory process by reducing the neutrophil recruitment in the

damaged tissue. Available safety data from trials using I-O combination strategies with nivolumab have shown that the safety profile varies depending on the agent being combined with nivolumab, but is generally consistent with the safety profiles observed with either agent alone and, in some cases, both the frequency and severity of AEs were greater than that observed with either agent alone. The safety of the combination of BMS-986253 with nivolumab will be carefully monitored in the study. [redacted] Overall, [redacted] participants experienced Grade ≥ 3 related AEs, and [redacted] participants discontinued study treatment because of AEs related to the study drugs (less than or similar to that expected with nivolumab monotherapy in an I-O naïve population). There were no deaths related to the study drugs, and there were no dose-dependent AEs identified. Based on these data, an increase in IMARs with the combination of BMS-986253 and nivolumab compared with nivolumab monotherapy is not expected.[24]

The triplet combination of BMS-986253, nivolumab, and ipilimumab has not been previously evaluated. However, based on the safety data generated on the combination of BMS-986253 and nivolumab, and the combination of nivolumab and ipilimumab, the triplet combination is expected to have a tolerable safety profile. For similar reasons, as stated in the previous paragraph (mainly that blocking IL-8 may reduce the inflammatory process and safety data generated on the combination of BMS-986253 and nivolumab), BMS-986253 is not expected to increase the rate of IMARs observed with the combination of nivolumab and ipilimumab.

[redacted]

Continuous safety assessments will be utilized by the investigators and Bristol Myers Squibb (BMS) to determine whether dose modification, additional safety measures, or termination of the study is required at any time. In addition, AEs and SAEs will be reviewed on an ongoing basis by the BMS Medical Monitor and Global Pharmacovigilance and Epidemiology representatives to monitor for any safety signals or trends. Additionally, in Part 2 of the study, an independent safety or Data Monitoring Committee (DMC) will be used [redacted] As BMS-986253 is an experimental agent, it is possible that unforeseen, unknown, or unanticipated reactions may occur. The protocol was developed while carefully balancing risks and benefits of treatment of a novel treatment in this patient population.

3.3.1 Safety Monitoring on Study Treatment

Frequent safety assessments will be carried out by the Sponsor/BMS Medical Monitor (or designee) and investigators throughout the study to determine whether dose modification, additional safety measures, or termination of the study treatment combination arm is required at any time. In addition, AEs and SAEs will be reviewed regularly by the BMS Medical Monitor (or designee) and the Pharmacovigilance group to look for trends and potential safety signals. Treatment of AEs will follow institutional guidelines and recommended management algorithms, as listed in the IBs and prescribing information, as applicable, for each combination agent, and provided as appendices to this protocol. Specific algorithms for the management of immune-related adverse events (irAEs) are provided in Appendix 6 and are applicable to irAEs for all I-O study treatment combinations.

The global coronavirus disease 2019 (COVID-19) pandemic has been identified as a potential risk to clinical trial participants in general. Whether BMS-986253 in combination with nivolumab or in combination with nivolumab and ipilimumab administration increases the risk for contracting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or increases the severity or duration of symptoms is currently unknown. This unknown risk must be considered when enrolling a participant.

No additional safety monitoring or routine screening tests will be required due to the SARS-CoV-2 pandemic. Participants with a recent or acute infection will be excluded or delay start of treatment as defined in Section 6.2. If a participant has a confirmed SARS-CoV-2 infection while on study treatment, dose delay or interruption of study treatment is required as described in Section 7.6.3.

The study has been designed with study visits that allow for close monitoring of participants' safety throughout the clinical trial (Section 9.1), 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.

Non-live COVID-19 vaccination is considered a simple concomitant medication within the study. However, the efficacy and safety of non-live vaccines (including non-live COVID-19 vaccines) in participants receiving BMS-986253 in combination with nivolumab or in combination with nivolumab and ipilimumab is unknown.

Additionally, in Part 2 of this study, an independent DMC will provide oversight. The DMC will act in an advisory capacity to BMS and will monitor participant safety and evaluate the available efficacy data for the study. They will advise the Sponsor regarding actions the committee deems necessary for the continuing protection of participants enrolled in the study and those yet to be recruited to the trial as well as for the continuing validity and scientific merit of the study results. The DMC is charged with assessing such actions in light of an acceptable benefit-risk profile for BMS-986253. [redacted] The oncology therapeutic area of BMS has primary responsibility for design and conduct of the study.

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints - Part 1

Objectives	Endpoints
Primary	
• To characterize safety, tolerability, and DLTs, and to determine the RP2D of BMS-986253 administered in combination with nivolumab, or in combination with nivolumab and ipilimumab in participants with advanced solid tumors.	• Incidence of AEs, SAEs, AEs meeting protocol-defined DLT criteria, and AEs leading to discontinuation, death, and laboratory abnormalities.
Secondary	
• To evaluate the preliminary efficacy of BMS-986253 in combination with nivolumab in participants with advanced solid tumors using RECIST v1.1. • To characterize the PK and immunogenicity of BMS-986253 when administered in combination with nivolumab, or in combination with nivolumab and ipilimumab in participants with advanced solid tumors. • To assess serum IL-8 levels at baseline (ie, screening) and changes in IL-8 levels on treatment.	• ORR and DOR per RECIST v1.1 per investigator. • Summary measures of PK parameters and incidence of ADA to BMS-986253. • Summary measures of IL-8 and change (or percent change) from baseline in IL-8 on treatment.
[redacted]	

Abbreviations: ADA, anti-drug antibody; AE, adverse event; DLT, dose-limiting toxicity; DOR, duration of response; [redacted] EOT, end of treatment; ORR, objective response rate; PK, pharmacokinetic(s); [redacted]

[redacted] RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended Phase 2 dose; SAE, serious adverse event.

Table 4-2: Objectives and Endpoints - Part 2

Objectives	Endpoints
Primary	
• To compare the ORR of BMS-986253 plus nivolumab plus ipilimumab with placebo plus nivolumab and ipilimumab using RECIST v1.1.	• ORR based on BICR assessments per RECIST v1.1 in all randomized participants.
Secondary	
• To estimate PFS of BMS-986253 plus nivolumab plus ipilimumab and placebo plus nivolumab and ipilimumab in participants with advanced melanoma using RECIST v1.1 (regardless of baseline serum IL-8 levels).	• mPFS and PFS hazard ratio based on BICR assessments per RECIST v1.1.
• To compare the safety of BMS-986253 plus nivolumab plus ipilimumab with placebo plus nivolumab plus ipilimumab in participants with advanced melanoma.	• Incidence of AEs, SAEs, and AEs leading to discontinuation, death, and laboratory abnormalities.
[redacted]	

Table 4-2: Objectives and Endpoints - Part 2

[redacted]

Abbreviations: ADA, anti-drug antibody; AE, adverse event; BICR, blinded independent central review; CI, confidence interval; DOR, duration of response; [redacted]; IL-8, interleukin 8; [redacted] ORR, objective response rate; [redacted] mPFS, median progression free survival; PFS, progression-free survival; [redacted] PMN, polymorphonuclear neutrophil; QTcF, QT interval corrected by the Fridericia correction formula; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event; [redacted]

5 STUDY DESIGN

5.1 Overall Design

This is a Phase 1/2 study of BMS-986253 administered in combination with nivolumab or in combination with nivolumab and ipilimumab in participants with advanced solid tumors. The study is comprised of 2 parts: Part 1 and Part 2.

In Part 1, the safety of BMS-986253 in combination with nivolumab, or in combination with nivolumab and ipilimumab will be evaluated in participants with advanced solid tumors. Part 1 is divided into 3 subsections: Part 1A (BMS-986253 plus nivolumab safety evaluation lead-in), Part 1B (BMS-986253 plus nivolumab dose finding), and Part 1C (safety evaluation of BMS-986253 in combination with nivolumab and ipilimumab). Parts 1A and 1B evaluate the doublet combination of BMS-986253 and nivolumab in participants with [redacted] Part 1C is a safety evaluation of the triplet combination of BMS-986253, nivolumab, and ipilimumab, in participants with any baseline level of serum IL-8 (see Figure 5.1-2). [redacted] The RP2D will be determined based on the totality of the data in Part 1, to define the safe and most biologically active dose. The following tumor types will be enrolled onto Part 1 as described in the inclusion criteria:

- Parts 1A and 1B [redacted]: melanoma, RCC, UCC, SCCHN, and NSCLC [redacted]
- Part 1C: melanoma, UCC, HCC, and CRC

Part 2 is a randomized, double-blind evaluation of BMS-986253 plus nivolumab plus ipilimumab versus placebo plus nivolumab plus ipilimumab in melanoma. The study design schematic is presented in Figure 5.1-3.

Part 1A: Safety Evaluation Lead-in (already enrolled, [redacted] participants, per BMS-986253 IB[24])

The safety evaluation lead-in (Part 1A) will begin with a cohort of participants who will receive a 2400 mg flat dose of BMS-986253 Q4W combined with 480 mg flat dose of nivolumab Q4W. A slightly higher dose (32 mg/kg or 2560 mg administered Q2W; yielding an overall dose of 64 mg/kg or 5120 mg per month) of BMS-986253 monotherapy has been shown to be safe and well tolerated in BMS Study CA027001 (see BMS-986253 IB[24]). [redacted] After review of the clinical safety, including dose-limiting toxicities (DLTs) for the first 4 participants, the dose-finding phase (Part 1B) will open.

Part 1B: Dose-finding (participants enrolled in each cohort are per BMS-986253 IB[24])

In Part 1B, participants will be randomly assigned to receive one of the following dosing regimens:

- Cohort 1B1: 2400 mg of BMS-986253 Q4W and 480 mg of nivolumab Q4W [redacted]
- Cohort 1B2: 1200 mg of BMS-986253 Q4W and 480 mg of nivolumab Q4W [redacted]
- Cohort 1B3: 600 mg of BMS-986253 Q4W and 480 mg of nivolumab Q4W [redacted]

Assignment into any dosing regimen arm may be suspended [redacted] In addition, up to 4 new dosing regimens assessing the combination of BMS-986253 and nivolumab may be initiated [redacted] Additional cohorts for alternate dosing regimens may include:

- Cohort 1B4: 2400 mg of BMS-986253 Q2W and 480 mg of nivolumab Q4W [redacted]
- Cohort 1B5: 1200 mg of BMS-986253 Q2W and 480 mg of nivolumab Q4W [redacted]
- Cohort 1B6: 3600 mg of BMS-986253 Q2W and 480 mg of nivolumab Q4W [redacted]

[redacted]

For any dosing regimen evaluating a higher dose of BMS-986253 than previously explored, an initial 4-participant safety-lead with a 28-day DLT period will be required. Approximately [redacted] participants will be dosed in the treatment arms. Additional exploration of a specific dosing regimen may be warranted in Part 1B, in which case additional participants will be assigned to that dosing regimen. [redacted] A maximum of approximately [redacted] participants will be dosed in Part 1A and Part 1B.

[redacted]

[redacted]

Part 1C: Safety Evaluation of BMS-986253 in Combination with Nivolumab and Ipilimumab

Part 1C is a safety evaluation of BMS-986253 in combination with nivolumab and ipilimumab. Part 1C will begin once the DLT period is completed for Cohort 1B6 (BMS-986253 3600 mg Q2W + nivolumab 480 mg Q4W), and will enroll simultaneously with Part 1 Cohort 1B6. [redacted]

The higher-dose triplet combination Cohort 1C1 will enroll first. The safety and tolerability of this part will be evaluated [redacted] to guide dose escalation decisions [redacted] and the overall assessment [redacted]

In Part 1C, participants will initially be enrolled onto Cohort 1C1. For the first 12 weeks, participants will receive BMS-986253 3600 mg Q2W from Part 1B + nivolumab 1 mg/kg Q3W + ipilimumab 3 mg/kg Q3W. After 12 weeks, participants will receive BMS-986253 3600 mg Q2W from Part 1B and nivolumab 480 mg Q4W. [redacted]

[redacted]

[redacted]

[redacted]

Part 2: Double-blind Randomized Evaluation of BMS-986253 plus Nivolumab plus Ipilimumab versus Placebo plus Nivolumab plus Ipilimumab in Advanced Melanoma

Part 2 will begin after determination of the RP2D of BMS-986253 based on Part 1A and 1B data [redacted] and generation of safety data on the triplet combination of BMS-986253 plus nivolumab plus ipilimumab in Part 1C. [redacted]

Part 2 is a double-blind randomized evaluation of BMS-986253 plus nivolumab plus ipilimumab (2A) versus placebo plus nivolumab plus ipilimumab (2B) to evaluate the efficacy of BMS-986253 in participants with advanced melanoma who are refractory to anti-PD-(L)1 therapy.

This portion of the study will include participants with unresectable or metastatic melanoma (non-ocular), who had progression on or after anti-PD-(L)1 therapy, but have not been treated with prior anti-CTLA-4 therapy (see Section 6.1). Participants will be randomly assigned in a 1:1 ratio to 1 of 2 treatment arms:

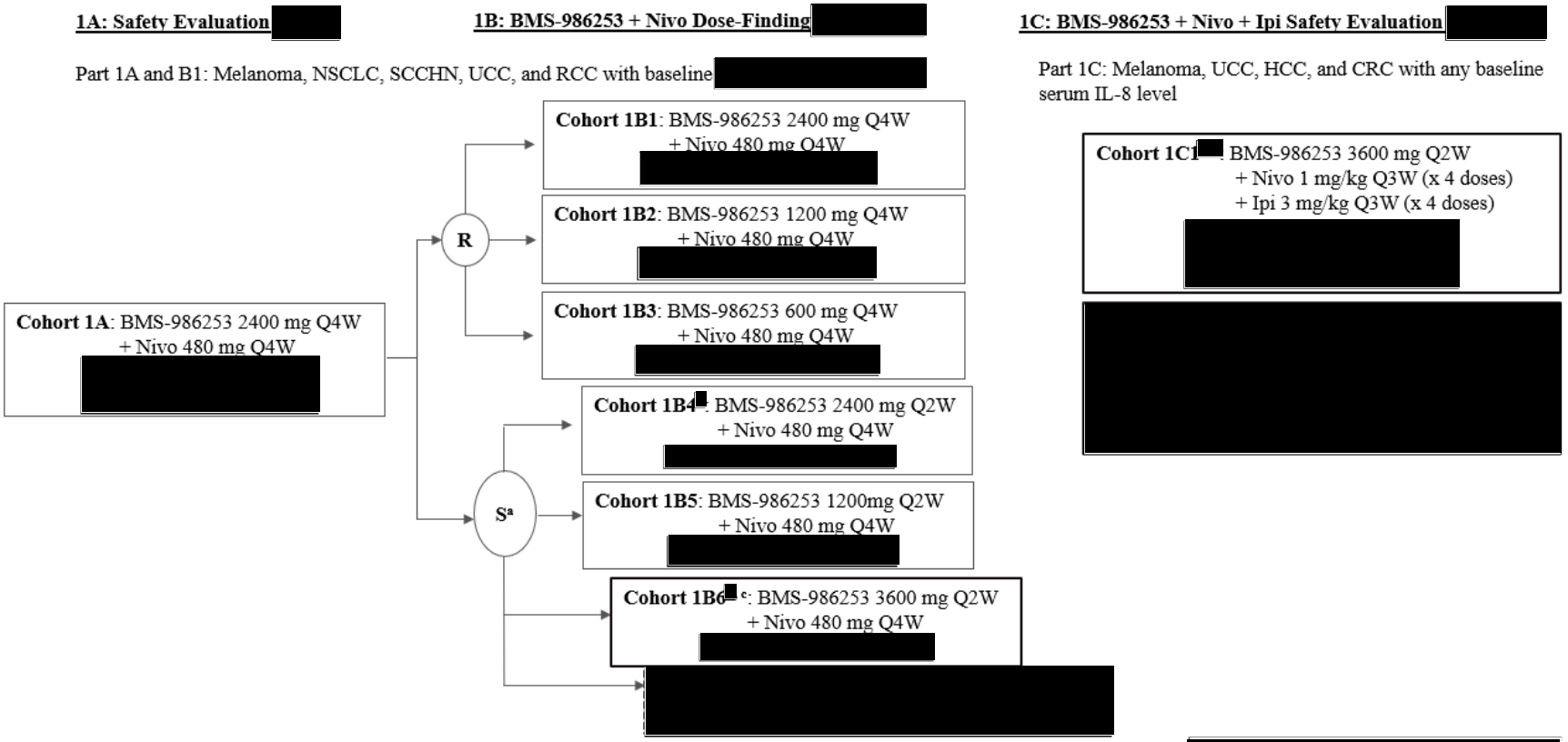
- 2A: BMS-986253 + nivolumab + ipilimumab
- 2B: placebo + nivolumab + ipilimumab

During randomization, participants will be stratified by the following factors as described in Section 7.4: screening serum IL-8 level, [redacted] and lactate dehydrogenase (LDH) levels.

The dose of nivolumab and ipilimumab will be determined by safety data from Part 1C, and the dose of BMS-986253 will be determined by the totality of Part 1 data. If safety is confirmed in Cohort 1C1, for the first 12 weeks, participants will receive ipilimumab 3 mg/kg Q3W IV (4 doses), nivolumab 1 mg/kg Q3W IV (4 doses), and BMS-986253 3600 mg Q2W or placebo IV (given at Q2W frequency for 6 doses). After 12 weeks, participants will be maintained on BMS-986253 3600 mg Q2W or placebo IV (Q2W) and nivolumab IV (480 mg Q4W). [redacted]

Approximately [redacted] participants will be included in Part 2 and randomized in a 1:1 ratio to each arm.

Figure 5.1-2:Study Design Part 1

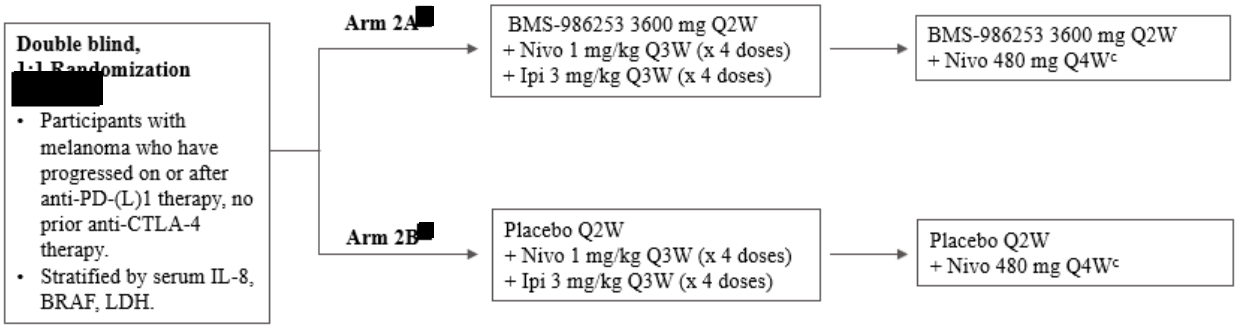


Abbreviations: CRC, colorectal cancer; HCC, hepatocellular carcinoma; IL, interleukin; Ipi, ipilimumab; max, maximum; Nivo, nivolumab; NSCLC, non-small cell lung cancer; QXW, every X weeks; R, randomized; RCC, renal cell carcinoma; S, sequential assignment; SCCHN, squamous cell carcinoma of the head and neck; UCC, urothelial cancer.

[a] Once sequential enrollment begins, up to 4 additional cohorts may be evaluated in Part 1B.

[redacted]

Figure 5.1-3:Study Design Part 2



Abbreviations: BRAF, proto-oncogene B-Raf; CTLA, cytotoxic T-lymphocyte-associated protein; IL, interleukin, Ipi, ipilimumab; LDH, lactate dehydrogenase; Nivo, nivolumab; PD-(L)1, programmed cell death (ligand) 1; QXW, every X weeks.

[redacted]

[c] After 12 weeks, nivolumab will be administered at 480 mg Q4W.

5.1.1 Pre-Screening Period (Applicable for Part 1 Only)

Participants will provide consent for pre-screening to obtain a serum IL-8 level; further screening procedures will not be completed until the IL-8 level is resulted (except for participants with HCC and CRC). Depending on availability of cohorts at the time of enrollment, serum IL-8 results may determine eligibility and cohort assignment.

- Enrollment into Part 1B requires [redacted]
- Enrollment into Part 1C does NOT require a minimum serum IL-8 level.
- For participants with HCC and CRC: results of screening IL-8 are NOT required prior to signing the Main Informed Consent, since all HCC and CRC participants will be assigned to Part 1C (Part 1C does not require a minimum serum IL-8 level). Participants with HCC and CRC may enroll only when Part 1C is open.
- For participants with melanoma or UCC only being considered for Part 1C (for example, if Part 1B is not actively enrolling participants), results of screening IL-8 are NOT required prior to signing the Main Informed Consent.

If the participant meets pre-screening criterion for study entry, the Main Informed Consent must be signed within 1 week of serum IL-8 positive result by the central laboratory. Participants will be enrolled using Interactive Response Technology (IRT) during Pre-Screening and will be assigned a designated subject identification number.

5.1.2 Screening Period

The screening period will be up to 28 days and begins by establishing the participant's initial eligibility and signing of the informed consent form (ICF). In order to establish eligibility for this study, participants will undergo baseline physical examinations, vital signs and oxygen saturation measurements, 12-lead electrocardiogram (ECG), [redacted] and clinical laboratory evaluations.

If a participant exceeds the 28-day screening period (eg, [redacted] waiting for a laboratory value), the participant must be reconsented, but does not require a new participant identification number. The fewest number of procedures from the initial screening should be repeated to qualify the participant, while maintaining participant safety and eligibility. Repeat serum IL-8 testing will not be required if the previous sample was obtained within 42 days of study treatment initiation.

Assignment to a Study Part 1 (1A, 1B, or 1C) must be designated in the IRT system prior to the participant's assignment to a dosing regimen. In Part 2, all participants will be randomly assigned to Arm 2A (BMS-986253 + nivolumab + ipilimumab) or 2B (placebo + nivolumab + ipilimumab). Prior to randomization in Part 2, screening laboratory test results for serum IL-8 and LDH must be received, and [redacted] must be entered in the electronic case report form (eCRF). Part 2 of the study is double-blind; the participant, Sponsor, and site staff (except as indicated in Section 7.5) will not be aware of treatment/cohort assignment, as described in Section 7.4.

5.1.3 Treatment Period

Physical examinations, vital sign or pulse oximetry measurements, 12-lead ECGs, and clinical laboratory evaluations will be performed at selected times throughout the study (see Section 2).

[redacted]

Participants will be closely monitored for AEs throughout the study. Blood samples will be collected at selected times for PK and pharmacodynamic analysis as per Section 9.8, [redacted] In Part 1, stool will be collected during screening, on treatment, and at progression to evaluate pharmacodynamic effect in relation to the gut microbiota (per Section 9.8, [redacted] In Part 2, stool will be collected during screening only (per Section 9.8, [redacted]

All participants will be treated for up to 3 calendar years from first dose or until disease progression, intolerance to treatment, meeting discontinuation criteria, or withdrawal of consent.

Participants enrolled in the safety evaluation lead-in period (Part 1A), will start with a 4-week DLT evaluation following the first dose (corresponding to the first cycle of the treatment period). A sentinel participant approach will be used with a 5-day interval between the treatment initiation of the first participant and the treatment of subsequent participants at each dose level that will be

tested in Part 1A. Participants enrolled in the dose-finding (Part 1B), in the triplet safety assessment (Part 1C), and in Part 2 of the study will start their treatment period at the dose regimen according to their assigned cohort, respectively. Additional cohorts in Part 1 may start with a safety lead-in (4-week DLT evaluation) as previously described.

Study visits and samples collections will vary based on cohort assignment as per Sections 9.5 and 9.8.

5.1.4 Window Visits

A ± 3-day window is permitted to accommodate study participants and schedules between treatment visits. [redacted]

5.1.5 Follow-up

5.1.5.1 Safety Follow-up Period

Upon completion of study therapy (or up to a maximum of 156 weeks if applicable), or once the decision is made to discontinue the participant from treatment, ie, at end of treatment (EOT), all participants will enter a safety follow-up period.

For participants who complete all scheduled cycles of therapy, the EOT visit will be the same visit as the last scheduled and completed on-treatment visit, and will be 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 next visit following the last study dose. If the EOT visit occurs 30 days or more after receipt of the last dose, then the EOT visit and Follow-up 1 visit can be completed at the same time.

All participants will be evaluated for any new AEs for a minimum of 100 days after discontinuing study treatment. Follow-up visits should occur at Days 30 and 100 (± 7 days for all study visits) after the last dose. All participants will be required to complete the 3 clinical safety follow-up visits, regardless of whether new anti-cancer therapy is started, except those participants who withdraw consent for study participation.

5.1.5.2 Response Follow-up Period

At the time of study treatment discontinuation, participants in Part 1 will continue to have radiologic and clinical tumor assessments on the same schedule, every 8 weeks (± 7 days), for the first 48 weeks after the first dose. After 48 weeks, radiological and clinical tumor assessments will occur 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 after EOT.

Participants in Part 2 will continue to have radiologic and clinical tumor assessments on the same schedule, every 8 weeks (± 7 days), starting from first dose for the first 48 weeks, then every 12 weeks (± 7 days), until blinded independent central review (BICR)-confirmed disease progression, final analysis, or treatment discontinuation (including treatment beyond progression), whichever occurs later.

5.1.5.3 Survival Follow-up Period

As of Protocol Amendment 07 Global, survival follow-up will no longer be performed.

All participants will begin survival follow-up after completion of safety follow-up every 12 weeks (± 2 weeks) until 2 years after last dose of study treatment. All participants will be followed-up by either a clinic visit or telephone contact Q12W (from completion of safety follow-up) for 2 years or until death, lost to follow-up, withdrawal of consent, or conclusion of the study, whichever comes first. Participants will have both the Response Follow-up Period and Survival Follow-up Period occur simultaneously during the 2-year follow-up period. The duration of this follow-up is up to 2 years after completion of safety follow-up, although a longer follow-up period could be considered in selected cases if an efficacy signal is apparent. New and subsequent cancer therapies will also be recorded in this Survival Follow-up Period.

5.1.6 Data Monitoring Committee and Other External Committees

For Part 1 of this study, BMS has elected not to use a DMC. In addition to the comprehensive safety monitoring plan outlined below, the following key points were considered for this decision:

- This is an open-label study.
- Participants will be observed frequently for clinical evaluation and blood counts during the study.
- The eligibility criteria exclude participants with disease characteristics that could predispose them to a higher risk of morbidity.
- Exclusion of participants with known autoimmunity (as per Section 6.2 exclusion criteria) also applies as they could be at risk for exacerbation of their current condition.
- Well-defined discontinuation criteria are established in the protocol for individual participants for both safety and treatment futility with clear criteria for treatment discontinuation, dose delay, and toxicity management.

BMS has in place a multi-layered process for ensuring participant safety through close collaboration of study site investigators, the BMS study team, and the BMS Worldwide Patient Safety (WWPS)-led Safety Management Team (SMT). This collaborative process constitutes the Data Safety Monitoring Plan for the study as detailed below:

Study safety is evaluated continuously by representatives of BMS WWPS, who operate independently from the clinical team and monitor safety across all BMS protocols. AEs are monitored continuously by WWPS. Signal detection is performed at least monthly and ad hoc throughout the study by the SMT composed, at a minimum, of the WWPS medical safety assessment physician (Chair of the SMT) and WWPS single case review physician, the study Medical Monitor(s), the study biostatistician, and epidemiologist. The SMT monitors actual or potential issues related to participant safety that could result in a significant change in the medical risk-benefit balance associated with the use of study treatments. Furthermore, investigators will be kept updated of important safety information, such as DLTs, during teleconferences between investigators and the BMS clinical team that will be held at least Q4W during dose escalation and

at least monthly during dose expansion. If appropriate, select safety issues may be escalated to a senior level, multidisciplinary, BMS-wide Medical Review Group for further evaluation and action.

To support safety oversight, BMS has established ongoing processes for collection, review, analysis, and submission of individual AE reports and their aggregate analyses. Because this is an open-label part, the BMS Medical Monitor and the investigators will have access to all data necessary for safety evaluation.

For Part 2 of this study (a randomized, double-blind evaluation of BMS-986253 plus nivolumab plus ipilimumab vs placebo plus nivolumab plus ipilimumab), an independent DMC will provide oversight. The DMC will act in an advisory capacity to BMS and will monitor participant safety and evaluate the available efficacy data for the study. They will advise the sponsor regarding actions the committee deems necessary for the continuing protection of participants enrolled in the study and those yet to be recruited to the trial as well as for the continuing validity and scientific merit of the study results. The DMC is charged with assessing such actions in light of an acceptable benefit-risk profile for BMS-986253. Details of DMC responsibilities and tasks are specified in the DMC charter.

[redacted] The oncology therapeutic area of BMS has primary responsibility for design and conduct of the study.

In addition, a BICR will be utilized in Part 2 for determination of BICR-assessed endpoints.

The BICR will review all available tumor assessment scans for all treated participants. Details of BICR responsibilities and procedures will be specified in the BICR charter.

5.2 Number of Participants

The maximum total number of participants will be approximately [redacted] Specifically, up to approximately [redacted] of these participants will be treated in Part 1, and approximately [redacted] participants will be treated in Part 2.

5.3 End of Study Definition

The date the first participant signs a study-specific ICF will be defined as the start of the study. A participant is considered enrolled when the study-specific ICF is signed. The date the last participant completes discharge procedures or last follow up visit will be defined as the end of the study.

5.4 Scientific Rationale for Study Design

BMS-986253 is being investigated in humans with advanced solid tumors in combination with nivolumab, and in combination with nivolumab and ipilimumab.

5.4.1 Rationale for Targeting IL-8 in Cancer

IL-8 (CXCL8) is a chemokine whose main physiologic function is the attraction of a polymorphonuclear inflammatory leukocyte infiltrate acting on CXCR1/2. Recently, it has been found that tumors frequently produce IL-8, which exerts different pro-tumoral functions, including

angiogenesis, provide growth factors and survival signaling for CSCs as well as the attraction of immunosuppressive myeloid cells endowed with the ability to dampen anti-tumor immunity. In the tumor, IL-8 is mainly produced by cancer cells themselves. IL-8 serum concentration has been shown to correlate with cumulative tumor size, stage, and prognosis in numerous cancer types.[28,29,30,31] Because of a short [redacted] concentrations closely follow in time the changes occurring in IL-8-producing cells. Recent data strongly support a correlation between serum IL-8 levels and tumor burden as well as clinical stage in patients with melanoma, RCC, NSCLC, and HCC.[3,21,23] In fact, patients with higher serum IL-8 levels had worse overall survival (OS).[3,21,23] Because of the roles that IL-8 plays in favoring tumor progression through several mechanism such as modulating chemotaxis, resistance to therapy, angiogenesis, and metastasis, therapeutic strategies aiming to interfere with IL-8 has the potential to alleviate these functions, thereby diminishing the risk of (further) metastatic spread and recurrent disease in these patients. Anti-IL-8 neutralizing antibody (HuMax-IL-8) was shown to decrease IL-8-induced neutrophil activation and migration in vitro resulting in beneficial anti-inflammatory responses in patients with palmoplantar pustulosis[32] which also provided support to test this antibody in cancer patients.

5.4.2 Rationale for the Combination of BMS-986253 and Nivolumab

Recent reports have shown that changes in serum IL-8 levels accurately correlate with tumor burden changes in metastatic melanoma and NSCLC patients during treatment with anti-PD-(L)1 mAbs and in metastatic melanoma patients during treatment with anti-PD-(L)1 plus anti-CTLA-4 mAbs.[20] In fact, increased expression of IL-8 by cancer cells could contribute to immuno-resistance by promoting the recruitment of immunosuppressive myeloid derived cells.[12] These cells are well known to dampen the cytotoxic ability of T-Cells by various mechanism.[33,34] Preliminary data, from multiple trials with nivolumab, show that a high level of serum IL-8 at baseline that persists or increases throughout therapy correlates with decreased response and survival in melanoma, NSCLC and RCC (see BMS-986253 IB[24]). In the preclinical models, the combination of a PD-(L)1 inhibitor and an IL-8 axis inhibitor was better at reducing tumor growth than either agent given as monotherapy suggesting a specific immunosuppressive role for IL-8.[35,36] IL-8 produced in the tumor attracts MDSCs into the tumor microenvironment and these cells can in turn inhibit the immunological response to the tumor by T-lymphocytes; further confirming that IL-8 signaling is involved in tumor immunosuppression.[12]

Based on these data, the combination of nivolumab with BMS-986253 could demonstrate a synergetic anti-tumor activity. IL-8 serum levels may be used to guide choice of dose in pivotal efficacy trials of BMS-986253 in advanced cancer participants with resistance to anti-PD-L1 therapies.

5.4.3 Rationale for Selecting Participants Based on Serum IL-8

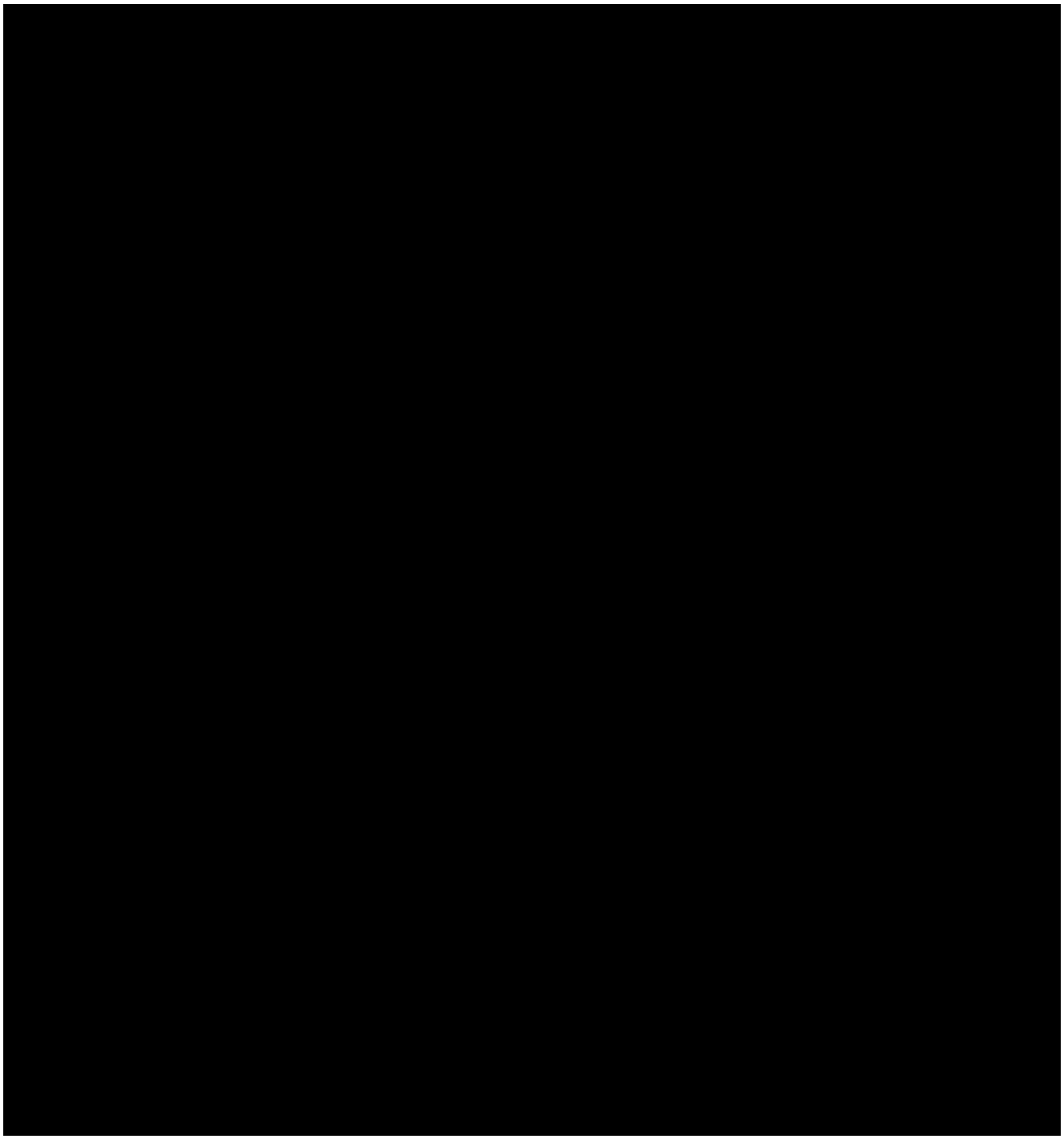
In healthy subjects, IL-8 is not typically present in the serum; however, it can be found in the serum of patients with various cancer types. [redacted]

[redacted]

Parts 1A and 1B will select participants with [redacted] for the following reasons: 1) these participants may be more likely to benefit from IL-8 blockade since higher IL-8 levels correlate with worse prognosis; 2) to allow for assessment of target engagement (reduction in IL-8) in the blood, which will in part be used to inform RP2D dose selection.

In Part 1C and in Part 2, participants will not be selected based on serum IL-8. The main purpose of Part 1C will be generation of safety data on the combination of BMS-986253 plus nivolumab plus ipilimumab, to support a randomized evaluation of BMS-986253 plus nivolumab plus ipilimumab versus placebo plus nivolumab plus ipilimumab in Part 2. In Part 2, the primary endpoints will be in all randomized participants regardless of baseline serum IL-8 level. [redacted]

[redacted]



5.4.4 Rationale for the Combination of BMS-986253, Nivolumab, and Ipilimumab

Combining immunotherapeutic agents with different mechanisms of action offers the possibility of synergistic response. Preclinical data indicate that the combination of PD-1 and CTLA-4 receptor blockade may improve antitumor activity. In vitro combinations of nivolumab plus ipilimumab increase IFN-γ production 2- to 7-fold over either agent alone in a mixed lymphocyte reaction. In a murine melanoma vaccine model, dual blockade with anti-CTLA-4 and anti-PD-1

antibodies increased tumor infiltration of T effector cells and decreased intratumoral T regulatory cells to a greater extent than either agent alone.[37] Furthermore, clinical trial data has led to FDA approval of the combination of nivolumab and ipilimumab in several cancers, including RCC, melanoma, NSCLC, and MSI-high CRC.

Baseline serum IL-8 levels correlate with prognosis in patients treated with anti-PD-1 therapy, including melanoma patients treated with a combination of nivolumab and ipilimumab on CA209067. Adding BMS-986253, a fully human mAb against IL-8, to nivolumab plus ipilimumab could improve clinical outcomes.[23]

Although the triplet combination of BMS-986253, ipilimumab, and nivolumab has not been previously evaluated, based on the safety data generated on the combination of BMS-986253 and nivolumab, and the combination of nivolumab and ipilimumab, the triplet combination is expected to have a tolerable safety profile.

5.4.5 Rationale for Testing Different Doses in Parallel in Part 1

In the CA027001 first-in-cancer study, treatment with BMS-986253 monotherapy was determined to be safe and well tolerated across the dose range of 4 to 32 mg/kg Q2W in 15 participants with advanced tumors (equivalent to 2560 mg flat dose for 80 kg body weight Q2W; and 5120 mg total accumulative dose Q4W). In this study, it was not possible to determine the dose which achieve a sustained neutralization of IL-8 to block its intratumoral- activity. Therefore, after the preliminary safety of the combination of 2400 mg BMS-986253 Q4W with 480 mg nivolumab Q4W is established in Part 1A, Part 1B will evaluate different doses and dosing frequencies of BMS-986253 combined with 480 mg of nivolumab Q4W. If a cohort in Part 1B evaluates a higher dose of BMS-986253 than previously assessed (maximum dose to be assessed BMS-986253 3600 mg Q2W or 5400 mg Q3W), a safety-lead in will be required for that cohort.

In addition, cohorts in 1C (triplet combinations of BMS-986253 + nivolumab + ipilimumab) may be evaluated simultaneously with cohorts in Part 1B, as long as initial safety data for the BMS-986253 dose used in Part 1C has been established in combination with nivolumab in Part 1B.

The totality of data from Part 1 [redacted] will further determine the RP2D of BMS-986253 in combination with nivolumab, or in combination with nivolumab plus ipilimumab.

5.4.6 Rationale for Treatment Beyond Progression

Immunotherapeutic agents produce atypical clinical response patterns that are not usually observed with conventional chemotherapy. Accumulating clinical evidence indicates that some participants treated with immune system stimulating agents may develop disease progression by the conventional response criteria before demonstrating clinical overall responses and/or stable disease.

Two distinct nonconventional patterns have been reported: 1) a reduction in target tumor burden despite the appearance of new lesion(s), and 2) a transient increase in target tumor burden in an initial phase, followed by subsequent tumor shrinkage.

These phenomena were observed in the Phase 2 Study (CA209003) of nivolumab in participants with solid tumors. Two hypotheses potentially explain these phenomena. First, enhanced inflammation within tumors could lead to an increase in tumor size, which would appear as enlarged index lesions and as newly visible small non-index lesions. Over time, both the malignant and inflammatory portions of the mass may then decrease, leading to overt signs of clinical improvement. Alternatively, in some individuals, the kinetics of tumor growth may initially outpace anti-tumor immune activity. With sufficient time, the anti-tumor activity will dominate and become clinically apparent. Therefore, it is important to avoid premature discontinuation of the study drug that might induce a nonconventional response pattern in some participants.

The decision to continue treatment beyond investigator-assessed progression should be discussed with the BMS Medical Monitor and documented in the study records. The assessment of clinical benefit should take into account whether the participant is clinically deteriorating and unlikely to receive further benefit from continued treatment.

5.4.7 Rationale for Tumor Selection

Part 1

Melanoma, RCC, and NSCLC were selected based on recent literature[19,20] and on retrospective preliminary analysis from nivolumab studies (see Section 5.4.3 and BMS-986253 IB[24]), showing a high level of serum IL-8 at baseline that persists or increases throughout therapy correlates with decreased response and survival in these tumor types, independently from baseline tumor burden. These tumor types were selected to explore the activity of neutralizing IL-8 in combination with nivolumab in participants resistant to anti-PD-L1 therapy. Additional tumor types (UCC, SCCHN, HCC, and CRC) were selected based on reports showing the role of IL-8 in tumor progression[38,39,40,41,42,43,44] high levels of MDSC,[45] [redacted] IL-8 correlating with outcome,[21,23] and suboptimal activity of nivolumab as single therapy[46] to determine if interfering with IL-8 and MDSC recruitment could sensitize these tumors to nivolumab therapy.

Part 2

Part 2 is a double-blind, randomized evaluation of BMS-986253 plus nivolumab plus ipilimumab versus placebo plus nivolumab plus ipilimumab in participants with melanoma who progressed on prior PD-(L)1 therapy. [redacted]

5.4.8 Rationale for Treatment of Post-PD-(L)1 Melanoma in Part 2

Part 2 is a randomized, double-blind evaluation of BMS-986253 plus nivolumab plus ipilimumab vs placebo plus nivolumab plus ipilimumab in participants with melanoma who have progressed on anti-PD-(L)1 therapy. Rationale for evaluation of the BMS-986253 plus nivolumab plus

ipilimumab is provided in Section 5.4.4. Rationale for selection of melanoma in Part 2 is provided in Section 5.4.7.

Patients with unresectable or metastatic melanoma who have progressed on prior anti-PD-(L)1 therapy have a poor prognosis. This is a patient population with a high unmet medical need and optimal treatment is not well defined. Ipilimumab is approved for the treatment of melanoma in the adjuvant and advanced/metastatic settings. In the advanced/metastatic setting, ipilimumab had been shown to lead to durable responses and improved OS in combination with nivolumab.

For melanoma patients whose cancer progressed on anti-PD-1 therapy, addition of ipilimumab to anti-PD-(L)1 therapy may lead to meaningful clinical activity. Olson et al performed a prospective study evaluating pembrolizumab plus ipilimumab in 70 patients with melanoma that previously progressed on anti-PD-(L)1 as the immediate prior therapy. The ORR was 29% by irRECIST and the median duration of response was 16.6 months.[47] Da Silva et al performed a multicenter, retrospective cohort study of 193 patients with metastatic melanoma resistant to anti-PD(L)1 who went on to receive ipilimumab plus anti-PD-(L)1 at centers in Australia, Europe, and USA. The overall objective response rate to combination treatment with 31% and median OS was 20.4 months.[48]

Thus the treatment of patients that have previously progressed on anti-PD(L)1 monotherapy with the combination of anti-PD-(L)1 with ipilimumab is an appropriate treatment option supported by widely utilized guidelines endorsed by the National Comprehensive Cancer Network (NCCN)[49] and the European Society for Medical Oncology (ESMO).[50] For patients with BRAF-mutated melanoma, the optimal timing of targeted therapy with respect to immunotherapy is not defined and may be based on individualized decision making. When these patients are treated with anti-PD-(L)1 monotherapy therapy prior to targeted therapy, use of targeted therapy or the combination of ipilimumab plus anti-PD-1 blockade as next therapy are both considered appropriate options supported by guidelines.[49]

Based on the aforementioned data, the combination of nivolumab and ipilimumab was chosen as the control arm in this patient population. Participants with BRAF-mutated melanoma must have either been previously treated with BRAF-targeted therapy, not be a candidate for such therapy, or declined targeted therapy after having been provided adequate information to make an informed decision as part of an individualized decision-making process. To reduce bias, the randomized evaluation will be double-blind, and participants in the control arm will receive placebo in place of BMS-986253.

5.4.9 Rationale for Stratification in Part 2

In order to minimize the potential for imbalance of factors that may impact efficacy endpoints, the following stratification factors will be used in the Part 2 randomized evaluation: [redacted] and peripheral LDH (≤ ULN or > ULN). Higher levels of serum IL-8 correlate with worse prognosis in melanoma (Section 5.4.3). [redacted]

[redacted] Lastly, elevated LDH is poor prognostic factor in melanoma patients treated with ICI.[51,52,53,54]

5.4.10 Rationale for Treatment Duration

Despite recent advances in immunotherapies for the treatment of cancer, the ideal treatment duration to achieve and perpetuate good durable response is still an area of ongoing investigation. Current clinical data on the time to response suggest that most I-O- naïve patients who show a response when treated with nivolumab do so within the first 24 weeks on therapy, but interruption of nivolumab after the first year of therapy might be deleterious compared with prolonged therapy until 2 years.[55]

In this study participants are treated with BMS-986253 combined with either nivolumab, or nivolumab plus ipilimumab. BMS-986253 is an antibody that blocks the cytokine IL-8, which is continuously produced by the tumor and other immune cells. The optimal duration of BMS-986253 treatment is unknown, and continuous treatment may be required. This study also primarily consists of patients who have progressed on or after anti-PD-1 or anti-PD-L1 therapy, and the optimal duration of nivolumab treatment in this setting is also unknown. Ipilimumab will be administered for a maximum of 4 doses or 12 weeks. Treatment on this study will be limited to 3 calendar years.

[redacted]

5.5 Justification for Planned Dose Selection

5.5.1 Rationale for Part 1A Dose Selection of BMS-986253 in Combination with Nivolumab.

Based on [redacted] from the single ascending dose and multiple ascending dose studies described in the BMS-986253 IB,[24] a combination of a flat dose of 2400 mg Q4W BMS-986253 with a flat dose of 480 mg nivolumab Q4W was selected as the starting dose for initial testing in this study.

There are several sources of data which support the choice of a 2400 mg Q4W flat dose of BMS-986253 as a rationale and safe starting dose:

[redacted]

[redacted]

4) Based on the known biology of IL-8, depletion of IL-8 is not expected to exacerbate nivolumab immune related AEs. Rather, it is anticipated (and supported by pre-clinical models) that depletion of IL-8 may lessen immune suppression of anti-tumor T-cells.

5.5.2 Rationale for Part 1B Dosing Schedules and Maximum Administered Dose

The dosing schedule for each part of Study CA027002 is summarized in Table 7.3-1 and Section 2, and the rationale for dose is presented in the following sections.

The rationale for including the option to explore Q2W dosing regimens of BMS-986253 was based on preliminary serum-free IL-8 data from the first 3 participants in this study. Based on these data, by C2D1 following Q4W dosing, a rise in serum IL-8 was observed, which may be prevented with Q2W dosing of BMS-986253. Preliminary safety data demonstrated that BMS-986253 Q2W monotherapy as well as the combination of 2400 mg BMS-986253 Q4W and 480 mg nivolumab Q4W was tolerable.[24]

[redacted]

The rationale for the maximum administered dose of BMS-986253 was based on interim analysis of safety and serum IL-8 data from Part 1 (as described in BMS-986253 IB),[24] and PK/ pharmacodynamic modeling. Based on safety data from Cohorts 1A and 1B1 through 1B5, BMS-986253 plus nivolumab was well tolerated at BMS-986253 2400 mg Q2W + nivolumab 480 mg Q4W (Cohort 1B4), and dose-dependent AEs were not identified based on available data. Furthermore, dose- and frequency-dependent-free serum IL-8 suppression was observed, with robust suppression at 2400 mg Q2W + nivolumab 480 mg Q4W. [redacted]

[redacted]

Based on the analysis of the totality of data from Part 1 Cohorts 1B1 through 1B6 and Part 1C, the BMS-986253 RP2D was selected for Part 2, where the additional clinical benefit of BMS-986253 in combination with nivolumab and ipilimumab, as compared with nivolumab and ipilimumab combination in melanoma patients will be evaluated. [redacted]

Table 5.5.2-1: Dose and Schedule by Study Part

Part	Dose and Schedule BMS-986253	Dose and Schedule Nivolumab	Dose and Schedule Ipilimumab
Part 1A: Safety Evaluation Lead-in	2400 mg Q4W[a]	480 mg Q4W	
Part 1B: Dose-finding[b]			
1B1	2400 mg Q4W	480 mg Q4W	
1B2	1200 mg Q4W	480 mg Q4W	
1B3	600 mg Q4W	480 mg Q4W	
1B4 (safety lead-in)	2400 mg Q2W	480 mg Q4W	
1B5	1200 mg Q2W	480 mg Q4W	
1B6 (safety lead-in)	3600 mg Q2W	480 mg Q4W	
[redacted]			
Part 1C: Safety Triplet Combination			
1C1 (safety lead-in)	3600 mq Q2W	1 mg/kg Q3W[c]	3 mg/kg Q3W (4 doses)
[redacted]			
Part 2: Double-blind Randomized Study in Melanoma Post PD-1			
Cohort 2A	3600 mg Q2W	1 mg/kg Q3W[c]	3 mg/kg Q3W (4 doses)
Cohort 2B	(Placebo) Q2W	1 mg/kg Q3W[c]	3 mg/kg Q3W (4 doses)

Abbreviations: BMS, Bristol Myers Squibb; QXW, every X weeks.

[a] If safety is not confirmed at 2400 mg, a lower dose will be evaluated prior to opening the Part 1B: randomized dose-finding phase.

[b] Up to 4 additional dosing regimens may be explored in Part 1B. If any dosing regimen evaluates a higher dose of BMS-986253 than previously explored, an initial 4 participant safety-lead with a 28-day DLT period will be required.

[c] After 12 weeks of treatment, nivolumab will be administered 480 mg Q4W.

[redacted]

5.5.3 Rationale for Flat Dosing of BMS-986253

A flat dose (mg) of BMS-986253 will be used in this study instead of a body size-based (ie, body weight or body surface area) dose. Therapeutic mAb doses have been routinely calculated on a body size basis. This practice assumes that dosing by body size significantly reduces variability in therapeutic mAb- exposure.[60] However, recent analyses of marketed and experimental mAbs have demonstrated that body size-based dosing did not always offer advantages over flat dosing in reducing exposure variability. Many mAbs are target-specific with a relatively large therapeutic window that increases the tolerability of exposure variability. Additionally, participant-specific, disease-specific, and physiologic characteristics often contribute to exposure variability, resulting in a generally smaller contribution of body size. Therefore, the dosing paradigm for mAbs should be assessed in the context of all of these unique characteristics.

With either dosing strategy, bias with respect to exposure is expected to occur in the extremes of the body weight distribution. In general, body size-based dosing could result in higher mAb concentrations in the heaviest participants (eg, 90th percentile), whereas flat dosing could lead to higher mAb concentrations in the lightest participants (eg, 10th percentile). Body weight distribution data from a clinical trial database of over 2,500 adults with solid or hematologic cancers suggested a log-normal distribution of body weight with median, 10th, and 90th percentiles of 78 kg, 56 kg, and 112 kg, respectively.[61] To minimize the potential risk of higher exposures in the lowest body weight participants, the flat doses of BMS-986253 will be based on a body weight of 70 kg.

In addition to the above rationale, flat dosing offers practical advantages over body size-based dosing, including a convenient approach with respect to pharmacy preparation and clinical administration, and is also more likely to reduce the potential for dosing errors related to body size-based calculations. Since the magnitude of the impact of body size on the human PK of BMS-986253 is not yet determined, the PK and safety data from the Phase 1/2 study will be evaluated to validate the flat dosing approach. If appropriate, based on the totality of the data, the Sponsor will consider a revision of the flat dosing strategy. BMS-986253 will be administered Q4W. However, the alternate dosing frequencies (with the most frequent dosing frequency of Q2W) may be explored based on continuous evaluation of the totality of safety, pharmacodynamic, and PK data. [redacted]

5.5.4 Rationale for Nivolumab Dose Selection

Nivolumab monotherapy has been extensively studied in multiple tumor types, including melanoma, NSCLC, RCC, SCCHN, and urothelial carcinoma, using body weight-normalized dosing (mg/kg), and has been safely administered at doses up to 10 mg/kg Q2W. Nivolumab is currently approved for the treatment of various tumor types with a monotherapy regimen of 240 mg Q2W, 3 mg/kg Q2W, or 480 mg Q4W across multiple markets.

In addition, nivolumab is approved in combination with ipilimumab or ipilimumab plus chemotherapy for the treatment of various cancers with dosing regimen of 1 mg/kg Q3W (in

melanoma and HCC), [redacted] 360 mg Q3W or 3 mg/kg Q2W (in NSCLC).

In Parts 1A and 1B, given a wide therapeutic window and quantitative clinical pharmacology understanding, nivolumab 480 mg Q4W or 360 mg Q3W infused over approximately 30 minutes is selected in combination with BMS-986253 to allow for aligning doses frequency in combination treatment.

In Part 1C, the safety of BMS-986253 3600 mg Q2W in combination with nivolumab and ipilimumab will be evaluated before starting Part 2. Since our primary efficacy evaluation in Part 2 will be in participants with advanced/metastatic melanoma, we will prioritize evaluation of the approved regimen of nivolumab 1 mg/kg Q3W infused over approximately 30 minutes (in combination with ipilimumab 3 mg/kg Q3W) for up to 4 combination doses for the first 12 weeks of treatment. [redacted] In Part 1C, after the first 12 weeks, the dose/frequency of nivolumab will be flat dose, 480 mg Q4W.

For Part 2, we will be using the approved doses of nivolumab and ipilimumab in advanced/metastatic melanoma: [redacted]

5.5.5 Rationale for Ipilimumab Dose Selection

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 3 mg/kg Q3W (in combination with nivolumab 1 mg/kg Q3W) for up to 4 combination doses, followed by nivolumab monotherapy is approved for the treatment of melanoma and HCC. Ipilimumab [redacted] for up to 4 combination doses, followed by nivolumab monotherapy is approved for the treatment of RCC and CRC.

The safety of BMS-986253 3600 mg Q2W in combination with nivolumab and ipilimumab will be evaluated in Part 1C before starting Part 2. Since our primary efficacy evaluation in Part 2 will be in participants with advanced/metastatic melanoma, we will prioritize evaluation of the approved regimen of ipilimumab 3 mg/kg Q3W infused over approximately 30 minutes [redacted]

For Part 2, we will be using the approved doses of nivolumab and ipilimumab in advanced/metastatic melanoma: [redacted]

[redacted]

5.5.6 *Rationale for Part 2 Dosing Schedules and Maximum Administered Dose/RP2D*

[redacted]

6 STUDY POPULATION

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

6.1 Inclusion Criteria

1) Signed Written Informed Consent

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

2) Type of Participant and Target Disease Characteristics

a) Participants must be at least 18 years old and have histologic or cytologic confirmation of a solid tumor that is advanced (metastatic, recurrent and/or unresectable) with radiographically measurable disease per RECIST v1.1 (Appendix 8) (Medical photos are

not allowed). [redacted]

i) Participants with lesions in a previously irradiated field as the sole site of measurable disease will be permitted to enroll provided the lesion(s) have demonstrated clear progression and can be measured accurately.

b) Participants must have an Eastern Cooperative Oncology Group Performance Status of 0 or 1 (Appendix 5).

c) The following tumor histologies will be permitted except for participants with CNS metastases as the only site of active disease. All participants must have received, and then progressed, relapsed, or been intolerant to at least 1 standard treatment regimen in the advanced or metastatic setting according to tumor type. Part 1 will include participants with RCC, SCCHN, melanoma, UCC, NSCLC, HCC, and CRC. Part 2 will include participants with melanoma. Separate inclusion criteria are listed for participants with melanoma in Part 1 and Part 2.

i) Non-Small Cell Lung Carcinoma (Only Part 1A and Part 1 Cohorts 1B1 through 1B5 [enrolled through Revised Protocol 03]. Participants with NSCLC will not be allowed in Parts 1B6, [redacted] and 1C as per Protocol Amendment 04).

(1) Not applicable as per Protocol Amendment 04

(2) ***Not applicable as per Revised Protocol 02***

(3) ***Not applicable as per Protocol Amendment 04***

(4) ***Not applicable as per Revised Protocol 02***

(5) ***Not applicable as per Protocol Amendment 04***

(6) ***Not applicable as per Revised Protocol 03***

(7) ***Not applicable as per Protocol Amendment 04***

(8) ***Not applicable as per Revised Protocol 03***

(9) ***Not applicable as per Protocol Amendment 04***

ii) Renal Cell Carcinoma with a clear cell component.

(1) ***Not applicable as per Revised Protocol 02***

(2) Participants in Part 1: Must have received and progressed/been intolerant of (or not be a candidate for) an anti-angiogenic therapy (eg, including but limited to bevacizumab, axitinib, cabozantinib, pazopanib, sorafenib, sunitinib and tivozanib).

(3) Not applicable as per Protocol Amendment 04

(4) ***Not applicable as per Revised Protocol 03***

(5) Participants in Part 1: Must have documented progressive or recurrent disease on or within 3 months of discontinuation of anti-PD-(L)1 therapy (administered as monotherapy or as part of a combination) as per RECIST 1.1 criteria.

(a) Prior anti-PD-(L)1 based therapy must be the most recent treatment.

iii) Melanoma in Part 1

(1) Histologically confirmed, unresectable Stage III or Stage IV melanoma, as specified in the American Joint Committee on Cancer staging system.

(a) Participants with ocular or uveal melanoma are ineligible.

(2) PD-L1 status must be documented if available. [redacted]

(3) Not applicable as per Revised Protocol 03

(4) [redacted] Both BRAF mutated and wild-type participants are permitted in this cohort.

(a) If participant has [redacted] they must have received (or not be a candidate for) BRAF inhibitor treatment, or declined targeted therapy after having been provided adequate information to make an informed decision.

(5) Must have documented progressive or recurrent disease on or within 3 months of discontinuation of anti-PD-(L)1 therapy (administered as monotherapy or as part of a combination) as per RECIST 1.1 criteria:

(a) Prior anti-PD-(L)1 based therapy must be the most recent treatment

iv) ***Not applicable as per Revised Protocol 02:*** **Expansion Cohort only**

v) ***Not applicable as per Protocol Amendment 04:*** **Triple negative breast cancer**

vi) Microsatellite Stable Colorectal cancer (Part 1C only)

(1) Histologically documented, locally advanced, unresectable, or metastatic MSS CRC.

(2) Microsatellite instability status (MSI) and/or mismatch repair status must be documented. Only MSS or pMMR participants are permitted in this cohort. *Note: pMMR is defined as expression of MLH1, MSH2, MSH6, and PMS2 by immunohistochemistry (IHC) and MSS is defined by the absence of instability in microsatellite markers by polymerase chain reaction (PCR) as determined by a local laboratory. If the MSI molecular test and mismatch repair IHC test results are both available, then both MSS and pMMR will be required for study entry. Patients with MSI high or MSI-low or mismatch repair deficiency will not be eligible.*

(3) Participants must have received and progressed on, or been intolerant to (not candidates for) a fluoropyrimidine, oxaliplatin, and irinotecan.

(4) Participants with epidermal growth factor receptor (EGFR)-expressing RAS wildtype tumors must have received (or not be a candidate for) EGFR-directed therapy (eg, cetuximab).

vii) ***Not applicable as per Protocol Amendment 04:*** **Pancreatic ductal adenocarcinoma**

viii) Hepatocellular carcinoma (Part 1C only)

(1) Participants cannot be eligible for liver transplant at the time of inclusion. For participants who progressed after locoregional therapy, locoregional therapy for HCC must be completed at least 4 weeks prior to the baseline scan. All acute toxic effects of any prior local treatment must have resolved to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03 Grade > 1 or been deemed irreversible.

(2) Participants may either have histologically or radiologically confirmed HCC. Participants with a radiological diagnosis may be enrolled for screening in the study but histological confirmation is mandatory prior to initiation of study therapy.

(3) Participants must have received and progressed/been intolerant of (or not be a candidate for) at least 1 line of therapy, including anti-PD-(L)1-based therapy.

(a) Prior anti-PD-(L)1-based therapy must be the most recent treatment

(4) Must be Child-Pugh Class A (6 points or less) (Appendix 9);

(5) Must have results of testing for hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody, hepatitis B deoxyribonucleic acid (DNA) PCR, hepatitis C antibody and hepatitis C ribonucleic acid (RNA) PCR;

(6) For participants with hepatitis B infection, hepatitis B DNA viral load must be < 500 IU/mL and the participant must be on anti-viral therapy per institutional guidelines.

(a) If the participant is receiving anti-viral therapy, the anti-viral therapy must have been started at least 4 weeks prior to screening.

(7) Participants with hepatitis B infection cannot have a co-infection with hepatitis C or hepatitis D (must obtain hepatitis D antibody testing).

(8) Participants with active hepatitis C virus (HCV), infection, as defined by any detectable HCV RNA and positive antibody titer, can be enrolled provided they are on anti-viral therapy. Participants with resolved HCV infection, as evidenced by undetectable HCV RNA and positive antibody titer, can be enrolled. Participants on antiviral therapy for HCV should continue treatment during the study. Participants with active HCV who are not on antiviral therapy at screening cannot be enrolled in the study.

(a) If the participant is receiving anti-viral therapy, the anti-viral therapy must have been started at least 4 weeks prior to screening.

ix) Other tumor types could be considered at the time of expansion based on scientific rationale and be added to the study by subsequent amendment.

x) Urothelial carcinoma (UCC)

(1) Histologically confirmed, advanced (ie, unresectable or metastatic) transitional cell carcinoma of the urothelium involving the bladder, urethra, ureter, or renal pelvis.

(2) ***Not applicable as per Revised Protocol 02***

(3) PD-L1 status must be documented if available. [redacted]

(4) Participants must have received and progressed/been intolerant of (or not be a candidate for) standard of care chemotherapy (eg, platinum-based regimen) in the recurrent or metastatic setting.

(5) Not applicable as per Revised Protocol 03

(6) Must have documented progressive or recurrent disease on or within 3 months of discontinuation of anti-PD-(L)1 therapy (administered as monotherapy or as part of a combination) as per RECIST 1.1 criteria.

(a) Prior anti-PD-(L)1 based therapy must be the most recent treatment.

xi) Squamous Cell Carcinoma of the Head and Neck (SCCHN) (Only Part 1A and Part 1B. Participants with SCCHN will not be allowed in Part 1C.)

(1) Histologically confirmed, advanced (ie, unresectable or metastatic) squamous cell carcinoma of the Oral Cavity, Pharynx, Larynx.

(2) Not applicable as per Revised Protocol 02

(3) PD-L1 status must be documented if available. [redacted]

(4) Participants must have received and progressed/been intolerant of (or not be a candidate for) standard of care chemotherapy (eg, platinum-based regimen) in the recurrent or metastatic setting.

(5) For SCC of the oropharynx, HPV status must be documented. Both HPV-positive or HPV-negative participants are permitted in this cohort.

(6) Not applicable as per Revised Protocol 03

(7) Must have documented progressive or recurrent disease on or within 3 months of discontinuation of anti-PD-(L)1 therapy (administered as monotherapy or as part of a combination) as per RECIST 1.1 criteria.

(a) Prior anti-PD-(L)1 based therapy must be the most recent treatment.

xii) Melanoma in Part 2

(1) Histologically confirmed, unresectable Stage III or Stage IV melanoma, as specified in the American Joint Committee on Cancer staging system.

(a) Participants with ocular or uveal melanoma are ineligible.

(2) PD-L1 status must be documented if available. PD-L1 status will also be re-tested using tissue acquired from the pre-treatment biopsy (if provided).

(3) [redacted] Both BRAF-mutated and wild-type participants are permitted in this cohort.

(a) If participant has [redacted] they must have received (or not be a candidate for) BRAF inhibitor treatment, or declined targeted therapy after having been provided adequate information to make an informed decision.

(4) Must have documented progressive or recurrent disease on or after discontinuation of anti-PD-(L)1 therapy (administered as monotherapy or as part of a combination) as per RECIST 1.1 criteria:

(a) Prior anti-PD-(L)1-based therapy (with at least 6 weeks of exposure) must be the most recent treatment. If the participant received palliative radiation after discontinuation of anti-PD-(L)1 therapy:

(i) The participant meets this criteria if the documented progressive/recurrent disease included sites outside the radiation field.

(ii) The participant does not meet this criteria if all the sites of progressive/recurrent disease were limited to the field that was subsequently irradiated.

(b) Participants who received anti-PD-(L)1 in the advanced/metastatic setting, must have documented progressive or recurrent disease on or within 3 months of discontinuation of anti-PD-(L)1 therapy (administered as monotherapy or as part of a combination) as per RECIST 1.1 criteria.

(c) Participants who received anti-PD-(L)1 in the adjuvant setting must have documented progressive or recurrent disease on or within 6 months of discontinuation of anti-PD-(L)1 therapy (administered as monotherapy or as part of a combination) as per RECIST 1.1 criteria.

(d) Confirmation of radiographic progression on prior anti-PD-(L)1 therapy is required with a scan confirming progression at least 4 weeks after the initial progression. Screening scans can be used as the confirmation of progression.

(5) Must not have received prior anti-CTLA-4 therapy.

3) Physical and Laboratory Test Findings

Participants must have:

a) Baseline [redacted] (only required for Part 1A and Part 1B)

b) Adequate hematologic function as defined by the following:

i) Neutrophils $\geq$ 1,500 μL

ii) Platelets $\geq 80 \times 10^3/\mu L$ (transfusion to achieve this level is not permitted within 2 weeks of first study treatment administration)

iii) Hemoglobin $\geq$ 8 g/dL (transfusion to achieve this level is not permitted within 2 weeks of first study treatment administration)

c) Adequate hepatic function

i) Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) $\leq$ 3× upper limit of normal (ULN)

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

iii) Specifically for participants with HCC:

(1) Prothrombin time-international normalized ratio $\leq$ 2.3 or prothrombin time $\leq$ 6 seconds above control

(2) Adequate hepatic function as documented by

(a) Serum albumin $\geq$ 2.8 g/dL (transfusion to meet this requirement is not permitted)

(b) Total bilirubin $\leq$ 3 mg/dL

(c) AST and ALT $\leq$ 5× the institutional ULN

d) Normal thyroid function or stable on hormone supplementation per investigator assessment

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

Female CrCl = [(140 - age in years) × weight in kg × 0.85]/(72 × serum creatinine in mg/dL);

Male CrCl = [(140 - age in years) × weight in kg]/(72 × serum creatinine in mg/dL);

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

4) Age and Reproductive Status

a) Males and females, aged at least 18 years old.

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

c) Women must not be breastfeeding.

d) WOCBP must agree to follow instructions for method(s) of contraception (Appendix 4) and included in the ICF. WOCBP are permitted to use hormonal contraception methods (as described in Appendix 4).

e) WOCBP who are continuously not heterosexually active are also exempt from contraceptive requirements but should still undergo pregnancy testing as described in this section.

f) ***Not applicable as per Protocol Amendment 04***

g) ***Not applicable as per Revised Protocol 03***

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

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

j) 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.

k) 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 highly effective (with a failure rate of <1% per year), with low user dependency, as described in Appendix 4 during the intervention period and for at least 5 months and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction for the same time period

Investigators shall counsel WOCBP, and male participants who are sexually active with WOCBP, on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise on the use of highly effective methods of contraception (Appendix 4), which have a failure rate of < 1% when used consistently and correctly.

6.2 Exclusion Criteria

1) Target Disease Exclusions

a) Participants with primary CNS malignancies, or tumors with CNS metastases as the only site of disease, will be excluded. Participants with controlled brain metastases; however, will be allowed to enroll. Controlled brain metastases are defined as no radiographic progression for at least 4 weeks following radiation and/or surgical treatment (or 4 weeks of observation if no intervention is clinically indicated), and no longer taking steroids for at least 2 weeks prior to first dose of study treatment, and with no new or progressive neurological signs and symptoms.

b) Participants with leptomeningeal metastases will be excluded.

2) Prohibited Treatments

a) Cytotoxic agents, unless at least 4 weeks have elapsed from last dose of prior anti-cancer therapy and initiation of study therapy.

b) Non-cytotoxic agents, unless at least 4 weeks or 5 half-lives (whichever is shorter) have elapsed from the last dose of prior anti-cancer therapy and the initiation of study therapy. If 5 half-lives are shorter than 4 weeks, agreement with the Sponsor/Medical Monitor is mandatory.

c) Prior participation in an anti-IL-8 clinical study.

3) Medical History and Concurrent Diseases

a) Participants with concomitant second malignancies (except adequately treated non-melanomas skin cancers or in situ urothelial, breast, or cervical cancers) are excluded unless a complete remission was achieved at least 2 years prior to study entry, and no additional therapy is required or anticipated to be required during the study period.

b) Participants with other active malignancy requiring concurrent intervention

c) Prior organ allograft

d) Toxicity (except for alopecia) related to prior anti-cancer therapy and/or surgery, unless the toxicity is either resolved, returned to baseline or Grade 1, or deemed irreversible.

i) Any active neuropathy > Grade 2 (NCI CTCAE v4.03)

e) Participants with the following:

i) Active, known, or suspected autoimmune disease:

(1) Participants with well controlled asthma and/or mild allergic rhinitis (seasonal allergies) are eligible

(2) Participants with the following disease conditions are also eligible:

(a) Vitiligo

(b) Type 1 diabetes mellitus

(c) Residual hypothyroidism due to autoimmune condition only requiring hormone replacement

(d) Euthyroid participants with a history of Grave's disease (participants with suspected autoimmune thyroid disorders must be negative for thyroglobulin and thyroid peroxidase antibodies and thyroid stimulating immunoglobulin (Ig) prior to the first dose of study treatment)

(e) Psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll

ii) History of life-threatening toxicity related to prior immune therapy or any toxicity that resulted in permanent discontinuation from prior immune therapy (eg, anti-CTLA-4 or anti-PD-(L)1 treatment or any other mAb or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways) except those that are unlikely to re-occur with standard countermeasures (eg, hormone replacement after adrenal crisis).

iii) Conditions requiring systemic treatment with either corticosteroids > 10 mg daily prednisone equivalents or other immunosuppressive medications within 14 days of study treatment administration. Participants requiring adrenal replacement steroid doses >10 mg daily prednisone equivalent in the absence of active autoimmune disease are allowed.

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

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

(1) Myocardial infarction or stroke/transient ischemic attack within the past 6 months

(2) Uncontrolled angina within the past 3 months

(3) Any history of clinically significant arrhythmias (such as ventricular tachycardia, ventricular fibrillation, or torsade de pointes)

(4) History of other clinically significant heart disease (eg, cardiomyopathy, congestive heart failure with New York Heart Association functional classification III to IV [Appendix 10], pericarditis, or significant pericardial effusion)

(5) History of myocarditis, regardless of etiology

(6) Cardiovascular disease-related requirement for daily supplemental oxygen therapy;

[redacted]

v) History of chronic hepatitis as evidenced by the following:

(1) Positive test for hepatitis B surface antigen

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

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

(b) Additional testing or substitute testing per institutional guidelines to rule out infection is permitted.

(3) Specific exclusions for participants with HCC:

(a) Active coinfection with both hepatitis B and C

(b) Hepatitis D infection in participants with hepatitis B

(c) Clinically significant ascites (prior ascites that required treatment and require on-going prophylaxis OR current ascites requiring treatment)

(4) Presence of portal hypertension with history of bleeding due to esophageal or gastric varices within 6 months prior to randomization

(5) Episodes of hepatic encephalopathy (≥ Grade 2) within 12 months prior to randomization

vi) Evidence of active infection that requires systemic antibacterial, antiviral, or antifungal therapy ≤ 7 days prior to the first dose of study treatment (except for viral infections that are presumed to be associated with the underlying tumor type required for study entry).

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

viii) Any major surgery within 4 weeks of the first dose of study treatment. 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.

ix) Receipt of a live/attenuated vaccine within 30 days of first treatment

(1) The use of inactivated seasonal influenza vaccines, eg, Fluzone®, will be permitted on study without restriction.

x) Receipt of packed red blood cells or platelet transfusion within 2 weeks of the first dose of study treatment

xi) Any known or underlying medical, psychiatric condition and/or social reason that, in the opinion of the investigator or Sponsor, could make the administration of study treatment hazardous to the participants or could adversely affect the ability of the participant to comply with or tolerate the study.

f) WOCBP who are pregnant or breastfeeding.

g) Previous SARS-CoV-2 infection within 10 days for mild or asymptomatic infections or 20 days for severe/critical illness prior to C1D1.

i) Acute symptoms must have resolved and based on investigator assessment in consultation with the Medical Monitor, there are no sequelae that would place the participant at a higher risk of receiving study treatment.

h) Previous SARS-CoV-2 vaccine within 14 days of C1D1.

i) History of hemophagocytic lymphohistiocytosis (HLH)/macrophage activation syndrome (MAS)

j) A history of disease related to chronic Epstein-Barr virus (EBV) infection including post-transplant lymphoproliferative disorders, Hodgkin's lymphoma, extranodal natural killer (NK)/T-cell lymphoma (nasal type), Burkitt's lymphoma, and chronic active EBV infection.

4) Allergies and Adverse Drug Reaction

a) History of allergy to study treatment(s), combination of study treatments or any of its components

b) History of severe hypersensitivity reaction to any mAb

5) Other Exclusion Criteria

a) Prisoners or participants who are involuntarily incarcerated (Note: under certain specific circumstances and only in countries where local regulation 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) Participants who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness.

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

6.3 Lifestyle Restrictions

There are no lifestyle restrictions applicable for this study given that the participants will receive the study investigational products (IPs) IV.

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but who are not subsequently randomized/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 Lead-In Period

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

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

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

Laboratory parameters and/or assessments that are included in Table 2-2, 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 RT-PCR or viral antigen is not required. However, some 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, subjects 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, and
- At least 24 hours have passed since last fever without the use of fever-reducing medications, and
- Acute symptoms (eg, cough, shortness of breath) have resolved, and
- In the opinion of the investigator, there are no SARS-CoV-2 infection 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 MM 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 MM (eg, safety laboratory tests, SpO2, chest CT scan) should be repeated.

7 TREATMENT

7.1 Treatments Administered

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

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

- BMS-986253
- Nivolumab
- Ipilimumab
- Placebo for BMS-986253 ([redacted] sodium chloride for injection or [redacted] dextrose for injection)

An IP, also known as IMP in some regions, is defined as a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

All drugs used in this study qualify as IPs, as per previous text, and their description and storage information are described in Table 7.1-1.

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, are considered as Non-investigational [Medicinal] Product (Non-IP/Non-IMP).

Table 7.1-1: Study Treatments for CA027002

Product Description/ Class and Dosage Form	Potency	IP/ Non-IMP	Blinded or Open Label	Packaging/ Appearance	Storage Conditions (per label)
BMS-986253 Injection	[redacted]	IP	Open label[a]	Vial	Refer to the label on container and/or pharmacy manual
BMS-986253 Injection		IP	Open label[a]	Vial	Refer to the label on container and/or pharmacy manual
Nivolumab (BMS-936558) solution for injection		IP	Open label[a]	Vial	Refer to the label on container and/or pharmacy manual
Ipilimumab solution for injection		IP	Open label[a]	Vial	Refer to the label on container and/or pharmacy manual
Ipilimumab solution for injection		IP	Open label[a]	Vial	Refer to the label on container and/or pharmacy manual
Normal saline solution for injection[b]		IP	Open label	Various (local commercial product)	Refer to the label on container
Dextrose solution for injection[b]		IP	Open label	Various (local commercial product)	Refer to the label on container

Abbreviation: IP, Investigational Product.

[a] The term "open label" refers to the medication as it is upon receipt at the pharmacy. In Part 2 of this trial, BMS-986253/placebo will be prepared, dispensed, and administered in a double-blinded fashion.

[b] This will be sourced by the investigative sites if permitted by local regulations.

7.2 Handling and Dispensing

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

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

Infusion-related supplies (eg, IV bags, in-line filters, and [redacted] sodium chloride solution) will not be supplied by the Sponsor and should be purchased locally if permitted by local regulations.

Placebo in Part 2 must be handled/dispensed/infused in an identical fashion as BMS-986253 in order to maintain the blind.

Please refer to the current version of the IB and/or pharmacy manual for complete storage, handling, dispensing, and infusion information for BMS-986253, placebo, nivolumab, and ipilimumab.

7.3 Schedule of Dose for Each Investigational Product

The dosing schedule for each IP is detailed below in Table 7.3-1 and Section 2 for all study parts. For BMS-986253, nivolumab, and ipilimumab, participants may be dosed within a ± 3-day window. Premedications are not recommended on Cycle 1 Day 1. Additional information can be found in the pharmacy manual.

Table 7.3-1: Dose, Frequency, Infusion Time, and Sequence of IPs

Cohort	BMS-986253 Dose and Frequency	BMS-986253 Infusion Time (min	Nivolumab Dose and Frequency	Nivolumab Infusion Time (min	Ipilimumab Dose and Frequency	Ipilimumab Infusion Time (min)	Order of Drug Administration
Part 1							
1A[a]	2400 mg Q4W		480 mg Q4W	30 min	NA		
1B1[a]	2400 mg Q4W		480 mg Q4W	30 min	NA		
1B2[a]	1200 mg Q4W		480 mg Q4W	30 min	NA		
1B3[a]	600 mg Q4W		480 mg Q4W	30 min	NA		
1B4	2400 mg Q2W		480 mg Q4W	30 min	NA		
1B5	1200 mg Q2W		480 mg Q4W	30 min	NA		
1B6	3600 mg Q2W		480 mg Q4W	30 min	NA		
1C1	3600 mg Q2W		1 mg/kg Q3W (x 4 doses), followed by 480 mg Q4W	30 min	3 mg/kg Q3W (x 4 doses)		

Table 7.3-1: Dose, Frequency, Infusion Time, and Sequence of IPs

Cohort	BMS-986253 Dose and Frequency	BMS-986253 Infusion Time (min)[h]	Nivolumab Dose and Frequency	Nivolumab Infusion Time (min)[h]	Ipilimumab Dose and Frequency	Ipilimumab Infusion Time (min)[h]	Order of Drug Administration
Part 2							
2A	3600 mg Q2W		1 mg/kg Q3W[g] (x 4 doses), followed by 480 mg Q4W		3 mg/kg Q3W (x 4 doses)		
2B	Placebo Q2W		1 mg/kg Q3W[g] (x 4 doses) followed by 480 mg Q4W		3 mg/kg Q3W (x 4 doses)		

Abbreviations: C, Cycle; D, Day; Ipi, ipilimumab; Nivo, nivolumab; QXW, every X weeks.

a

7.4 Method of Treatment Assignment and Stratification

During the pre-screening visit, the investigative site will enroll the participant in IRT for assignment of a unique 5-digit participant number designated by BMS. Enrolled participants, including those not dosed, will be assigned sequential participant numbers starting with [redacted] The participant identifier number (PID) will ultimately be comprised of the site number and participant number. For example, the first participant screened (ie, enrolled) at site number 1, will have a PID of [redacted]. To distinguish Part 1 and Part 2 participants, the first digit of the participant number will always be a 2 for Part 2 participants [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 panel (Part 1) or blinded treatment arm (Part 2). Study treatment will be dispensed at the study visits as listed in Schedule of Activities (Section 2).

Part 1

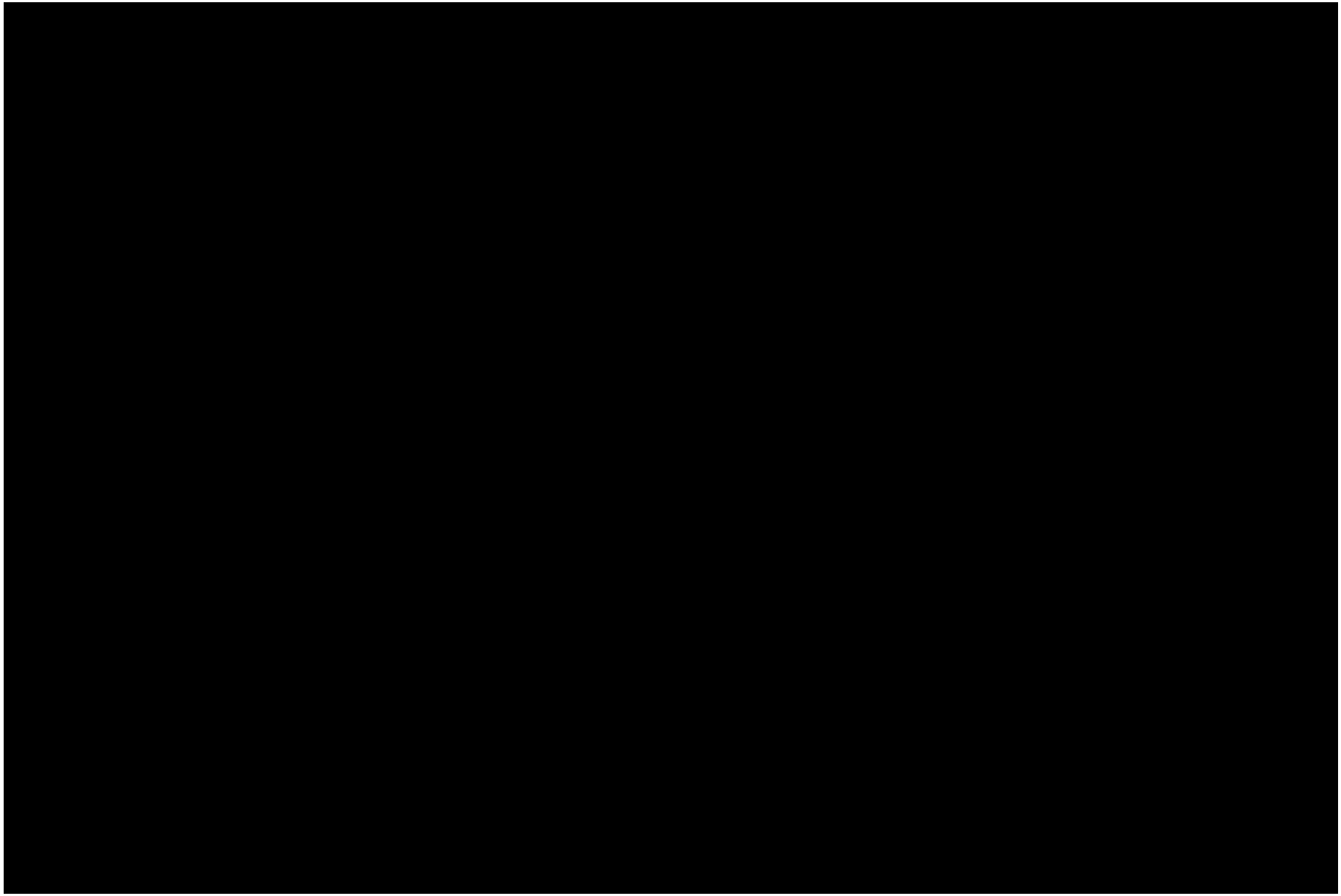
[redacted] provides a summary of treatment assignment in Part 1. The safety evaluation lead-in (Part 1A) will start with a cohort of participants dosed at 2400 mg of BMS-986253 combined with 480 mg of nivolumab Q4W. [redacted] After the review of clinical safety assessment of the first 4 participants, the DLT, and the totality of available data, up to approximately [redacted] additional participants will be enrolled in the dose-finding phase (Part 1B). Participants will be randomly assigned in an approximately 1:1:1 ratio to Cohorts 1B1, 1B2, and 1B3. Randomization will be performed using an equal randomization with each cohort capped at approximately [redacted] participants, such that corresponding entries for capped cohort in the randomization list will be skipped.

In the event that the safety lead-in evaluation recommends to evaluate a lower dose of BMS-986253 (1200 mg) prior to start of the randomized dose-finding phase (Part 1B), a cohort of 4 participants will be treated in combination with 480 mg of nivolumab. If there are no safety concerns after the clinical safety assessment, then participants will be randomized in a similar fashion in approximately 1:1 ratio to Cohorts 1B2 and 1B3.

If PK, pharmacodynamic, and/or safety analyses indicate further assessment of a dosing regimen is not warranted and/or assessment of additional dosing regimens is indicated, then randomization will be stopped, and subsequent participants will be assigned sequentially to dosing regimens available at that time. If any dosing regimen evaluates a higher dose of BMS-986253 than previously explored, an initial 4-participant safety lead-in with a 28-day DLT period will be required. Approximately [redacted] participants will be dosed in the dosing regimen(s) of interest. Additional exploration of a specific dosing regimen may be warranted, in which case a maximum of approximately [redacted] additional participants will be assigned to a dosing regimen of interest in Part 1B. A maximum of approximately [redacted] participants will be dosed in Part 1B.

Part 1C is a safety evaluation of BMS-986253 in combination with nivolumab and ipilimumab. Part 1C will begin once the DLT period is completed for Cohort 1B6 (BMS-986253 3600 mg Q2W + nivolumab 480 mg Q4W), and will enroll simultaneously with Part 1B. In Part 1C, participants

will be enrolled onto Cohort 1C1. [redacted]



Part 2

Part 2 will begin after determination of the RP2D from Part 1 and generating safety data on the triplet combination of BMS-986253 plus nivolumab plus ipilimumab in Part 1C. Part 2 is a double-blind randomized evaluation of BMS-986253 plus nivolumab plus ipilimumab versus placebo plus nivolumab plus ipilimumab and will be conducted to evaluate the efficacy of BMS-986253 in participants who are refractory to anti-PD-(L)1 therapy.

IRT will be used to track the enrollment number.

Once assigned a subject ID in IRT, participants that have met all eligibility criteria will be randomized through IRT (up to 3 days prior to C1D1). The following information is required prior to participant randomization:

- Participant subject ID
- Date of birth
- Gender
- Screening serum IL-8 level
- [redacted]
- Screening LDH

Participants will be randomized in a 1:1 ratio to treatment and control arms. Three stratification factors will be used during randomization: screening [redacted] and screening LDH (≤ ULN or > ULN). Screening serum IL-8 data will be transferred directly from the analyzing laboratory to IRT. BRAF status and screening LDH must be entered in eCRF by the site.

Approximately [redacted] participants will be randomized in Part 2.

The exact procedures for using the IRT will be detailed in the IRT manual.

7.5 Blinding

7.5.1 Part 1

Part 1 of this study is open label, with randomized and non-randomized portions. Data emerging from this portion of the study may be necessary to inform timely decisions for adjusting procedures in subsequent portions of the study, including early termination of the study, requiring access to IRT treatment codes in either the randomized or non-randomized portions of the study. Additionally, treatment assignments may facilitate optimization of the bioanalytical analysis of samples.

Designated members of the study team, as well as the Bioanalytical and/or clinical pharmacology groups of the Sponsor can access IRT treatment codes prior to the formal locking of the study database ***for these purposes***. This access to the treatment codes will not impact the data integrity of the study.

7.5.2 Part 2

Part 2 of the study will be conducted as a double-blind study. The Sponsor, participants, investigator, and site staff will be blinded to the study therapy administered. Each investigative site must assign an unblinded pharmacist/designee, and an unblinded site monitor will be assigned by Sponsor to provide oversight of drug supply and other unblinded study documentation.

Before breaking the blind of an individual participant's treatment, the investigator should determine that the unblinded information is necessary (ie, that it will alter the participant's immediate management). In many cases, particularly when the emergency is clearly not related to the investigational product, the problem may be properly managed by assuming that the participant is receiving active product. It is highly desirable that the decision to unblind treatment assignment be discussed with the Medical Monitor, but the investigator always has ultimate authority for the decision to unblind. The actual TASK of unblinding can be delegated by the investigator to a designee assigned the task on the Delegation of Authority. The principal investigator or appointed designee should only call in for emergency unblinding AFTER the decision to unblind the participant has been documented.

For this study, the method of unblinding for emergency purposes is via the IRT system. For information on how to unblind in an emergency, consult the IRT manual.

In cases of accidental unblinding, contact the BMS Study Director/Medical Monitor (or designee) and ensure every attempt is made to preserve the blind.

Any request to unblind a participant for non-emergency purposes should be discussed with the BMS Study Director/Medical Monitor (or designee).

In case of an emergency, the investigator(s) has unrestricted access to randomization information via the IRT and is capable of breaking the blind through the IRT system without prior approval from Sponsor. Following the unblinding, the investigator shall notify the Medical Monitor and/or study director.

Designated staff of Bristol-Myers Squibb Company may be unblinded prior to database lock to facilitate the bioanalytical analysis of pharmacokinetic samples and immunogenicity. Bioanalytical scientists in the Bioanalytical Sciences department of Bristol-Myers Squibb Company (or a designee in the external central bioanalytical laboratory) may be unblinded to (may obtain) the randomized treatment assignments in order to minimize unnecessary bioanalytical analysis of samples.

If a participant is assessed by the investigator to have disease progression, and unblinding is considered necessary to inform the appropriate subsequent anti-cancer therapy, the study treatment assignment for the participant can be obtained by the investigator through IRT for non-emergency unblinding. The investigator should follow the procedures outlined in the IRT manual to obtain the participant's study treatment assignment. The BMS central study team (including but not limited to clinical, statistics, data management) will remain blinded to treatment assignment.

The study will remain blinded until the database lock for [redacted] as described in the statistical analysis plan. If an interim analysis is conducted, the Sponsor may be unblinded

to the results after accrual to the study has completed and if the primary endpoint is met (as per Section 10).

Once the database lock for the final analysis is completed, the Sponsor and Investigators will be unblinded to treatment assignments; participants on the control arm will no longer receive placebo and will no longer have study visits on Day 15 of each cycle. Similarly, if BMS-986253 is discontinued for any participants (in accordance with Sections 7.6.1, 7.6.4, or 8.1), they will no longer have study visits on Day 15 of each cycle.

7.6 Dosage Modification

[redacted]

7.6.1 Dose-limiting Toxicities

DLTs will be defined based on the incidence, intensity, and duration of AEs that are possibly related to study treatment. The DLT period will be 4 weeks (28 days). Any toxicities that occur beyond the DLT period will be accounted for in making final dose level decisions.

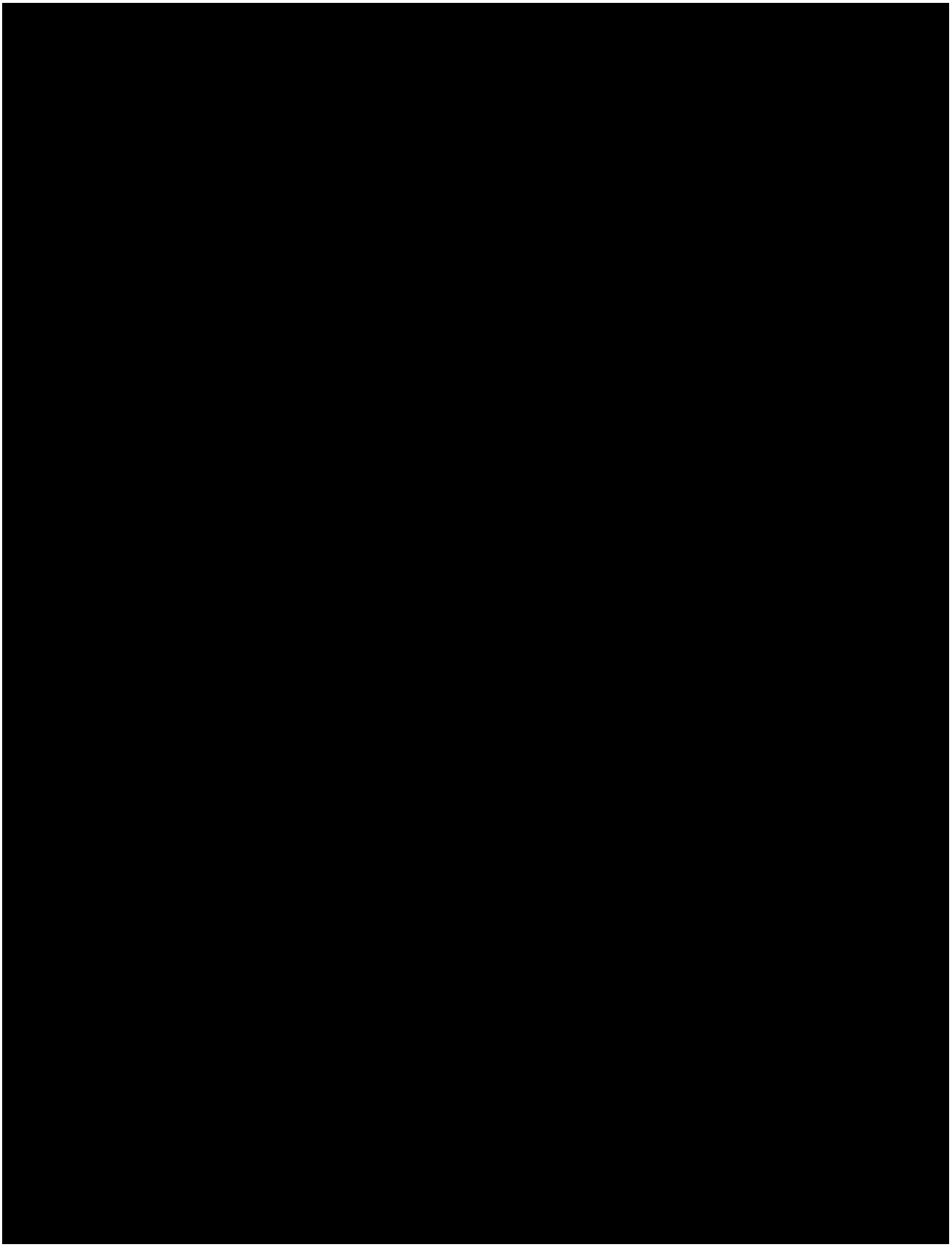
Participants that experience a DLT or are discontinued due to a DLT in the 4-week combination treatment DLT period, will be considered as DLT-evaluable participants for the safety evaluation period. Participants who withdraw from the study during the DLT evaluation period, for reasons other than a DLT, will not be considered as DLT-evaluable participants and may be replaced with a new participant at the same dose level. All participants who receive treatment will be included in the evaluation, regardless of whether they are DLT evaluable or not.

The incidence of DLT(s) during the 4-week DLT evaluation period will be used in the dose decisions for rest of the study, including in the dose-finding phase to define the RP2D or MTD. AEs occurring after the DLT period will be considered for the purposes of defining the RP2D upon agreement between the Sponsor, Medical Monitor, and investigators.

Participants experiencing a DLT will not be re-treated with study treatment, and will enter the safety follow-up period of the study, unless the investigator determines that one of the agents must be discontinued due to a DLT attributed to that agent alone.

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

[redacted]



7.6.2 Management Algorithms for Immuno-oncology Agents

I-O agents are associated with irAEs that can differ in severity and duration from AEs caused by other therapeutic classes. BMS-986253, nivolumab, and ipilimumab are considered I-O agents in this protocol. Early recognition and management of irAEs associated with I-O agents may mitigate severe toxicity. Management algorithms have been developed from extensive experience with nivolumab to assist investigators in assessing and managing the following groups of irAEs:

- Gastrointestinal
- Renal
- Pulmonary
- Hepatic
- Endocrinopathies

- Skin
- Neurological
- Myocarditis

The clinical nature of AEs noted with BMS-986253 will determine the role of the algorithms for use in toxicities related to its use in this study. The algorithms recommended for the management of irAEs in this protocol are in Appendix 6.

7.6.3 Dose Delays Due to Toxicity

Dose delay criteria apply for all drug-related AEs, regardless of whether the event is attributed to BMS-986253 (or placebo), nivolumab, or ipilimumab. Delay administration of all study drugs if any of the delay criteria listed below are met.

- Potential DLTs, until DLT relatedness is defined.
- Select AEs and laboratory abnormalities:
  - ≥ Grade 2 pneumonitis.
  - ≥ Grade 2 abnormality in AST, ALT, or total bilirubin.
  - ≥ Grade 2 creatinine.
  - ≥ Grade 2 diarrhea or colitis.
  - ≥ Grade 2 neurological AE.
  - AE, laboratory abnormality, or concurrent illness that, in the judgment of the investigator, warrants delaying study treatment administration.
- Confirmed SARS-CoV-2 infection.

For participants who require delay, re-evaluate weekly, or more frequently, if clinically indicated and resume dosing when criteria to resume treatment are met (see Section 7.6.4). Continue tumor assessments per protocol even if dosing is delayed.

Criteria for participants who are required to permanently discontinue study treatments is listed in Section 8.1. Participants not meeting guidelines for permanent discontinuation will be permitted to resume therapy based on the criteria specified below in Section 7.6.4. Participants eligible to resume study therapy will resume study therapy at the nominal treatment visit following their last received study medication dose.

The end of cycle tumor assessments, such as CT, MRI, or positive emission tomography (PET), will continue on an every 8 weeks (Q8W) schedule relative to the participant's first dose, regardless of any treatment delay incurred.

7.6.3.1 Criteria for Dose Delay Secondary to Changes in AST or ALT for Participants with HCC

Participants with HCC who experience the following must have the study drug delayed:

- If a participant has a baseline AST or ALT that is within normal limits, delay dosing for drug-related > Grade 2 toxicity (2 grade shift). If a participant has baseline AST or ALT within the Grade 1 toxicity range, delay dosing for drug-related > Grade 3 toxicity (2 grade shift)
- If a participant has baseline AST or ALT within the Grade 2 toxicity range, delay dosing for a 2-fold drug-related increase in AST or ALT or for AST or ALT values 8× ULN (whichever is lower)
- [redacted]
- It is recommended to monitor elevations in AST or ALT approximately every 3 days until levels peak and begin to decline. Dosing of study drugs can be resumed where criteria to resume treatment are met (Section 7.6.4).

7.6.3.2 Protocol-Specific Recommendation for Management of Hepatic Events in HCC Participants

The algorithms recommended for the management of irAEs in this protocol are in Appendix 6. Protocol-specific recommendation for the management of hepatic events in HCC participants are as follows:

- Dose delay criteria for hepatic events are outlined in Section 7.6.3.1. If AST or ALT levels do not improve with a dose delay of 3 to 5 days, or if the levels worsen, steroid therapy should be initiated at 0.5 mg/kg/day to 2 mg/kg/day methylprednisolone or oral equivalent
- For ALT or AST levels > 8× ULN, steroid therapy should be initiated promptly at 1 mg/kg/day to 2 mg/kg/day methylprednisolone IV, intramuscularly, or oral equivalent
- For all participants receiving steroid treatment for hepatic events, the BMS Medical Monitor should be consulted within 24 hours after initiation of steroids. Gastroenterology consult is recommended
- If AST or ALT levels do not improve within 3 to 5 days after the start of steroid therapy, or the levels worsen after the start of steroid therapy, discussion with the BMS Medical Monitor regarding the possibility of adding mycophenolate mofetil 1 g twice daily should occur
- Tapering of steroids can start once AST or ALT levels have declined by 1 CTCAE grade. Steroids should be tapered slowly, over no less than 1 month
- As outlined in Section 7.6.4, study therapy may resume when AST or ALT have returned to Grade 1 or baseline unless the AE meets the criteria for permanent discontinuation (Section 8.2). The BMS Medical Monitor must be consulted prior to resuming study treatment for all participants who required steroid intervention.

7.6.4 Criteria to Resume Treatment

Participants may resume treatment with study drug if they have completed AE management (ie, corticosteroid taper) or are on ≤ 10 mg daily prednisone or equivalent and meet the requirements per described below.

Prior to re-initiating treatment in a participant with a dosing delay lasting > 8 weeks, 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 weekly or more frequently if clinically indicated during such dosing delays.

When criteria to resume treatment for nivolumab, ipilimumab, and BMS-986253 (or placebo) are met, resume all study drugs unless the investigator determines that one of the agents must be discontinued due to toxicity attributed to that agent alone.

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

Participants experiencing AEs not meeting criteria for permanent discontinuation for the drugs being resumed as outlined in Section 8.1 may resume treatment with study medication under the following criteria:

- Participants may resume treatment with study treatment when the drug-related AE(s) resolve to Grade ≤ 1 or baseline value, with the following exceptions:
  - Participants may resume treatment in the presence of Grade 2 fatigue.
  - Participants who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
  - Participants with Grade 2 uveitis, episcleritis, iritis, eye pain, or blurred vision not meeting DLT criteria (Section 7.6.1) must resolve to baseline prior to resuming study therapy.
- For participants with Grade 2 AST, ALT, or total bilirubin elevations, dosing may resume when laboratory values return to baseline and management with corticosteroids (if needed) is complete.
- Participants with combined Grade 2 AST/ALT and total bilirubin values meeting DLT criteria (Section 7.6.1) should have treatment permanently discontinued.
- **Criteria for HCC Participants:**
  - Participants with baseline Grade 1 AST, ALT, or total bilirubin who require dose delays, for reasons other than a drug-related hepatic event, may resume treatment in the presence of Grade 2 AST, ALT, or total bilirubin increases.
  - Participants who require dose delays for drug-related increased AST, ALT, or bilirubin may resume treatment when hepatic parameters are at baseline or Grade 1, and after discussion with the BMS Medical Monitor
  - Participants with AST, ALT or bilirubin values meeting permanent discontinuation parameters (Section 7.6.1) should have treatment permanently discontinued.

- Drug-related pulmonary toxicity, diarrhea, or colitis, must have resolved to baseline before treatment is resumed. Participants with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month, may be eligible for re-treatment if discussed with, and approved by, the BMS Medical Monitor.
- Participants with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment.
- Participants with confirmed SARS-CoV-2 infection may resume treatment after 1) at least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared, positive RT-PCR test result, or positive viral antigen test result, 2) resolution of acute symptoms (including at least 24 hours has passed since last fever without fever reducing medications), 3) evaluation by the investigator with confirmation that there are no sequelae that would place the participant at a higher risk of receiving investigational treatment, and 4) consultation by the Medical Monitor. For suspected cases, treatment may also resume if SARS-CoV-2 infection is ruled-out and other criteria to resume treatment are met.
  - Prior to re-initiating on-study treatment in a participant with a dosing delay lasting ≥ 8 weeks due to SARS-CoV-2 infection, the Medical Monitor/designee must be consulted.

7.6.5 Exceptions to Permanent Discontinuation Criteria

Any drug-related AE occurring at any time that meets DLT criteria as outlined in Section 7.6.1 will require permanent discontinuation of all study drugs, unless the investigator determines that one of the agents must be discontinued due to toxicity attributed to that agent alone.

Permanent discontinuation is not required for the following:

- Grade 3 diarrhea, nausea, vomiting, or abdominal pain that returns to Grade 1 or baseline within 3 days with medical intervention.
- Grade 3 pruritus or rash that returns to Grade 1 or baseline within 7 days with medical intervention.
- Isolated Grade 3 or 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 3 days of their onset.
- Grade 4 neutropenia < 7 days in duration.
- Grade 4 lymphopenia or leukopenia.
- Grade 3 or 4 increase in amylase or lipase that is not associated with clinical or radiographic evidence of pancreatitis.
- Grade 3 infusion reaction that return to Grade 1 in < 6 hours.
- Grade 3 CRS that returns to Grade 1 in < 6 hours.
- Grade 3 fever not associated with hemodynamic compromise (eg, hypotension, clinical, or laboratory evidence of impaired end-organ perfusion).
- Grade 3 tumor flare (defined as pain, irritation, or rash that localizes to sites of known or suspected tumor).

- Grade 3 fatigue.
- Grade 3 or 4 drug-related endocrinopathy AEs, such as adrenal insufficiency, adrenocorticotropic hormone, hyper- or hypothyroidism, or glucose intolerance, which resolve or adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS Medical Monitor.

All participants who discontinue IP should comply with protocol specified follow-up procedures as outlined in Section 8.1. The only exception to this requirement is when a participant withdraws consent for all study procedures including post treatment study follow-up or loses the ability to consent freely (eg, imprisonment, involuntarily incarceration for the treatment of either a psychiatric or physical illness).

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

7.6.6 Management of Drug-related Infusion Reactions

Since BMS-986253, nivolumab, and ipilimumab contain only human Ig protein sequences, they are unlikely to induce hypersensitivity reactions. However, infusion reactions due to T-cell activation and cytokine release may occur in combination of both agents. If such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgia, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the BMS Medical Monitor and reported as an SAE. Infusion reactions should be graded according to NCI CTCAE v4.03 guidelines.

Treatment recommendations for infusion reactions are provided below and may be modified based on local treatment standards and guidelines, as appropriate.

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

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

For Grade 2 symptoms (moderate reaction requiring therapy or infusion interruption but responding promptly to symptomatic treatment such as antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids, or prophylactic medications indicated for ≤ 24 hours):

- Stop the study treatment infusion, begin an IV infusion of [redacted] sodium chloride and treat the participant with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 mg to 1000 mg; remain at bedside and monitor participant

until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor participant closely. If symptoms recur, then no further BMS-986253 or nivolumab will be administered at that visit.

- For future infusions, the following prophylactic pre-medications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 mg to 1000 mg should be administered at least 30 minutes before study treatment infusions. If necessary, corticosteroids (up to 25 mg of hydrocortisone or equivalent) may be used.

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

- Immediately discontinue infusion of study treatment. Begin an IV infusion of [redacted] sodium chloride and treat the participant as follows: recommend bronchodilators, epinephrine 0.2 mg to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 mg to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Participant should be monitored until the investigator is comfortable that the symptoms will not recur. Study treatment will be permanently discontinued except for a Grade 3 infusion reaction that returns to Grade 1 in less than 6 hours. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor participant until recovery of the symptoms.

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).

7.6.7 Management of Cytokine Release Syndrome (CRS)

- Cytokine release plays a role in the pathophysiology of drug-related infusion reactions, which should be managed as per guidelines in Section 7.6.6. Infusions of immune-stimulating agents can also be associated with a cytokine-associated toxicity known as CRS, which has unpredictable onset and could occur many days following treatment.[62] CRS is a clinical syndrome typically associated with infusions of immune-stimulating agents such as chimeric antigen receptor T cell (CAR T-cell) and bispecific antibodies.[63] Cytokine release syndrome is characterized by fever, fatigue, nausea, headache, dyspnea, tachycardia, rigors, hypotension, hypoxia, myalgia/arthralgia, and anorexia. Clinical symptoms and severity of CRS are highly variable,[63] and management can be complicated by concurrent conditions.

- Fever (≥ 38.5°C or ≥ 101.3°F) is a commonly-observed hallmark of CRS, and many features of CRS mimic infection. Hence, infection must be considered in all participants presenting with CRS symptoms, and appropriate cultures should be obtained, and empiric antibiotic therapy initiated per institution standard of care.
- Less common symptoms associated with CRS include cardiac dysfunction, adult respiratory distress syndrome, renal and/or hepatic failure, coagulopathies, disseminated intravascular coagulation, and capillary leak syndrome.
- Neurologic toxicity has been observed concurrently with CRS.
- High baseline levels of other commonly measured inflammatory markers, such as ferritin and C-reactive protein (CRP), were also associated with CRS.

The potential for BMS-986253 in combination with nivolumab or nivolumab plus ipilimumab to cause CRS is not yet defined, and CRS due to immune checkpoint inhibitors is rare.[63] Most guidelines for management of CRS are intended for recipients of CAR T-cell therapy, and widely adopted algorithms to manage CRS specifically due to immune checkpoint blockade have not been established. If CRS is suspected, local guidelines for CRS management with input from BMS Medical Monitor or designee should be followed. General principles for CRS management include use of acetaminophen, steroids, IV fluids, and vasopressors. Interleukin-6 (IL-6), a pleiotropic cytokine with anti-inflammatory and proinflammatory properties, has been identified as a central mediator of toxicity in CRS. In more severe cases, use of tocilizumab, an anti–interleukin-6 receptor monoclonal antibody, may be considered. CRS severity should be documented by CTCAE v4.03 criteria which primarily grades CRS based on clinical judgment as to interventions needed and subsequent response to these treatments. Management of study treatment should be per the table below.

Table 7.6.7-1: Management of Cytokine Release Syndrome (CRS)

Grade (CTCAE v4.03)	Intervention
1	No change to study treatment.
2	Study treatment may resume at next scheduled dose but consider prophylactic supportive therapy, eg, with acetaminophen 500-1000 mg
3	Permanently discontinue study treatment if does not improve to Grade 1 within 6 hours and contact BMS MM or designee.
4	Permanently discontinue BMS-986253 and contact BMS MM or designee.

Abbreviations: BMS, Bristol-Myers Squibb Company; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; MM, medical monitor.

7.6.8 Hemophagocytic Lymphohistiocytosis (HLH)

HLH (or macrophage activation syndrome [MAS]) is a rare, potentially fatal immune-mediated disease, with a wide range of causes, symptoms, and outcomes, but all lead to a hyperinflammatory

response. [redacted]

HLH is divided into primary (genetic) and secondary (reactive) forms. Secondary HLH has both infectious and non-infectious triggers.[64] Amongst the infectious triggers of secondary HLH, viral EBV is the most commonly described, but other viruses including SARS-CoV-2 have been associated with HLH.[64,65,66] Bacterial and fungal infections can also trigger HLH.[64] An alternative diagnostic term of macrophage activation-like syndrome (MALS) has been proposed for patients with sepsis and co-occurrence of signs/symptoms of HLH. However, clinical criteria for the entity of MALS have not been widely adopted.[67]

Malignancy and immune checkpoint inhibitors (ICIs) are potential non-infectious triggers of HLH. BMS conducted a review of Pharmetrics and Marketscan US claims databases, which indicated that the incidence of HLH was 0.12% and 0.07% in melanoma patients treated with any immune checkpoint inhibitor (ICI), respectively, and 0.2% and 0% in melanoma patients treated with any combination of tyrosine kinase inhibitors consisting of BRAF plus mitogen-activated protein kinase kinase inhibitor, respectively. Among 49,883 ICI-related Adverse Drug Reactions collated in VigiBase (the largest pharmacovigilance database in the world) as of 30-Sep-2018, HLH was reported in 38 cases, with the highest reported rate of ICI-related HLH occurring in France, and melanoma being the most common cancer type.[68]

In September 2019, an HLH assessment for nivolumab and ipilimumab was requested by the European Medicines Agency Pharmacovigilance Risk Assessment Committee.[69] Based on the conclusions originating from that request, HLH was included on the nivolumab and ipilimumab United State Prescribing Information/Summary of Product Characteristics as a post-marketing adverse drug reaction with unknown frequency.

The presentation of secondary HLH is heterogeneous and can be acute or subacute with non-specific symptoms appearing over a few days to 4 weeks.[70] The diagnosis of HLH in adults may be established if either of the 2 criteria below is fulfilled[71]:

1) Documentation of a verified HLH-associated gene mutation with clinical findings associated with HLH

OR

2) Five out of the 8 criteria below for MAS/HLH are fulfilled:
   a) High persistent fever (≥ 38.5°C)
   b) Splenomegaly
   c) Cytopenias (affecting 2 of 3 lineages in the peripheral blood)
      i) Hemoglobin < 9.0 g/dl

ii) Platelets < 100 x 10^9/L

iii) Neutrophils < 1.0 x 10^9/L

d) Triglycerides: ≥ 3.0 mmol/L (ie, 265 mg/dl) or fibrinogen ≤ 1.5 g/L
e) Hemophagocytosis in bone marrow, spleen and/or lymph nodes
f) Low or absent NK-cell activity (according to local laboratory reference)
g) Ferritin ≥ 500 µg/L
h) Soluble CD25 (ie, soluble IL-2 receptor) ≥ 2400 U/mL

An alternative diagnostic scoring system (measured with an online tool) that may also be utilized considers hepatic function as well as the magnitude of laboratory test result abnormalities to derive an "H-score," which estimates a probability of HLH.[72] When potential clinical features of HLH are identified (eg, high fever, splenomegaly, coagulopathy, cytopenia, elevated transaminases), further laboratory testing to evaluate for additional HLH diagnostic criteria should be considered. In particular, hyperferritinemia has been suggested to be a key laboratory feature, with levels >10,000 µg/L having high specificity and sensitivity for HLH.[64] Serum ferritin is closely related to HLH disease activity and may be useful to monitor treatment response.[64] Bone marrow is the preferred anatomical site for investigation of hemophagocytosis and may be evaluated as clinically warranted. If a genetic predisposition is suspected, testing for an HLH-associated gene mutation should be considered.

Detection of any ongoing infection acting as a trigger for HLH is critical. Standard tests should be used to screen for infections caused by the most common viruses such as herpes simplex virus, cytomegalovirus and Epstein-Barr virus (EBV), and SARS-CoV-2. Other infectious agents (eg, mycobacteria, parasites, and fungi, particularly Candida and Mucor) should be ruled out according to specific clinical or epidemiological features.[71,72]

7.6.8.1 HLH Management Approaches

Effective treatment of HLH requires multiple simultaneous approaches:

1) Supportive care: Life-threatening severe manifestations may be present and should be managed with appropriate supportive interventions.
2) Elimination of triggers (particularly infection): Appropriate broad-spectrum antiviral, antibacterial, antifungal therapy should be initiated based on clinical suspicion and infectious work-up.
3) Suppression of the inflammatory response: Treatment specific for cancer immunotherapy-related HLH is not established, but HLH treatment generally may include: glucocorticoids, IL-1 blockade with anakinra, intravenous immunoglobulin (IVIG), cytotoxic agents (eg, etoposide), IL-6 blockade (eg, tocilizumab), and/or IFN-γ blockade (eg, emapalumab). Specific treatment should be guided by local standards and clinical judgment. A potential algorithm adapted from Carter et al[64] for treating HLH in adults is provided below:

a) First-line treatment: IV methylprednisolone 1 g daily for 3 to 5 days (followed by steroid taper) plus IVIG 1 g/kg for 2 days (consider repeating at 14 days due to half-life of 14-21 days).
b) Second-line treatment (consider if there is clinical deterioration despite first-line treatment): Anakinra starting at 1-2 mg/kg, increasing to a maximum of 8 mg/kg/day.
c) Third-line/refractory treatment: Discuss with hematologist/other consultants and consider cytotoxic therapy or other additional anti-cytokine therapy.

All participants that develop HLH while on study therapy must be permanently discontinued all study treatments, regardless of which (if any) study therapies are considered related to the adverse event.

7.7 Preparation/Handling/Storage/Accountability

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

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

Study treatment not supplied by BMS will be stored in accordance with the prescribing information.

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

For study drugs not provided by BMS and obtained commercially by the site, storage should in accordance with the product label.

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

7.7.1 Retained Samples for Bioavailability / Bioequivalence

Not applicable.

7.8 Treatment Compliance

Not applicable.

7.9 Concomitant Therapy

7.9.1 Prohibited and/or Restricted Treatments

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

- Immunosuppressive agents.
- Immunosuppressive doses of systemic corticosteroids. Participants are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Adrenal replacement steroid doses > 10 mg daily prednisone are permitted. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.
- Any concurrent approved or investigational anti-neoplastic therapy (ie, chemotherapy, hormonal therapy, or immunotherapy) for treatment of study disease.
- Any non-palliative radiation therapy. Radiation therapy administered with palliative intent (ie, for pain, bleeding, spinal cord compression, brain metastasis, new or impending pathologic fracture, superior vena-cava syndrome, or obstruction) is permitted.
- Any complementary medications (eg, herbal supplements or traditional Chinese medicines) intended to treat the disease under study. Such medications are permitted if they are used as supportive care.
- Any live/attenuated vaccine (eg, varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella [MMR]) during treatment and until 100 days post last dose.
- Administration of investigational SARS-CoV-2 vaccines is not allowed during the study. Participants may receive authorized or approved SARS-CoV-2 vaccines while continuing on study treatment at the discretion of the investigator.
- Treatment of active SARS-CoV-2 infections or high-risk exposures, including use of investigational therapies, is allowed and should be discussed with the Medical Monitor.

7.9.2 Other Restrictions and Precautions

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

7.9.2.1 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 for each participant. Imaging contraindications and contrast risks should be considered in this assessment. Participants with renal insufficiency should be assessed whether or not they should receive contrast and if so, what type and dose of contrast is appropriate. Specific to MRI, participants with severe renal insufficiency (ie, estimated glomerular filtration rate

< 30 mL/min/1.73 m^2) are at increased risk of nephrogenic systemic fibrosis. MRI contrast should not be given to this participant population. In addition, participants are excluded from MRI if they have tattoos, metallic implants, pacemakers, etc.

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

7.10 Permitted Therapy

Participants are permitted the use of the following treatments:

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

7.10.1 Palliative Local Therapy

Part 1

If clinically indicated, palliative and supportive care for disease-related symptoms may be offered to participants in Part 1 of the study, after the DLT evaluation period. Limited radiation treatment or surgery to control isolated lesions may be permitted for participants following consultation with the BMS Medical Monitor (or designee).

Participants should not receive study treatment during radiation because the potential for overlapping toxicities with radiotherapy and study treatment is not known. If palliative radiotherapy in short courses and for isolated fields is required to control symptoms not clearly related to disease progression, then study treatment administration should be withheld, if possible, for at least 1 week before radiation and for at least 1 week after its completion.

Participants should be closely monitored for any potential toxicity during and after receiving radiotherapy. Prior to resuming study treatment, radiotherapy-related AEs should resolve to Grade ≤ 1 or baseline, and participants must meet relevant eligibility criteria as determined by the BMS Medical Monitor (or designee) in discussion with the investigator. The BMS Medical Monitor (or designee) must be consulted prior to re-initiating study treatment in a participant with a dosing delay lasting > 8 weeks from the previous dose.

Details of palliative radiotherapy should be documented in the source records and electronic case report form (eCRF). Details in the source records should include dates of treatment, anatomic site, dose administered and fractionation schedule, and AEs.

Symptoms requiring palliative radiotherapy should be evaluated for objective evidence of disease progression. If a participant is considered to have progressed at the time of palliative therapy, then they must meet the treatment beyond progression criteria (Section 8.1.1) prior to re-initiating study treatment. Participants receiving palliative radiation of target lesions will have the evaluation of objective response rate (ORR) just prior to radiotherapy if ORR was not assessed in 4 weeks prior

to start of radiotherapy, these participants will no longer be evaluable for the determination of response subsequent to the date palliative radiation occurs.

For participants who need to undergo surgery during the study, it is recommended to hold study treatment(s) for at least 4 weeks before (if elective) and 2 weeks after surgery, or until the participant recovers from the procedure, whichever is longer. Prior to resuming study treatment, surgically related AEs should resolve to Grade 1 or baseline, and participants must meet relevant eligibility criteria as determined by the BMS Medical Monitor (or designee) in discussion with the investigator. The BMS Medical Monitor (or designee) must be consulted prior to re-initiating study treatment in a participant with a dosing delay lasting > 8 weeks from the previous dose.

Part 2

Palliative (limited-field) radiation therapy and palliative surgical resection are permitted if either of the following criterion is met:

1) The participant has radiographic disease progression at the time of palliative therapy and meets criteria to continue with treatment beyond progression (Section 8.1.1).
2) If the participant has symptoms not clearly related to disease progression, they may receive a short course of palliative radiation to an isolated field or limited tumor-directed surgical intervention.

Details of palliative therapy should be documented in the source records and eCRF. Details in the source records should include dates of treatment, anatomic site, dose administered and fractionation schedule, and AEs. Participants who started tumor-directed radiotherapy or tumor-directed surgery, without a prior reported radiographic progression per RECIST v1.1, will be censored at the last evaluable tumor assessment prior to initiation of radiotherapy. Participants receiving palliative radiation should undergo a radiographic tumor assessment just prior to radiotherapy/tumor-directed surgery if no such assessment has occurred in the 4 weeks prior to start of the radiotherapy/surgery. Participants receiving palliative radiation or surgery impacting a target lesion will no longer be evaluable for the determination of response subsequent to the date the palliative procedure occurs.

Participants should not receive study treatment during radiation because the potential for overlapping toxicities with radiotherapy and study treatment is not known. Study treatment administration should be withheld, if possible, for at least 1 week before radiation and for at least 1 week after its completion. Participants should be closely monitored for any potential toxicity during and after receiving radiotherapy. Prior to resuming study treatment, radiotherapy-related AEs should resolve to Grade ≤ 1 or baseline, and participants must meet relevant eligibility criteria.

For participants who need to undergo surgery during the study, it is recommended to hold study treatment(s) for at least 4 weeks before (if elective) and 2 weeks after surgery, or until the participant recovers from the procedure, whichever is longer. Prior to resuming study treatment, surgically related AEs should resolve to Grade 1 or baseline, and participants must meet relevant eligibility criteria.

7.11 Treatment After the End of the Study

At the conclusion of the study, participants who continue to demonstrate clinical benefit may be eligible to receive BMS-supplied study treatment.

Those participants who demonstrate clinical benefit from treatment without unacceptable toxicity may continue treatment beyond the 3-year treatment period, up to a maximum of 5 years from the first dose of study treatment, at the discretion of the investigator and after discussion with the Medical Monitor, until loss of that benefit, unacceptable toxicity, or participant/physician decision to withdraw.

If a participant continues study treatment beyond the 3-year treatment period, procedures during the extended treatment duration will be minimized to clinical and laboratory safety monitoring, AE collections, and tumor assessments every 12 weeks until the final analysis.

BMS reserves the right to terminate access to BMS-supplied study treatment if any of the following occur: a) the study is terminated due to safety concerns; b) the development of BMS-986253 is terminated for other reasons, including but not limited to lack of efficacy and/or not meeting the study objectives; c) the participant can obtain medication from a government-sponsored or private health program. In all cases, BMS will follow local regulations.

8 DISCONTINUATION CRITERIA

8.1 Discontinuation from Study Treatment

Participants MUST discontinue IP for any of the following reasons:

- Documented disease progression as defined by RECIST v1.1 (Appendix 8) unless participants meet criteria for treatment beyond progression (Section 8.1.1).
- Clinical deterioration while receiving active study therapy that, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant.
- Any drug-related AE occurring at any time that meets DLT criteria as outlined in Section 7.6.1 will require permanent discontinuation of the implicated study drug. Exceptions to permanent discontinuation are listed in Section 7.6.5.
- Participant's request to stop study treatment. Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information.
- Any clinical AE, laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant.
- Termination of the study by BMS for reasons stated in Section 8.2.1.
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness. (Note: Under specific circumstances and only in countries where local regulations permit, a participant who

has been imprisoned may be permitted to continue as a participant. Strict conditions apply and BMS approval is required.)

- Inability to comply with protocol.
- Discretion of the investigator.
- Pregnancy.
- Individual participants with confirmed complete response (CR), and all participants after final analysis results are available, will be given the option to discontinue any or all of the study therapies on a case by case basis after specific consultation and agreement between the investigator and BMS Medical Monitor in settings where benefit/risk justifies discontinuation.
- Any event that leads to delay in dosing, lasting > 8 weeks from the previous dose, requires discontinuation, with the exception of the following:
  - Dosing delays for prolonged steroid tapers to manage drug-related AEs are allowed. Prior to re-initiating treatment in a participant with a dosing delay lasting > 8 weeks from the previous dose, the BMS Medical Monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue per protocol, or more frequently if clinically indicated, during such dosing delays.
  - Dosing delays lasting > 8 weeks from the previous dose that occur for non-drug-related reasons may not require discontinuation, if approved by the BMS Medical Monitor. Prior to re-initiating treatment in a participant with a dosing delay lasting > 8 weeks, the BMS Medical Monitor must be consulted.
- Any AE, laboratory abnormality, or concurrent illness, which, in the judgment of the investigator, presents a substantial clinical risk to the participant with continued study treatment dosing.

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.

In the case of pregnancy, the investigator must immediately, within 24 hours of awareness of the pregnancy, notify the BMS Medical Monitor/designee of this event. In most cases, the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). Refer to Section 9.2.5 Pregnancy.

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

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

The assessment for discontinuation of BMS-986253 (or placebo), nivolumab, and ipilimumab should be made separately. For example, if the AEs are assessed to be related to ipilimumab only and meet the discontinuation criteria, BMS-986253 (or placebo) and/or nivolumab may resume.

If a participant in any of the combination cohorts meets criteria for discontinuation and the investigator is unable to determine whether AE is attributable to individual or combination study drugs, the participant should discontinue all study drugs.

8.1.1 Treatment Beyond Progression

As described in Section 5.4.6, accumulating evidence indicates that a minority of participants with tumors treated with immunotherapy may derive clinical benefit despite initial evidence of disease progression. Participants will be permitted to continue treatment beyond initial RECIST v1.1-defined disease progression, as assessed by the investigator (see Appendix 8), as long as they meet the following criteria:

- Investigator-assessed clinical benefit, and no rapid disease progression.
- Continue to meet all other study protocol eligibility criteria.
- Tolerance of study treatment.
- Stable performance status.
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases).
- Participant provides written informed consent prior to receiving any additional nivolumab, ipilimumab, and BMS-986253 treatment, using an ICF describing any reasonably foreseeable risks or discomforts, or other alternative treatment options.

The assessment of clinical benefit should take into account whether the participant is clinically deteriorating and unlikely to receive further benefit from continued treatment. If the investigator feels that the participant continues to achieve clinical benefit by continuing treatment with the study treatments, 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 the BMS Medical Monitor, and an assessment of the risk/benefit of continuing with study therapy must be documented in the study records (see Appendix 2).

Participants must be re-consented with an ICF addendum or similar document to continue treatment beyond progression. Treatment beyond progression will require continued tumor assessments and scans should continue to be submitted to the imaging core laboratory.

Participants who continue study therapy beyond progression will continue to receive monitoring according to the on-treatment assessments in Section 2, and radiographic assessment per Section 9.4.1 and Section 2 to determine whether there has been continued disease progression or not.

Further progression is defined as an additional 10% increase in tumor burden with a minimum 5 mm absolute increase from time of initial progression of 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 progression of disease. It is recommended that study treatment should be discontinued permanently upon documentation of further progression.

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 that become measurable, these new lesions must demonstrate an absolute increase of at least 5 mm.

8.1.2 Post Treatment Follow-up

Post treatment follow-up is of critical importance and is essential to preserving participant safety and the integrity of the study. Participants who discontinue study treatment must continue to be followed for safety follow-up as required and in line with Section 5.1.5.

8.2 Discontinuation from the Study

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

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

8.2.1 Study Termination

BMS reserves the right to terminate the study at any time for reasons including but not limited to the following: safety concerns, termination of drug development, lack of efficacy, and lack of meeting study objectives/endpoints.

8.3 Lost to Follow-up

- All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant.

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

9 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the Schedule of Activities (See Section 2).
- Protocol waivers or exemptions are not allowed.
- All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.
- Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before randomization. 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.

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

If a participant shows pulmonary-related signs (hypoxia, fever) or symptoms (eg, dyspnea and cough) consistent with possible pulmonary AEs, the participant should be immediately evaluated

to rule out pulmonary toxicity, according to the suspected pulmonary toxicity management algorithm in the BMS-936558 (nivolumab) IB.

Some of the assessments referred to in this section may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician.

Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

9.1 Safety Assessment

Safety assessments will be based on reported AE and the measurement results of vital signs including oxygen saturation, ECGs, physical examinations, and clinical laboratory tests. AEs will be coded using the most current version of Medical Dictionary for Regulatory Activities and the incidence of observed AEs will be tabulated and reviewed for potential significance and clinical importance. AEs will be assessed continuously during the study and for a minimum of 100 days after the last dose of study treatment. A 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 NCI CTCAE v4.03.

Planned timepoints for all safety assessments are listed in the Schedule of Activities in Section 2.

9.1.1 Physical Examinations

A full physical exam will be obtained during select times during study participation. Refer to the Schedule of Activities for timing of assessments in Section 2.

9.1.2 Vital signs

Pre and post dose vital signs will be obtained during the dosing visits. Vital signs including oxygen saturation will be obtained during select times during study participation. Refer to the Schedule of Activities for timing of assessments in Section 2.

9.1.3 Electrocardiograms

Refer to the Schedule of Activities for timing of ECG assessments for safety in Section 2. The investigators will review the 12-lead ECGs using their site's standard ECG machines throughout the study. [redacted]

Refer to the Schedule of ECG collection for effect of BMS-986253 in combination with nivolumab [redacted] Electrocardiogram recording should be obtained prior to PK samples at each time point as indicated [redacted] The ECGs will be assessed by an independent core laboratory until final analysis. A separate manual will include additional details and instructions. All ECG tests will be performed in triplicate for Cycles 1 and 4 in Part 1A and 1B, and for Cycles 1, 2, and 3 in Part 1C (ie, 1 ECG test equals 3 consecutive individual 12-lead ECGs performed at least 5 minutes apart). Special Restrictions: Subjects should refrain from strenuous physical activity and use of (methyl) xanthines (eg, coffee, tea, cola, chocolate) or alcohol on the days when ECG measurements will be obtained.

9.1.4 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 must be available prior to dosing. Laboratory samples may be obtained up to 48 hours prior to dosing.
- The laboratory tests that will be performed for study participants are shown in Table 9.1.4-1.
- 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 9.1.4-1: Laboratory Tests

Hematology	
Hemoglobin and hematocrit	
Total leukocyte count, including differential	
Platelet count	
Prothrombin time, activated partial thromboplastin time, and international normalized ratio (screening only)	
Chemistry	
Alanine aminotransferase Aspartate aminotransferase Total bilirubin Direct bilirubin (only if total bilirubin is abnormal) Alkaline phosphatase Lactate dehydrogenase Creatinine Blood Urea Nitrogen Uric acid Glucose Lipase (screening only for Part 2) Amylase (screening only for Part 2) Thyroid stimulating hormone T3 and free T4 (**screening and only** if TSH is abnormal when checked every third cycle)	Total Protein Albumin Sodium Potassium Chloride Calcium Phosphorus Magnesium Creatine kinase Creatinine clearance - screening only Troponin (screening and at each cycle for Part 1 and screening only for Part 2)
Urinalysis	
Protein	
Glucose	

Blood
Leukocyte esterase
Specific gravity
pH
Serology
Serum for hepatitis B surface antigen, hepatitis C antibody (screening only) For HCC participants: hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody, hepatitis B DNA PCR, hepatitis C antibody and hepatitis C RNA PCR, and hepatitis D antibody testing for those with concurrent hepatitis B infection
Other Analyses:
Pregnancy test (WOCBP only: screening, predose at each cycle, EOT).
Follicle stimulating hormone (screening only for post-menopausal women < 55 years old)
AFP only for HCC participants in Part 1C

Abbreviations: AFP, alpha fetoprotein; CRC, colorectal cancer; DNA, deoxyribonucleic acid; EOT, end of treatment; HCC, hepatocellular carcinoma; PCR, polymerase chain reaction; RNA, ribonucleic acid; T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone; WOCBP, women of childbearing potential.

9.2 Adverse Events Assessments

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

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

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue before completing the study. All SAEs and AEs will be assessed using NCI CTCAE v4.03.

Contacts for SAE reporting specified in Appendix 3.

9.2.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All nonserious adverse events (not only those deemed to be treatment related) must be collected starting with the first dose of study drug and for a minimum of 100 days after discontinuing study treatment.

All SAEs must be collected from the time of signing the ICF and for a minimum of 100 days after discontinuing study treatment. Death due to disease progression within 100 days of discontinuation of dosing must be reported as an SAE. Time points are specified in the Schedule of Activities (Section 2).

Sections 5.6.1 and 5.6.2 in the BMS-986253, nivolumab, and ipilimumab IBs represent the Reference Safety Information to determine expectedness of SAEs for expedited reporting.

After the participant signs the Pre-Screen ICF for serum IL-8 collection, all SAEs related to the blood draw must be collected and followed until resolution or stabilization.

After the participant signs the main ICF to participate in the study, all SAEs whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures.

After the Pre-Screen ICF is signed:

- Only SAEs related to the blood draw for IL-8 serum will be collected and followed until resolution or stabilization.

All related SAEs will be recorded and reported to Sponsor or designee within 24 hours, as indicated in Appendix 3.

- The investigator will submit any updated SAE data to the Sponsor within 24 hours of this being available.
- All SAEs related to the blood draw for IL-8 serum in Pre-Screening will be followed until resolution or stabilization.

After the Main ICF is signed:

- All SAEs must be collected that occur during the participant's written consent and for a minimum of 100 days after discontinuing study treatment, or if the last scheduled visit occurs at a later time.
- The investigator must report any SAE that occurs after these time periods and that is believed to be related to study treatment or protocol-specified procedure.
- Medical occurrences that begin before the start of study treatment but after signing the main informed consent will be recorded on the appropriate section of the eCRF section.
- All SAEs will be recorded and reported to Sponsor or designee within 24 hours, as indicated in Appendix 3. Death due to disease progression within 100 days of discontinuation of dosing must be reported as an SAE regardless of assessed relatedness to the study drug.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of this being available.

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

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

9.2.2 Method of Detecting AEs and SAEs

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 judgment in the context of known AEs, when appropriate for the program or protocol.

9.2.3 Follow-up of Adverse Events and Serious Adverse Events

Nonserious AEs should be followed to resolution or stabilization, or reported as an SAEs if they become serious (see Section Appendix 3).

Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study treatment and for those present at the end of study treatment as appropriate.

All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic). Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts.

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

9.2.4 Regulatory Reporting Requirements for SAEs

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

Sponsor or designee will be reporting AEs to regulatory authorities and ECs according to local applicable laws including European Regulation 536/2014 and FDA Code of Federal Regulations (CFR) 21 CFR Parts 312 and 320. A SUSAR (Suspected, Unexpected Serious Adverse Reaction) is a subset of SAEs and will be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

9.2.5 Pregnancy

If, following initiation of the study treatment, it is subsequently discovered that a participant is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half-lives after product administration, the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Appendix 3.

In most cases, the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). Please call the BMS Medical Monitor within 24 hours of awareness of the pregnancy.

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

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to Sponsor or designee. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an ICF for disclosure of this information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

9.2.6 Laboratory Test Result Abnormalities

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

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

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

9.2.7 Immune-mediated Adverse Events

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

9.2.8 Potential Drug-induced Liver Injury

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

Potential DILI is defined as:

1) ALT or AST elevation > 3× ULN

AND

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

AND

3) No other immediately apparent possible causes of ALT 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.

Specifically for HCC: p-DILI is defined as:

- Concurrent ALT > 10× ULN AND total bilirubin > 2× ULN or baseline value (if elevated bilirubin at study entry), AND
- No other immediately apparent possible causes of ALT elevation and hyperbilirubinemia, including, but not limited to, tumor progression, acute viral hepatitis, cholestasis, preexisting hepatic disease or the administration of other drug(s), herbal medications and substances known to be hepatotoxic.

This is the standard DILI definition across the BMS HCC program.

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: (iii) timely evaluation and triaging of p-DILI cases, (iv) expedited reporting of p-DILI cases and (v) 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, total bilirubin, 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: 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.

9.2.9 Other Safety Considerations

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

9.3 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section 9.2).

For this study, any dose of BMS-986253, nivolumab, and/or ipilimumab greater than the assigned dose and considered excessive and medically important by the investigator will be considered an overdose.

In the event of an overdose the [investigator/treating physician] should:

1) Contact the Medical Monitor immediately
2) Closely monitor the participant for AEs/SAEs and laboratory abnormalities until BMS-986253, nivolumab, and/or ipilimumab can no longer be detected systemically
3) Obtain a plasma sample for PK if requested by the Medical Monitor (determined on a case-by-case basis)
4) Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions or modifications secondary to an overdose will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

9.4 Efficacy Assessments

Following the database lock for the final analysis, efficacy will no longer be assessed. Imaging should be performed per standard of care at the discretion of the treating physician.

Efficacy assessments for the anti-tumor activity of BMS-986253, in combination with nivolumab or in combination with nivolumab and ipilimumab, will use investigator assessed tumor measurements, per RECIST v1.1 (Appendix 8).

Assessments of partial response (PR) and CR must be confirmed at least 4 weeks after initial response. Changes in tumor measurements and tumor responses will be assessed by the investigator per study design using RECIST v1.1 criteria (Appendix 8). Investigators will also report the number and size of new lesions that appear while on study. The timepoint of tumor assessments will be reported on the eCRF based on the investigator's assessment.

A BICR will be utilized in this study for determination of BICR-assessed endpoints. The BICR will review all available tumor assessment scans for all treated participants until the final analysis is completed. Details of BICR responsibilities and procedures will be specified in the BICR charter.

A Best Overall Response of SD requires a minimum of 49 days on study from the date of first dose to the date of the first imaging assessment.

[redacted]

9.4.1 Imaging Assessment for the Study

Following the final analysis, images will no longer be submitted for BICR evaluation. Imaging should be performed per institutional standard of care.

Until final analysis, images will be submitted to an imaging core laboratory and may be reviewed by BICR at any time during the study. Sites should be qualified prior to scanning the first participant and understand the image acquisition guidelines and submission process as outlined in the CA027002 Imaging Manual provided by the core laboratory.

Baseline images should be acquired as outlined in Table 2-2. On-study images should be acquired as outlined in Table 2-3, Table 2-4, and Table 2-5 from the date of first dose. Tumor assessments at other timepoints may be performed if clinically indicated and should be submitted to the central imaging vendor as soon as possible. Unscheduled CT/MRI should be submitted to the central imaging vendor. X-rays and bone scans that clearly demonstrate interval progression of disease, for example most commonly as unequivocal lesions that are unmistakably new since the prior CT/MRI, should be submitted to the central imaging vendor. Otherwise, they do not need to be submitted centrally.

Images will be acquired within 28 days prior to the first treatment dose. Images acquired as part of care prior to signing the ICF, but within the 28-day limit, will be acceptable if there is no intervening treatment, and all required scanning acquisition parameters are met (if feasible per local regulations).

For Part 1: On-treatment images will be acquired every 8 weeks (± 7 days) up until Week 48 and then every 12 weeks (± 7 days) until withdrawal of consent, death, or initiation of another anti-cancer treatment, whichever occurs first. For Part 2: On-treatment images will be acquired every 8 weeks (± 7 days) up until Week 48 and then every 12 weeks (± 7 days) until BICR-confirmed disease progression, or treatment discontinuation (including treatment beyond progression), whichever occurs later.

For Part 1: At the time of study treatment discontinuation, participants should continue to have radiologic and clinical tumor assessment on the same schedule, every 8 weeks (± 7 days), starting from first dose for the first 48 weeks, then every 12 weeks (± 7 days), until withdrawal of consent, death, or initiation of another anti-cancer treatment or for up to a maximum of 2 years, whichever occurs first. For Part 2: At the time of study treatment discontinuation, participants in Part 2 will continue to have radiologic and clinical tumor assessments on the same schedule, every 8 weeks

(± 7 days), starting from first dose for the first 48 weeks, then every 12 weeks (± 7 days), until BICR-confirmed disease progression, or treatment discontinuation (including treatment beyond progression), whichever occurs later.

Tumor assessment with contrast-enhanced CT scans acquired on dedicated CT equipment is preferred for this study. Contrast-enhanced CT of the chest, abdomen, pelvis, and all other known/suspected sites of disease should be performed for tumor assessments.

For participants with SCCHN, a CT or MRI the neck is required for all tumor assessments.

For participants with HCC, imaging of the abdomen should include multi-phasic (at least three of the following four phases: precontrast, arterial, venous, delayed) CT or MRI of the liver.

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 timepoints. 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 1.1 criteria (Appendix 8).

Should a participant have contraindication for a CT IV contrast, a non-contrast CT of the chest and a contrast-enhanced MRI of the abdomen, pelvis, and all other known/suspected sites of disease should be obtained. If the primary tumor is not of lung origin, a contrast-enhanced MRI of the chest may be obtained instead of a non-contrast CT of the chest.

Should a participant have contraindication for both MR and CT IV contrasts, a non-contrast CT of the chest and a non-contrast MRI of the abdomen, pelvis, and all other known/suspected sites of disease should be obtained. If the primary tumor is not of lung origin, a non-contrast MRI of the chest, abdomen, pelvis, and other known/suspected sites of disease is also acceptable.

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

Use of CT component of a PET-CT scanner: Combined modality scanning such as with PET-CT is increasingly used in clinical care, and is a modality/technology that is in rapid evolution; therefore, the recommendations outlined here may change rather quickly with time. At present, low dose or attenuation correction CT portions of a combined PET-CT are of limited use in anatomically-based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for anatomically-based RECIST measurements. However, if a site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the PET-CT can be used for RECIST 1.1 measurements. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Bone scan or PET scan is not adequate for assessment of RECIST 1.1 response in target lesions. In selected circumstances where such modalities are the sole modality used to assess certain

non-target organs, those non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when CR is identified in target disease or when progression in bone is suspected.

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

MRI of 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.

9.4.2 BICR Confirmation of Progression (Part 2)

Following the final analysis, images will no longer be submitted to BICR for evaluation. Imaging should be performed per institutional standard of care.

Until final analysis, sites should submit all scans to the central imaging vendor on a rolling basis, throughout the duration of the study. BICR of scans will occur on a rolling basis, blinded to treatment arm, clinical data, and investigator assessment of submitted scans. For Part 2, when progression per RECIST 1.1 criteria is assessed by the investigator, the site will inform the central imaging vendor, in order for BICR assessment of progression to be performed. The BICR will be completed and the results provided to the site as specified in the imaging vendor documents, provided there are no pending imaging queries to the site. All details on the timelines and associated process requirements will be outlined in the Imaging Manual.

Participants whose progression is not confirmed by the BICR will be required to continue tumor assessments (if clinically feasible) according to the protocol-specified schedule, or sooner if clinically indicated. Also, if participants discontinue treatment without radiographic progression, tumor assessments will continue according to the protocol-specified schedule, as noted in Section 2 (Schedule of Activities) until progression has been confirmed by BICR.

All study treatment decisions will be based on the investigator's assessment of tumor images and not on the BICR assessment.

9.5 Pharmacokinetics and Immunogenicity Assessments

Following the final analysis, PK and IMG samples will no longer be collected.

Pharmacokinetic (PK) and immunogenicity (IMG) assessment data for BMS-986253, nivolumab, and ipilimumab will be collected from study participants assigned to the study at the time points indicated [redacted] All time points are relative to the start of the first drug administration on that day. All on-treatment time points are intended to align with days on which study drug is administered; if dosing occurs on a different day, the PK and IMG sampling should be adjusted accordingly. If it is known that a dose is going to be delayed, then the predose sample should be collected just prior to the delayed dose. However, if a predose sample is collected but the dose is subsequently delayed, an additional predose sample should not be collected. All pre-dose samples should be taken within 30 minutes before the start of any dose infusion. End of infusion (EOI) samples should be taken immediately prior to completion of the infusion, preferably within 2 minutes. Blood samples should be drawn from a site other than the infusion site (ie, contralateral arm) on days of infusion.

Pharmacokinetics of BMS-986253 will be derived, if feasible, from serum concentration versus time data following administration of BMS-986253. PK parameters that will be assessed are shown below:

Table 9.5-1: Pharmacokinetic Parameters

Cmax	Maximum observed serum concentration
Tmax	Time of maximum observed serum concentration
AUC(0-T)	Area under the serum concentration-time curve from time zero to time of last quantifiable concentration; may be calculated if concentrations are not quantifiable up to TAU across a treatment group
AUC(TAU)	Area under the serum concentration-time curve in 1 dosing interval
Ctau	Observed serum concentration at the end of a dosing interval
Ctrough	Trough observed serum concentrations (this includes pre-dose concentrations [C0] and Ctau)
[redacted]	[redacted]

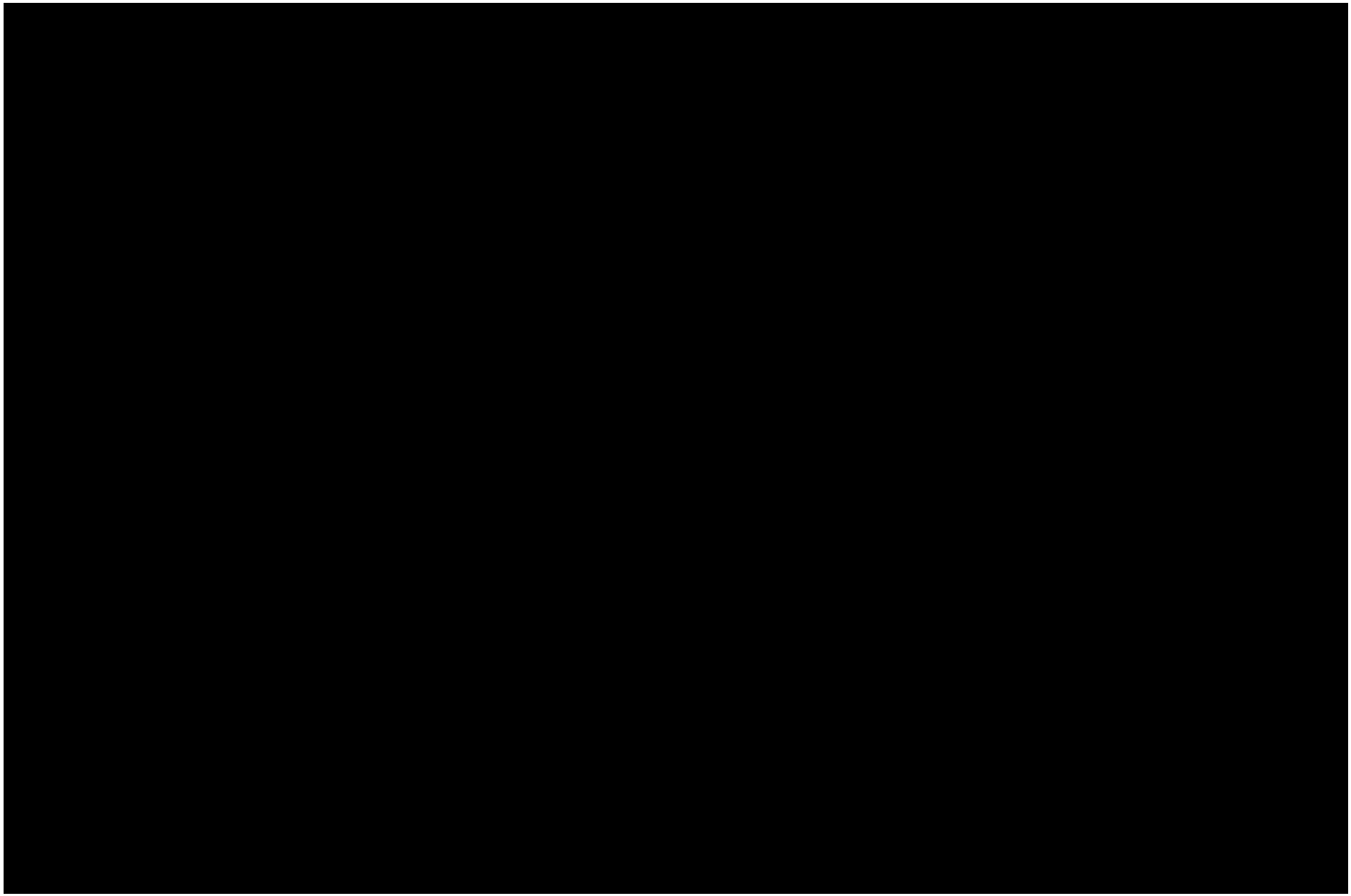
Table 9.5-2: Pharmacokinetic Parameters that May be Assessed Following the Administration of BMS-986253

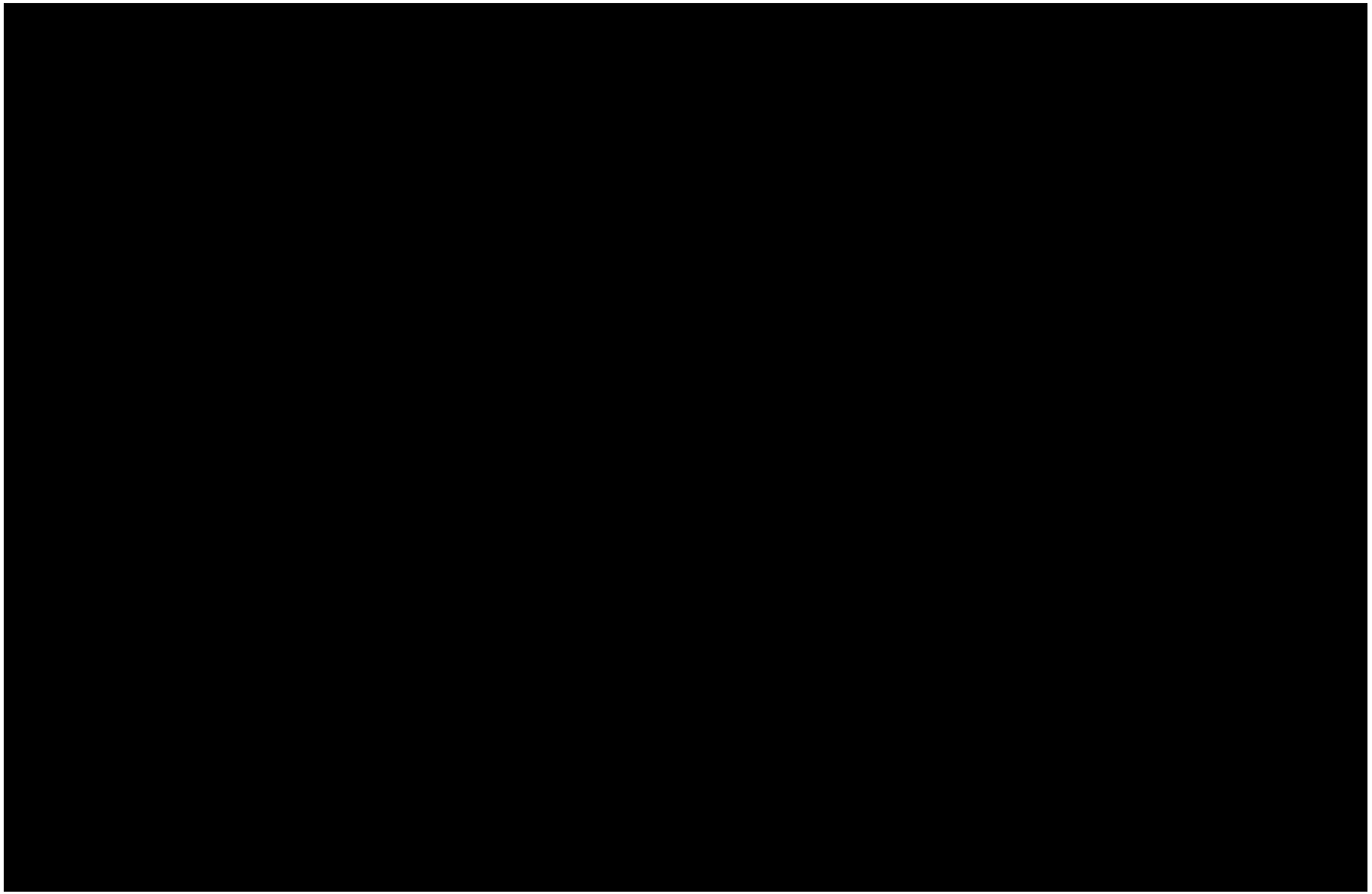
CLT	Total body clearance
Css-avg	Average serum concentration over a dosing interval (AUC[TAU]/tau) at steady state
AI	Ratio of an exposure measure at steady state to that after the first dose (exposure measure includes AUC[TAU] and Cmax)
[redacted]	[redacted]

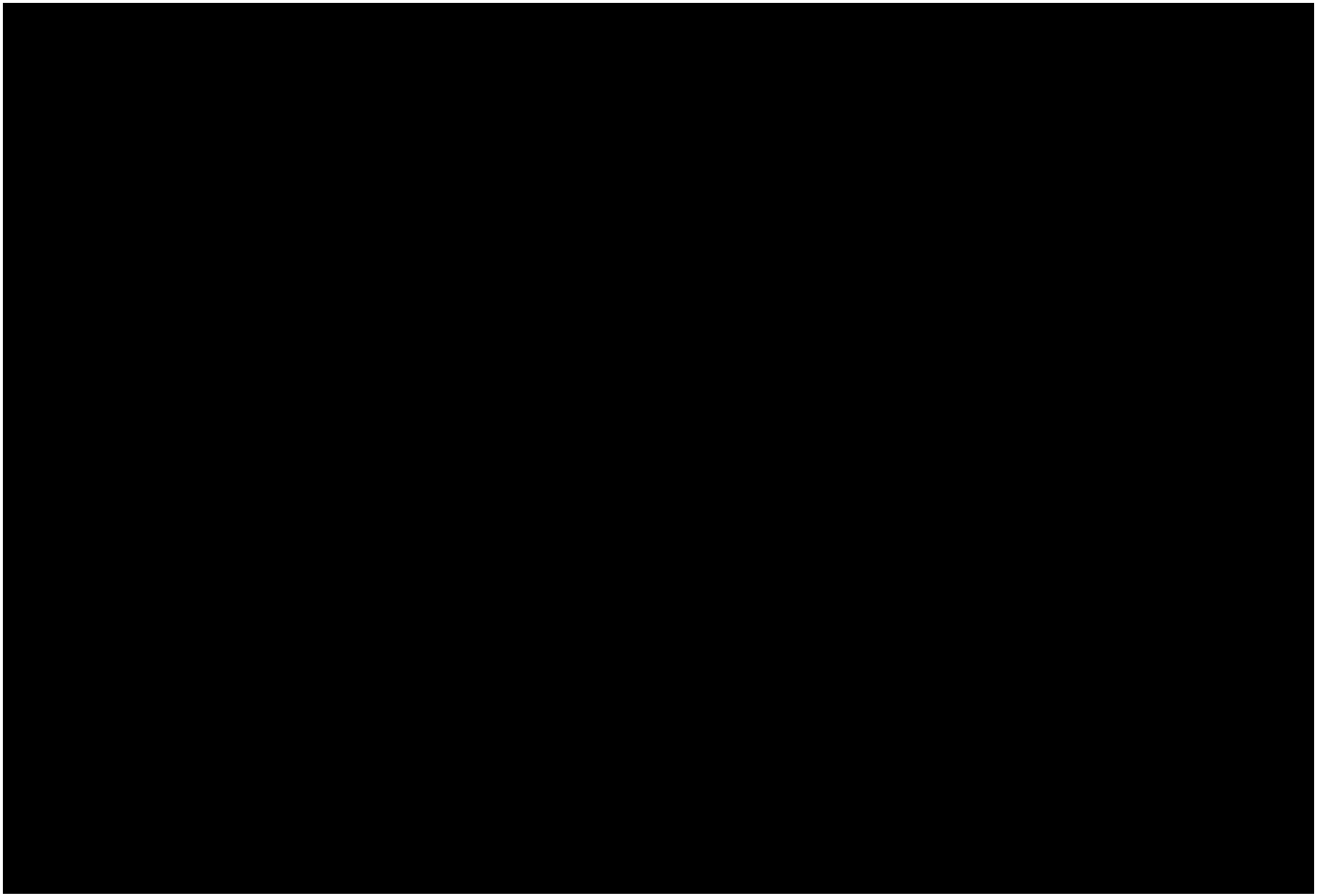
Abbreviations: AUC(TAU), area under the serum concentration-time curve in 1 dosing interval; Cmax, maximum observed plasma concentration; tau, dosing interval.

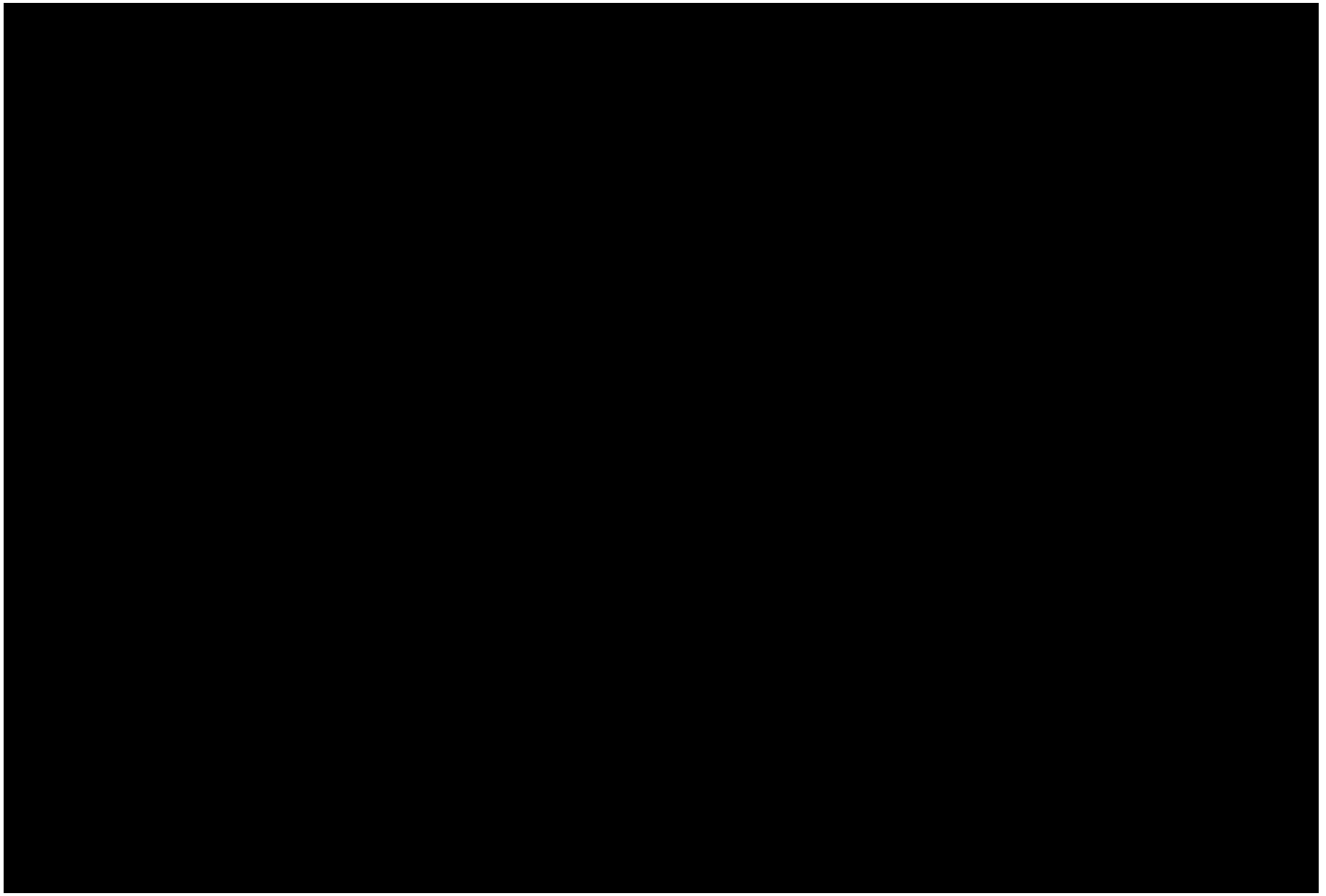
Individual participant PK parameter values will be derived by non-compartmental methods using a validated PK analysis program (Part 1 only). Actual times will be used for all formal analyses.

Sparse nivolumab and ipilimumab concentration-time data will be collected and may be used in an integrated population pharmacokinetics (PPK) or exposure response analysis along with data from other studies, which will be the subject of a separate report. Separate samples will be collected for PK and IMG assessments.









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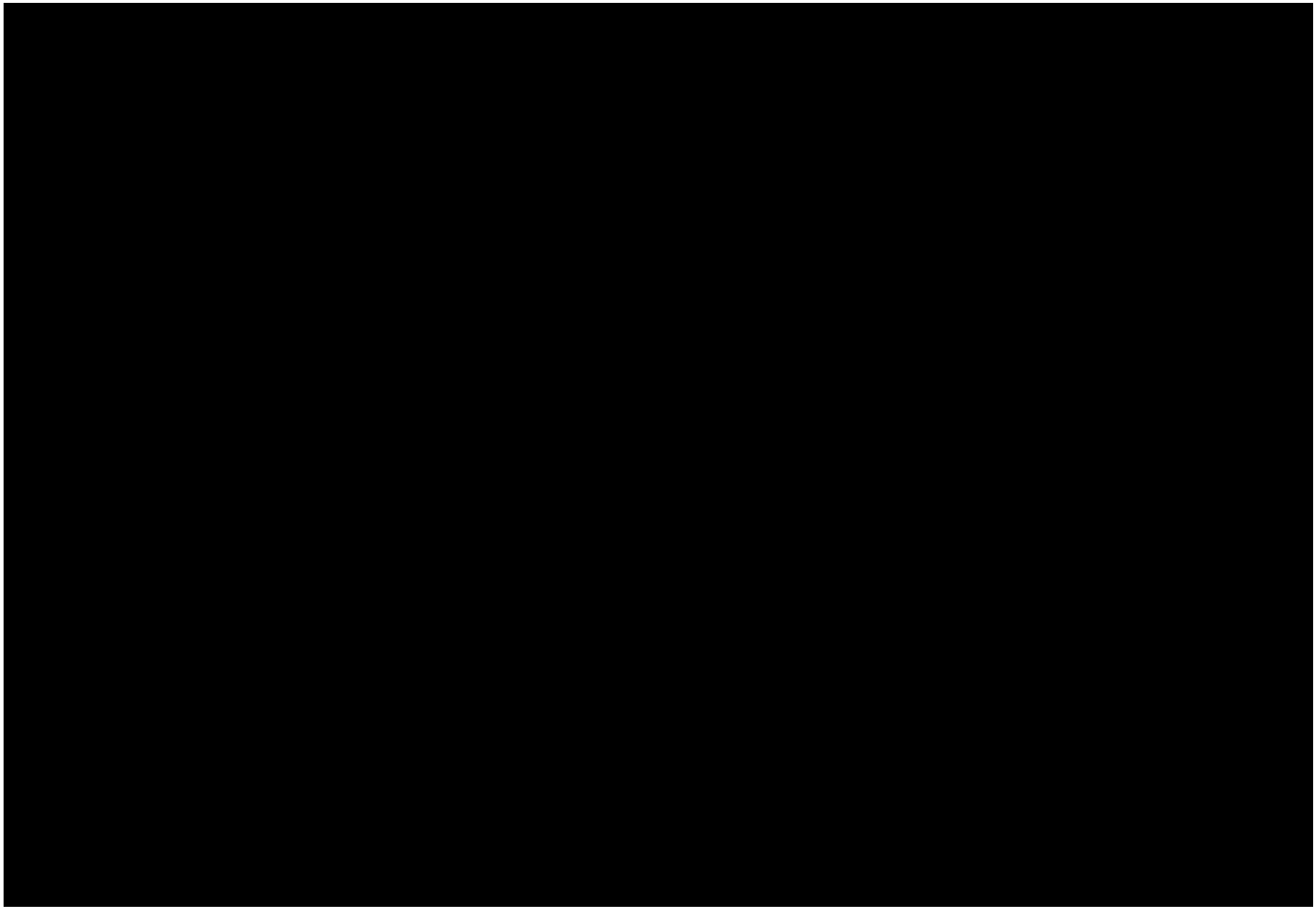

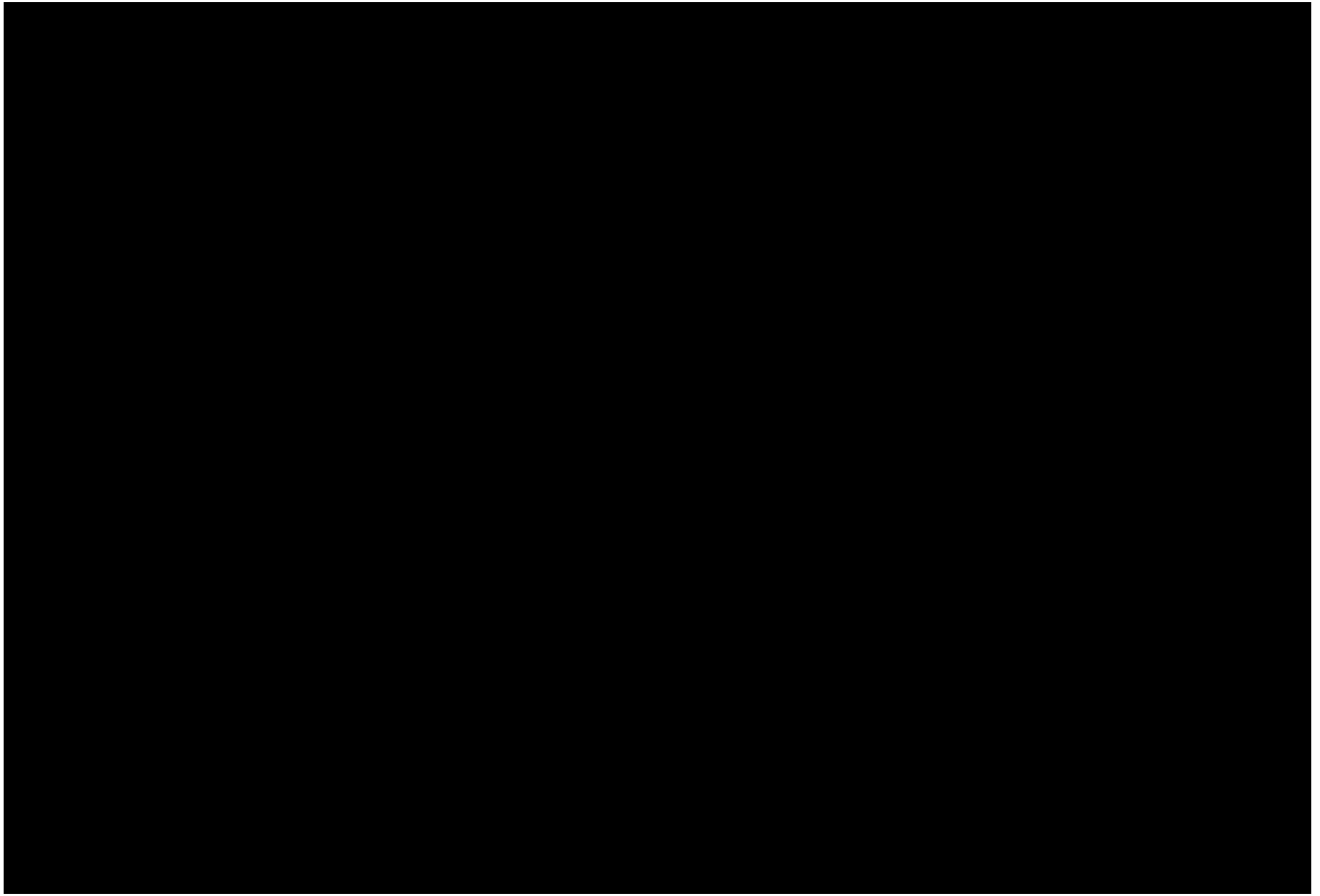

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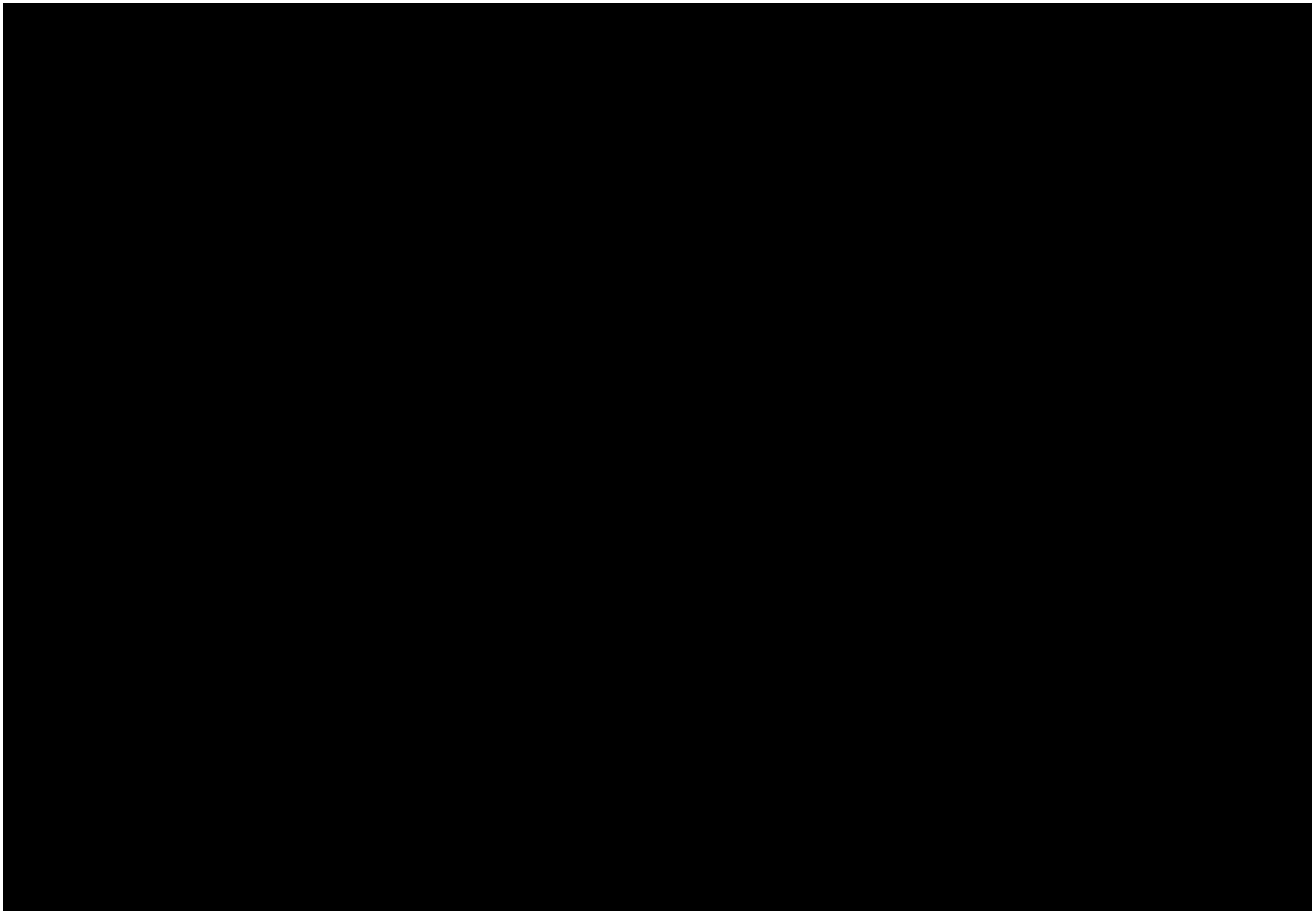
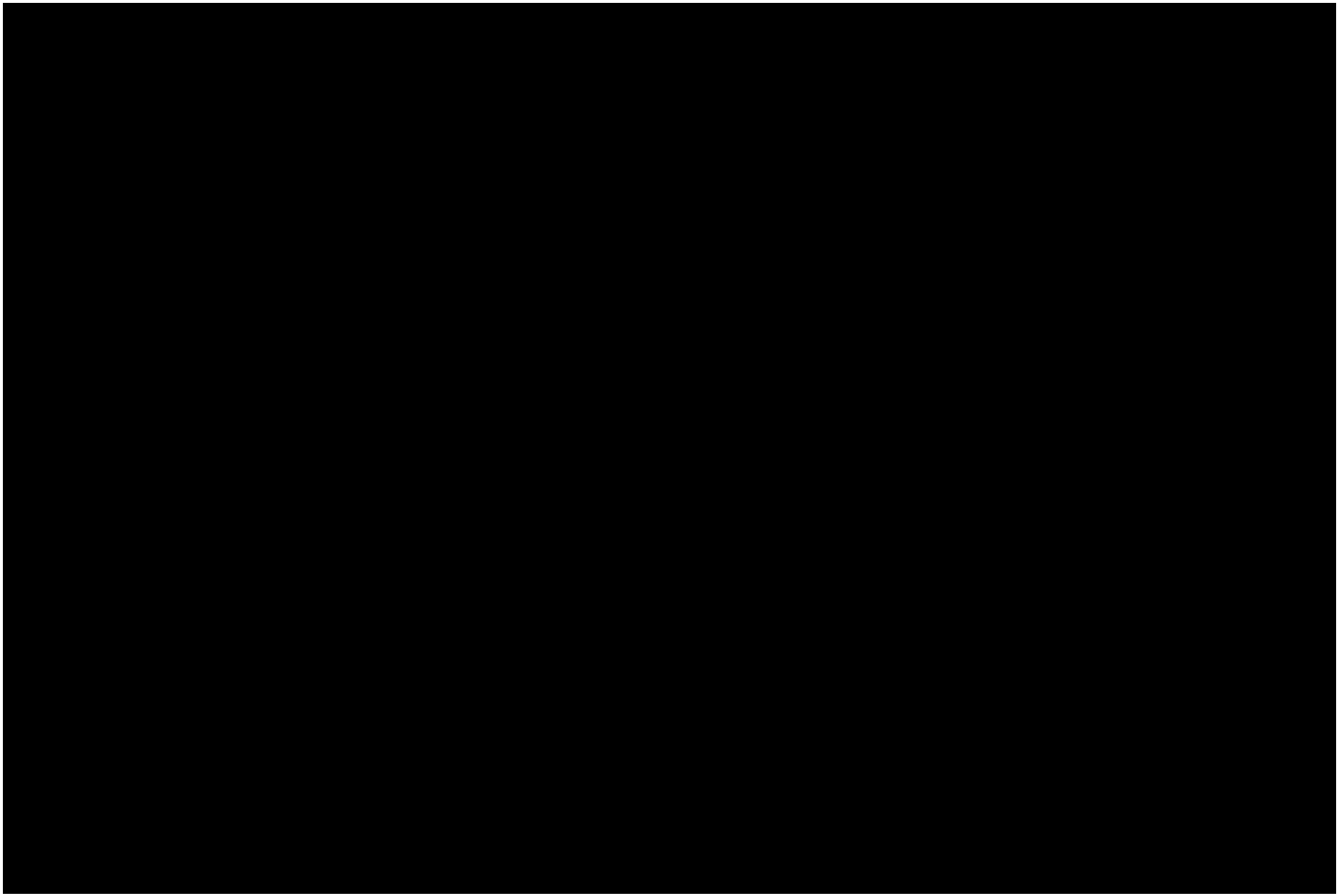
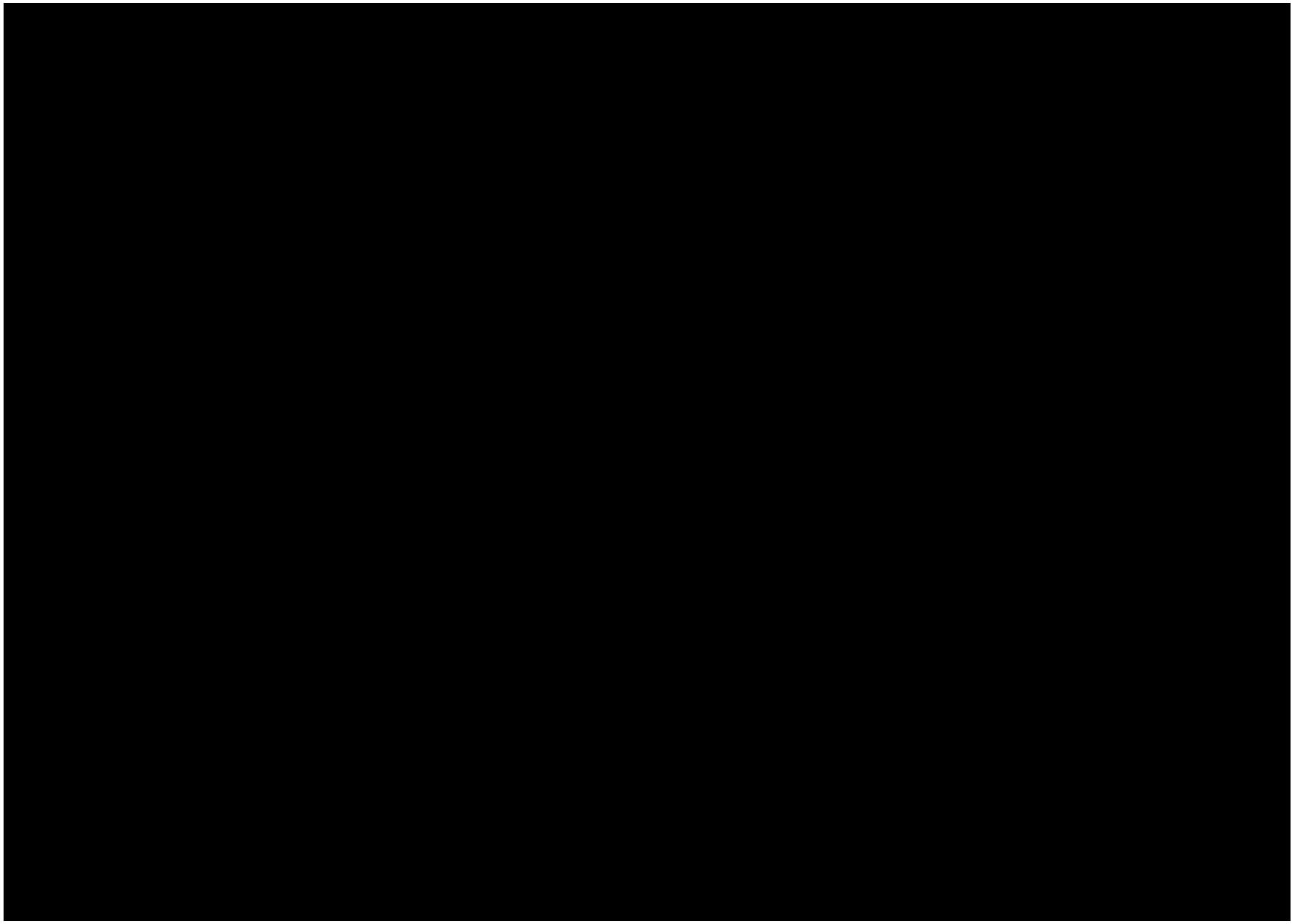
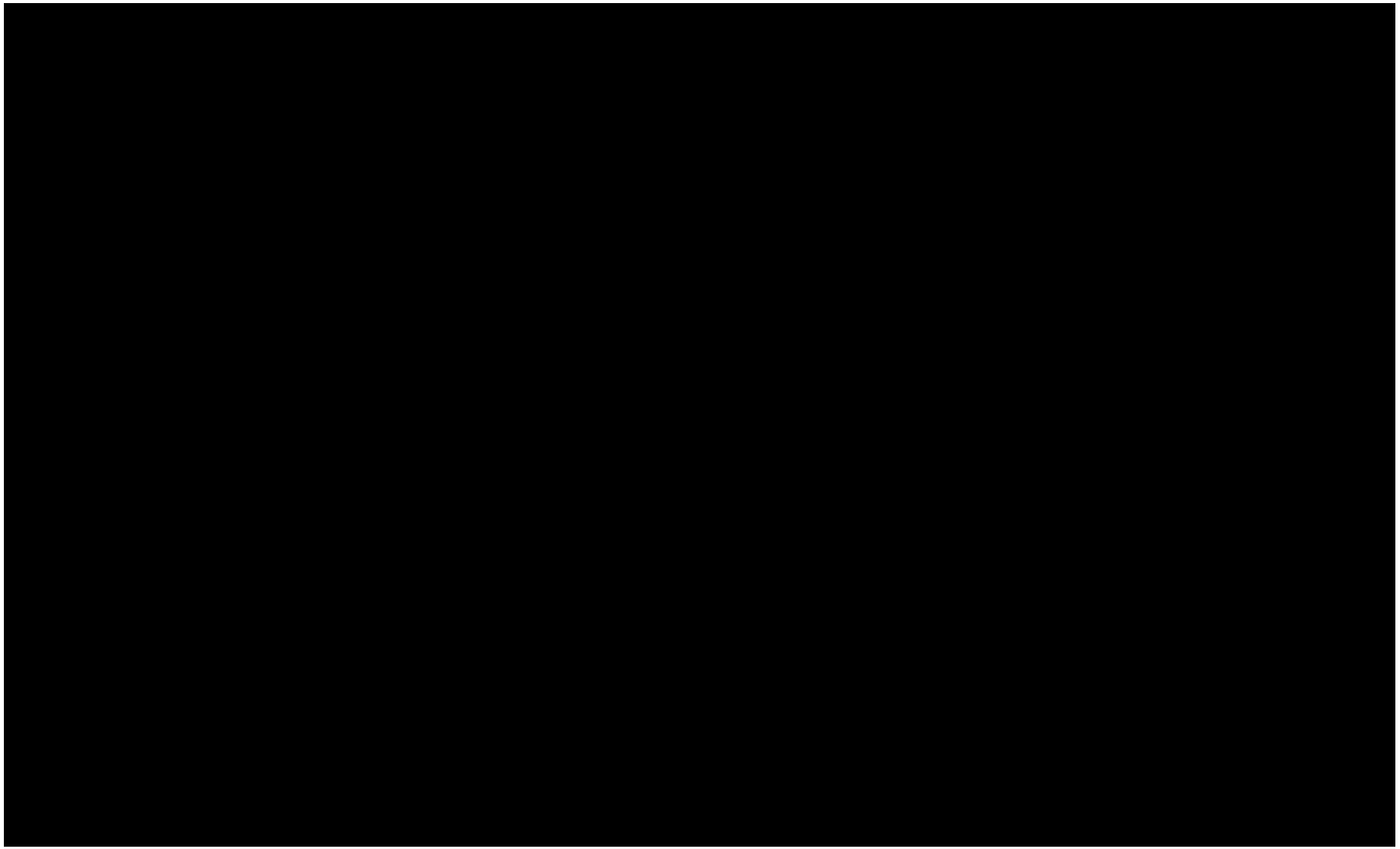








[redacted]

Immunogenicity samples will be analyzed for anti-nivolumab/anti-ipilimumab/anti-BMS-986253 antibodies by validated bioanalytical method(s). Immunogenicity samples positive for any anti-nivolumab, anti-ipilimumab, or anti-BMS-986253 antibodies may be analyzed for neutralizing antibodies by validated bioanalytical method(s). Exploratory results will not be reported. 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). For all PK and immunogenicity plasma/serum samples, the date and actual time collected must be recorded. For participants whose only peripheral access is via a venous access device or peripherally inserted central catheter, refer to the Laboratory Manual for the proper technique to ensure undiluted whole blood for PK assessments.

Further details of sample collection, processing, and shipment will be provided in the laboratory procedures manual.

9.6 Pharmacodynamics

Details on pharmacodynamic biomarker assessments are in Section 9.8.2.1.

9.7 Pharmacogenomics

Not applicable.

9.7.1 Absorption, Distribution, Metabolism, and Excretion Sampling

Not applicable.

9.8 Biomarkers

Following the final analysis, biomarker samples will no longer be collected.

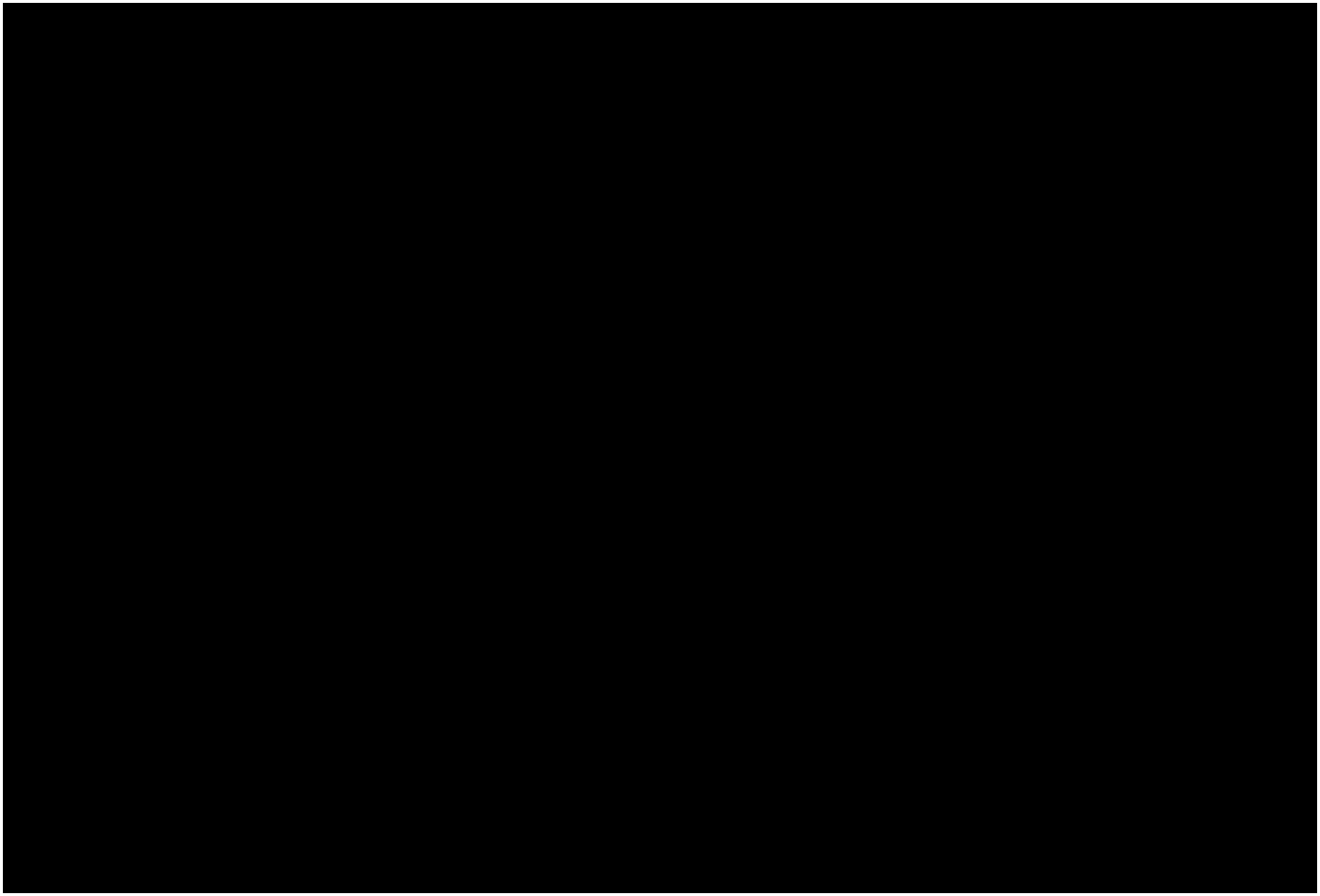
[redacted]

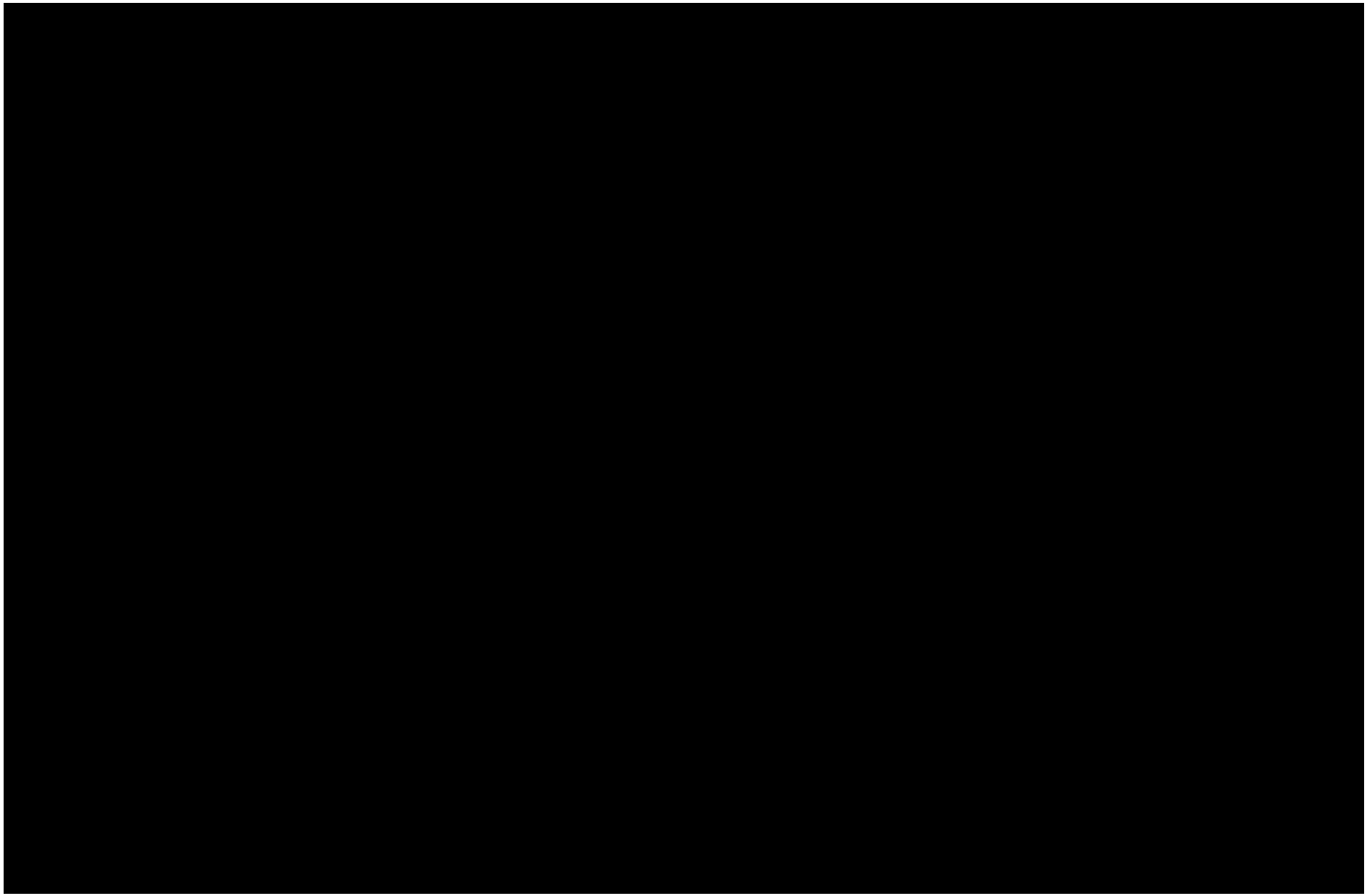
If biomarker samples are drawn but study treatment(s) is not administered, samples will be retained. A detailed description of each biomarker sample analysis and assessment is described below, and a schedule of biomarker sample collections is provided [redacted] Further details of blood, serum, and tumor tissue collection and processing will be provided to the site in the procedure manual.

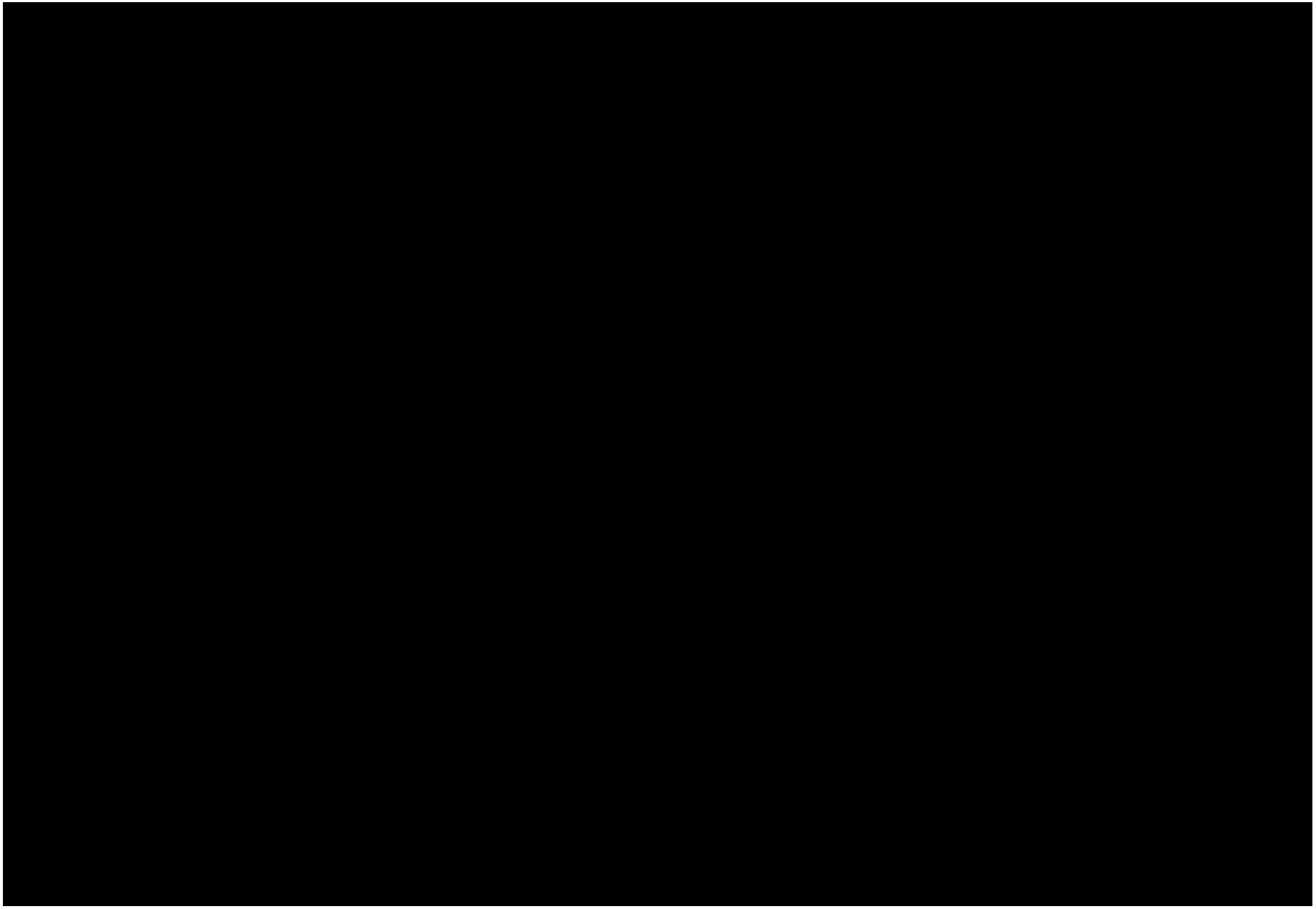
9.8.1 Serum IL-8 Levels for Participant Selection

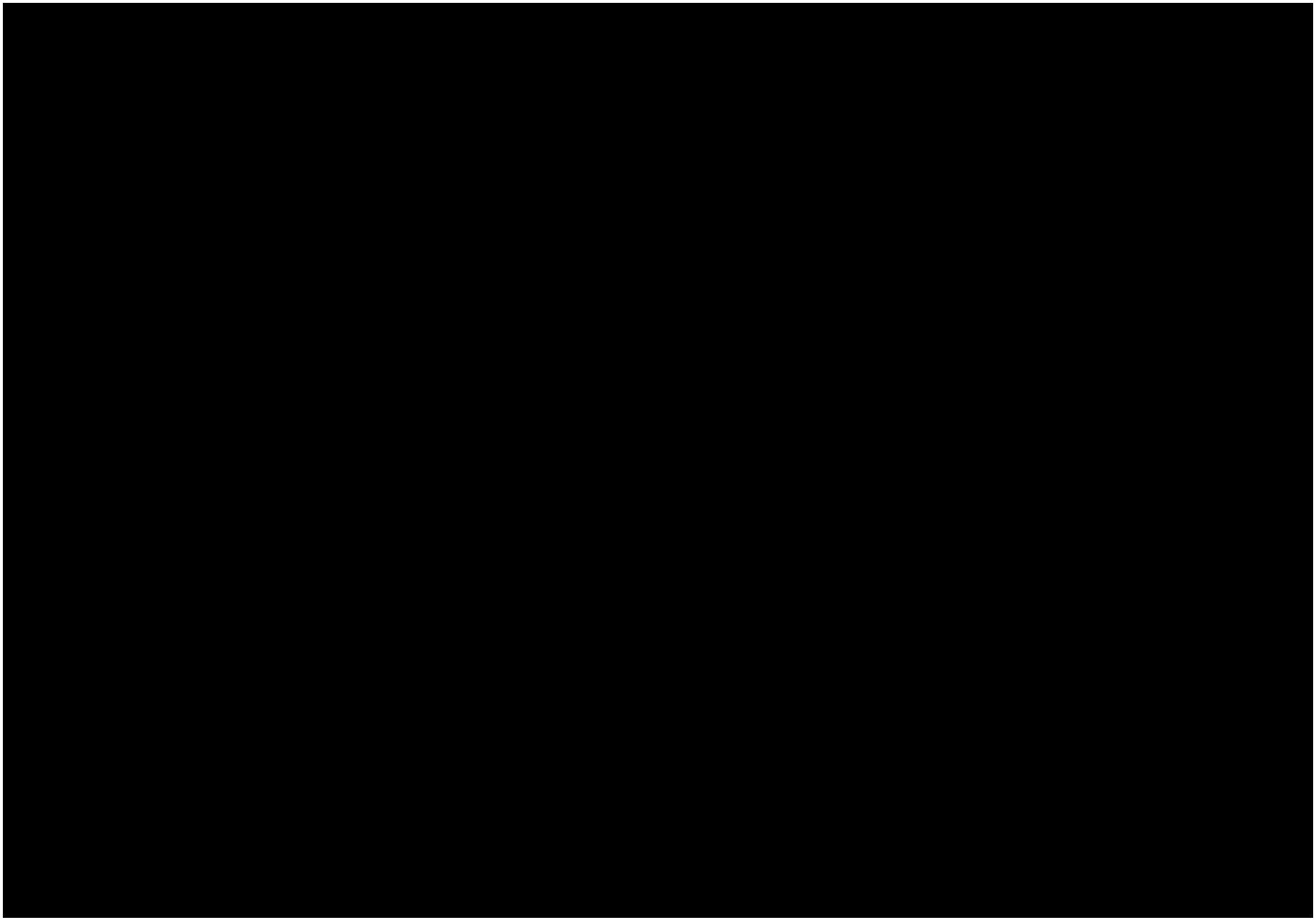
Previous studies have demonstrated that changes in serum IL-8 levels are associated with response to nivolumab or pembrolizumab in patients with metastatic melanoma and NSCLC. In addition, it has been shown that early changes in serum IL-8 levels post-treatment can predict response and OS.[20] It has also been demonstrated that expression of CXCR2, one of two IL-8 receptors, is upregulated in metastatic melanoma lesions that progressed following treatment with nivolumab compared to lesions from the same patient that regressed during nivolumab treatment.[19] Finally, a relatively high median level of serum IL-8 at baseline has been shown to correlate with OS in melanoma, NSCLC, and RCC patients in response to ipilimumab.[3] In light of these findings and of the concept that BMS-986253 can compromise IL-8-mediated immunosuppression, serum IL-8 levels at baseline could conceivably be used as a biomarker to select participants more likely to benefit from nivolumab when combined with BMS-986253.

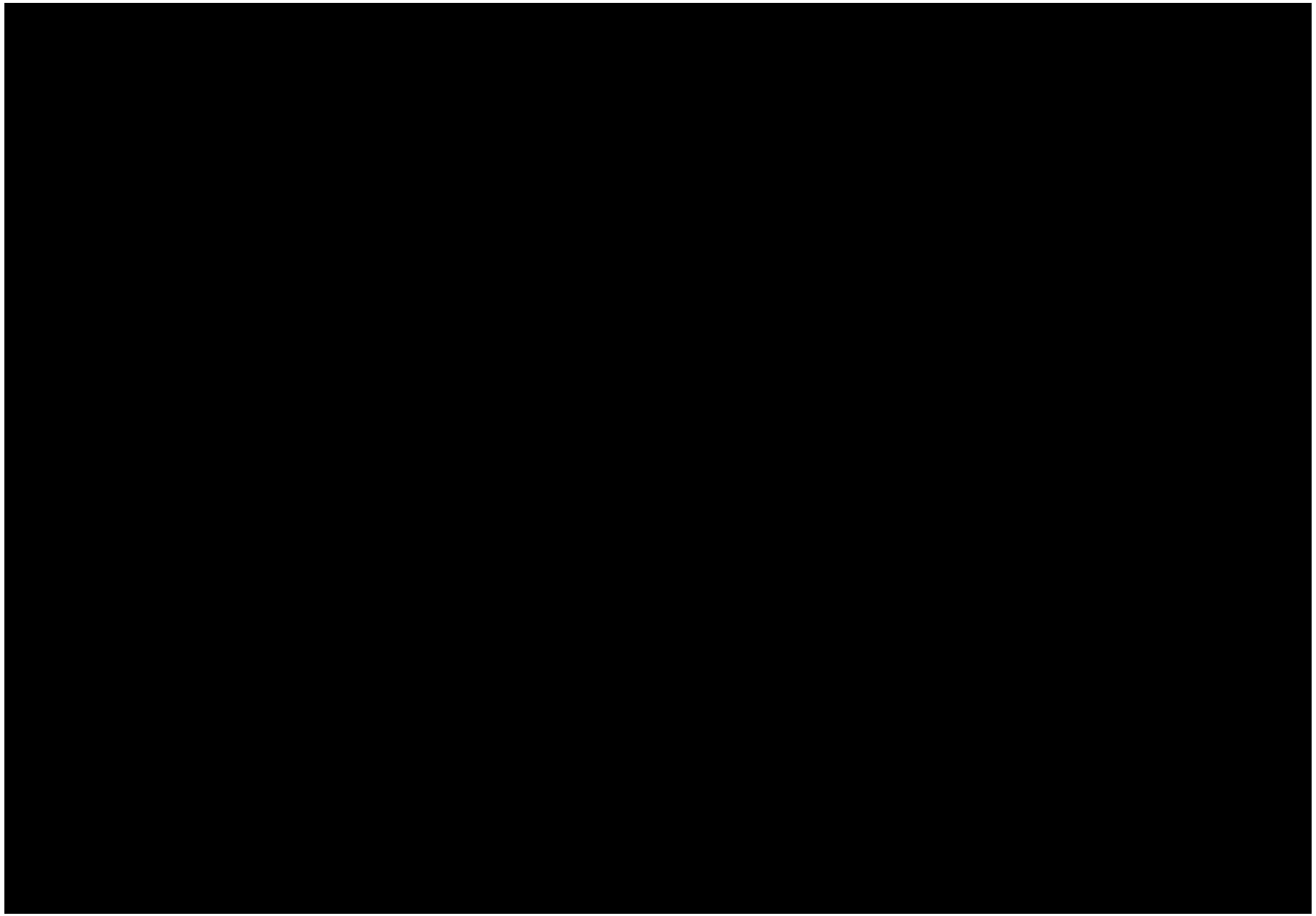
To participate in Parts 1A and 1B, participants must have a screening [redacted] To participate in Parts 1C and 2, participants will have screening IL-8 measured, but may enroll regardless of the serum IL-8 level. [redacted] Rationale for selection based on serum IL-8 is provided in Section 5.4.3. Any further segregation will be based upon post-hoc allocation of participants into intermediate or low- versus high-expression categories based upon IL-8 level cut-offs determined from the aforementioned analyses but inclusion will be based solely upon the Clinical Laboratory Improvement Amendments-certified analytical cut-off.

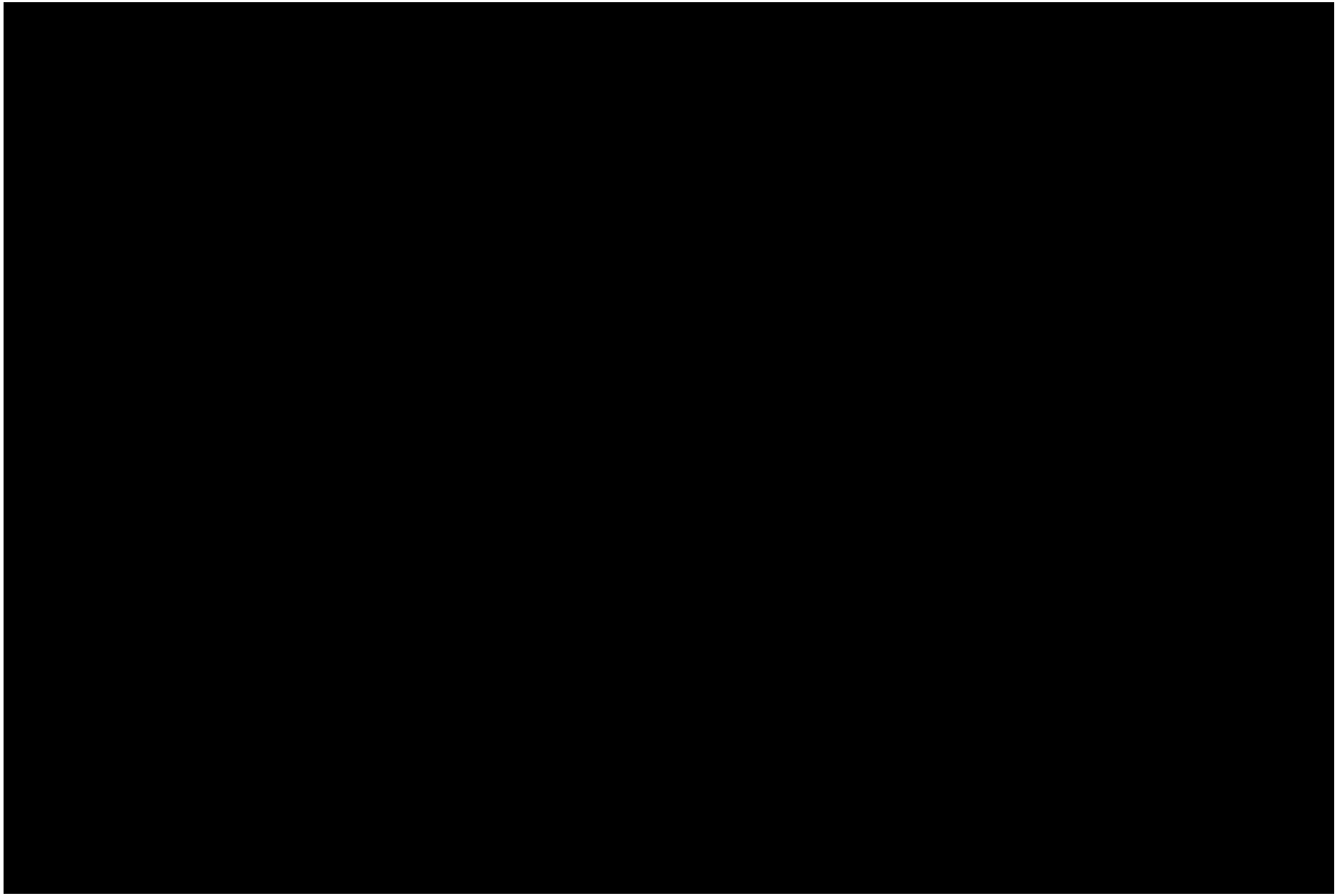


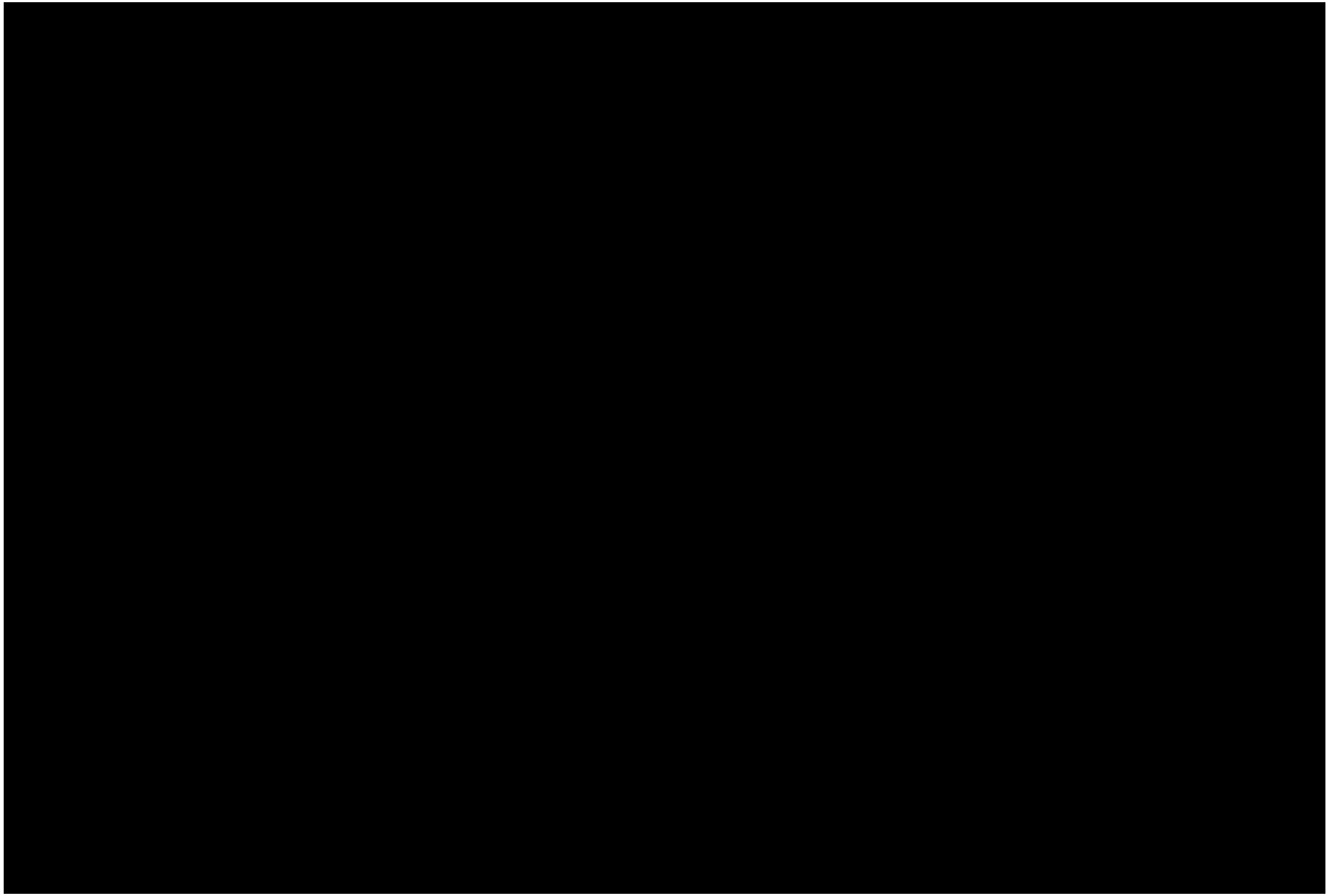


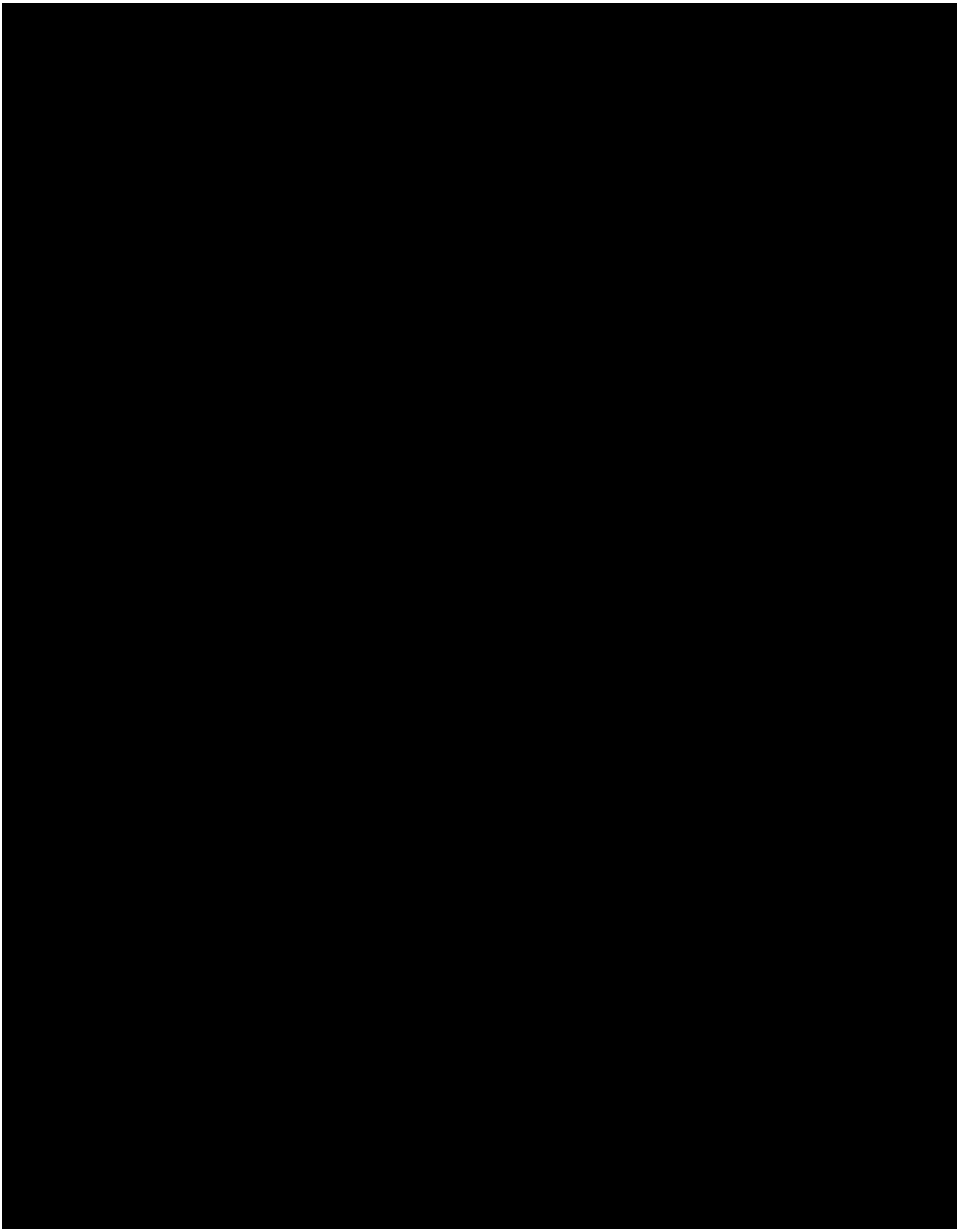












[redacted]

[redacted]

9.8.4 Additional Research Collection

This protocol will include residual sample storage for additional research.

For All US sites:

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

For non-US Sites

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

This collection for additional research is intended to expand the translational Research and Development capability at BMS, and will support as yet undefined research aims that will advance our understanding of disease and options for treatment. It may also be used to support health authority requests for analysis, and advancement of pharmacodiagnostic development to better target drugs to the right participants. This may also include genetic/genomic exploration aimed at exploring disease pathways, progression, and response to treatment etc.

Sample Collection and Storage

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

- Residual samples (see Table 9.8.4-1) will 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 fifteen (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 9.8.4-1: Residual Sample Retention for Additional Research Schedule

Sample Type	Timepoints for which residual samples will be retained
Serum/Plasma (including PK/IMG samples)	All
Peripheral Blood	All
[redacted]	All

Abbreviations: IMG, immunogenicity; PK, pharmacokinetics.

9.8.5 Methods to Detect HPV Status of SCCHN Originating in the Oropharynx

HPV status for oropharyngeal cancer must be determined locally [redacted] as described below. If HPV status was previously determined using an acceptable method listed below, re-testing is not necessary.

[redacted]

[redacted]

9.9 Health Economics OR Medical Resource Utilization and Health Economics

- Number and duration of medical care encounters, including surgeries, and other selected procedures (inpatient and outpatient)
- Duration of hospitalization (total days length of stay, including duration by wards; eg, intensive care unit)
- Number and character of diagnostic and therapeutic tests and procedures
- Outpatient medical encounters and treatments (including physician or emergency room visits, tests and procedures, and medications).

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

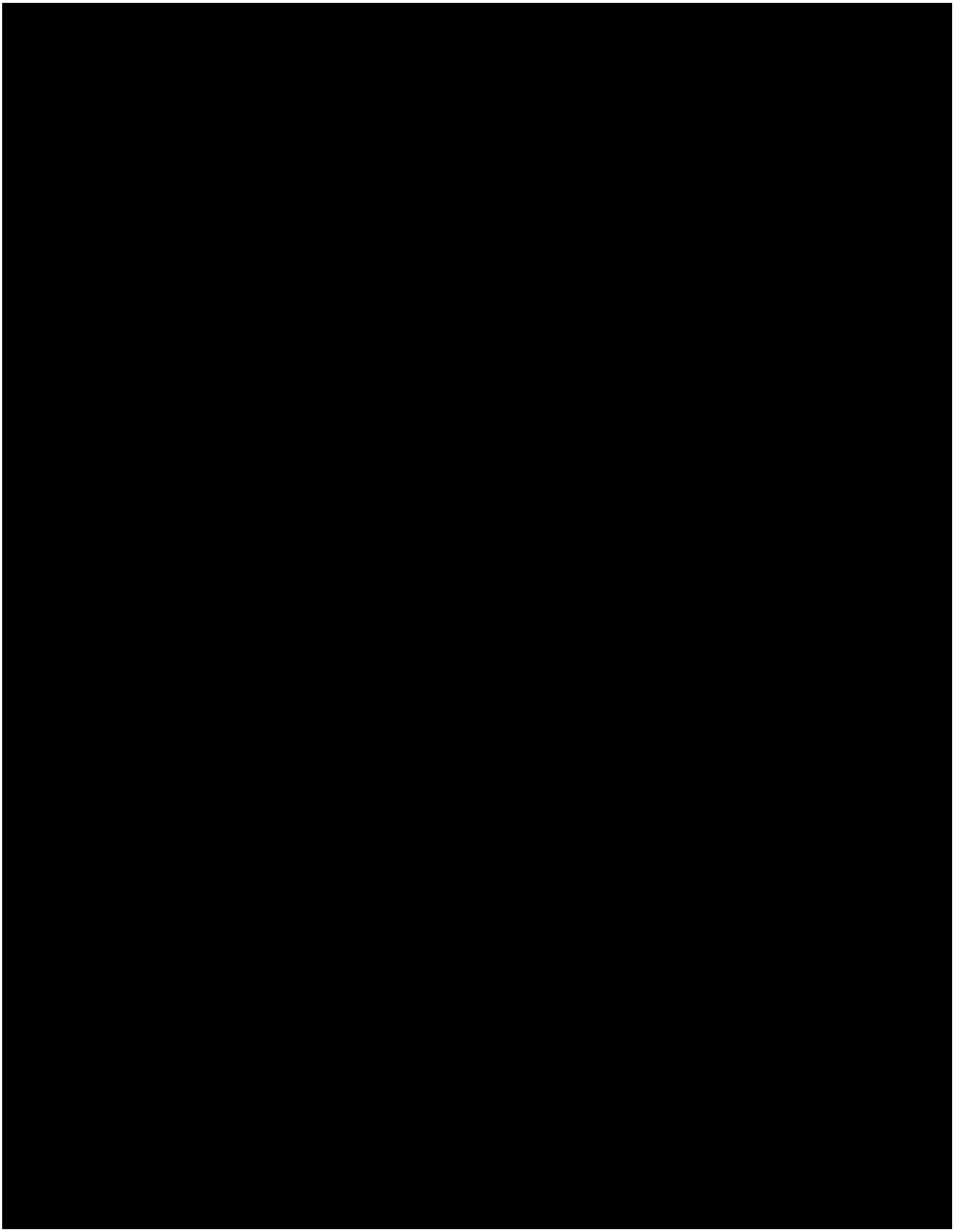
10.1.1 Parts 1A and 1B

Participants will be dosed in Cohorts 1B1, 1B2, and 1B3, and may be dosed in up to 4 other treatment regimens based on PK, pharmacodynamic, and/or safety analyses (Cohorts 1B4, 1B5, 1B6, [redacted]. Approximately [redacted] participants will be initially dosed in the treatment arm(s) of interest in Part 1.

Approximately 4 participants were treated initially with BMS-986253 2400 mg in combination with 480 mg nivolumab Q4W in Part 1A. With no safety concern identified, participants will be randomly assigned in an approximately 1:1:1 allocation ratio into 3 dose combinations, BMS-986253 2400 mg, 1200 mg, and 600 mg Q4W in combination with 480 mg nivolumab Q4W. See Section 7.4 for details regarding randomization.

There will be continuous analysis [redacted]. If these analyses indicate that further assessment of a treatment regimen is not warranted and/or a need for assessing additional treatment regimens is indicated, then the randomization will be stopped, and subsequent participants will be assigned sequentially to either existing treatment regimens, or treatment regimens with alternative dosing schedules. The highest dosing regimen used will be 3600 mg BMS-986253 Q2W in combination with 480 mg nivolumab. If any dosing regimen evaluates a higher dose of BMS-986253 than previously explored, an initial 4-participant safety lead-in with a 28-day DLT period will be required.

[redacted]



10.1.2 Part 1C

The purpose of Part 1C is to generate safety data on the triplet combination of BMS-986253, nivolumab, and ipilimumab. Although the number of participants is not based on statistical power considerations,

A maximum of approximately [redacted] participants will be dosed in Part 1 as a whole.

10.1.3 Part 2

The purpose of Part 2 is to evaluate efficacy and gather additional safety, tolerability, PK, and pharmacodynamic information between BMS-986253 RP2D in combination with nivolumab and ipilimumab versus placebo in combination with nivolumab and ipilimumab. Participants with anti-PD-(L)1-refractory unresectable or metastatic melanoma (non-ocular) who have not been treated with prior anti-CTLA-4 therapy will be randomly assigned in a 1:1 ratio to 1 of 2 treatment arms. [redacted]

10.2 Populations for Analyses

Population	Description
Enrolled/Randomized	All participants who have signed informed consent and are registered into the IRT
Treated	All participants who received at least 1 dose of study treatment
Efficacy	All participants who take at least 1 dose of their planned full combination treatment.
Response-evaluable	All treated participants with measurable disease at baseline and one of the following: (1) at least 1 post-baseline tumor assessment, (2) clinical progression, or (3) death
Pharmacokinetic	All treated participants who have evaluable concentration-time data

Population	Description
Immunogenicity	All treated participants who have baseline and at least one post baseline immunogenicity assessment
Biomarker	All treated participants with available biomarker data

Abbreviation: IRT, Interactive Response Technologies.

10.3 Statistical Analyses

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

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

10.3.1 Efficacy Analyses

The main efficacy analyses will be performed on the efficacy population for the final analysis. Efficacy analyses based on the response-evaluable population may be performed for interim analyses (as per Section 10.3.8). Efficacy analyses may be performed on selected subgroups, including biomarker-selected subgroups. Efficacy analyses will be performed using the RECIST v1.1 criteria. Additional details on efficacy analyses are provided in Table 10.3.1-1.

Table 10.3.1-1: Part 1 Efficacy Analysis

Endpoint	Statistical Analysis Methods
ORR is defined as the proportion of participants whose BOR is either CR or PR in the population of interest. BOR for a participant will be assessed per RECIST v1.1 by investigator, otherwise specified	Estimate of ORR and corresponding two-sided exact 95% CI using the [redacted] by treatment for each tumor type
DOR DOR for a participant with a BOR of CR or PR, is defined as the time between the date of first response and the date of the first objectively documented tumor progression per RECIST v1.1 or death, whichever occurs first.	Median duration of response using [redacted] and corresponding two-sided 95% CI using Brookmeyer and Crowley methodology (using log-log transformation) by treatment for each tumor type

Abbreviations: BOR, best overall response; CI, confidence interval; CR, complete response; DOR, duration of response; ORR, objective response rate; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors.

Table 10.3.1-2: Part 2 Efficacy Analysis

Endpoint	Statistical Analysis Methods
BICR-assessed ORR ORR is defined as the proportion of participants whose BOR is either CR or PR in the population of interest. BOR for a participant will be assessed per RECIST v1.1. BOR per RECIST v1.1 is defined as the best response designation recorded between the date of the first dose and the date of first objectively documented progression per RECIST v1.1 or the date of subsequent therapy, whichever occurs first. For participants who continue treatment beyond progression per RECIST v1.1 or begin subsequent therapy, the BOR should be determined based on response designations recorded up to the time of the initial progression or subsequent therapy, whichever occurs first. For participants without documented progression or subsequent therapy, all available response designations should contribute to the BOR assessment.	[redacted] will be used to compare ORR between 2 treatment groups. The associated odds ratio and CI will also be calculated.
DOR DOR for a participant with a BOR of CR or PR is defined as the time between the date of first response and the date of the first objectively documented tumor progression per RECIST v1.1 or death, whichever occurs first. Participants who die without a reported progression will be considered to have progressed on the date of their death. Participants who did not progress or die will be censored on the date of their last evaluable tumor assessment. Participants who did not have any on-study tumor assessments and did not die will be censored on the date of first dose. Participants who started any subsequent anticancer therapy, including tumor-directed radiotherapy and tumor-directed surgery, without a prior reported progression will be censored at the last evaluable tumor assessment prior to initiation of the subsequent anticancer therapy. The approach to handling events such as subsequent cancer therapy will be consistent between ORR and DOR.	Median duration of response using [redacted] method and corresponding two-sided 95% CI [redacted]

Table 10.3.1-2: Part 2 Efficacy Analysis

BICR-assessed PFS PFS is defined as the time from first dose to the date of first objectively documented progression, per RECIST v1.1, or death due to any cause, whichever occurs first. Clinical deterioration in the absence of objectively documented progression per RECIST v1.1 is not considered progression for the purpose of determining PFS. Participants who die without a reported progression will be considered to have progressed on the date of their death. Participants who did not progress or die will be censored on the date of their last evaluable tumor assessment. Participants who did not have any on study tumor assessments and did not die will be censored on the date of first dose. Participants who started any subsequent anticancer therapy, including tumor-directed radiotherapy and tumor-directed surgery, without a prior reported progression will be censored at the last evaluable tumor assessment prior to initiation of the subsequent anticancer therapy. The PFSR at time T is defined as the probability that a participant has not progressed and is alive at time T following first dose.	The estimate of the PFS hazard ratio between treatment groups will be calculated using a stratified [redacted] with treatment and stratification factors as covariates. A two-sided 95% CI for the hazard ratio will also be presented. The PFS curves for each treatment group will be estimated using [redacted] product limit method and will be displayed graphically. Median PFS with corresponding two-sided 95% CI in each treatment group will be computed via the log-log transformation method. PFS rates at fixed time points (eg, 3, 6, 9 months, depending on the minimum follow-up) will be presented along with their associated 95% CIs. These estimates will be derived from [redacted] estimate and corresponding CIs will be derived based on [redacted] for variance derivation and on log-log transformation applied to the survivor function.
OS OS is defined as the time between the date of first dose and the date of death due to any cause. For participants that are alive, their survival time will be censored at the date of last contact date (or "last known alive date"). OS will be censored at the date of first dose for participants who were dosed but had no follow-up.	A 2-sided 95% CI for median OS in each treatment group will be computed via the log-log transformation method. OS rates at fixed time points (eg, 12 months, depending on the minimum follow-up) will be presented along with their associated 95% CIs. These estimates will be derived from [redacted] estimate and corresponding CIs will be derived based on [redacted] for variance derivation and on log-log transformation applied to the survivor function.

Abbreviations: BICR, blinded independent central review; BOR, best overall response; CI, confidence interval; [redacted] CR, complete response; DOR, duration of response; [redacted] ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors.

10.3.2 Safety Analyses

All safety analyses for will be performed on the treated population.

Endpoint	Statistical Analysis Methods
Incidence of AEs, SAEs, AEs meeting protocol-defined DLT criteria, AEs leading to discontinuation, deaths AEs will be graded according to CTCAE v4.03.	DLT rate by dose level; Frequency distribution of treated participants with AE using the worst CTC grade. Participants will only be counted (1) once at the PT level, (2) once at the SOC level, and (3) once in the 'Total participants' row at their worst CTC grade, regardless of SOC or PT.
Laboratory abnormalities Laboratory values will be graded according to CTCAE v4.03.	Laboratory shift table using the worst CTC grade on treatment per participant

Abbreviations: AE, adverse event; CTC, Common Terminology Criteria; CTCAE, Common Terminology Criteria for Adverse Events; DLT, dose-limiting toxicity; PT, Preferred Term; SAE, serious adverse event; SOC, System Organ Class.

10.3.3 Pharmacokinetic Analyses

Endpoint	Statistical Analysis Methods
Cmax, AUC(0-T), AUC(TAU), Ctau, CLT, Css-avg, AI_AUC, AI_Cmax, AI_Ctau, T-HALF	Summary statistics: geometric means and coefficients of variation
Tmax	Summary statistics: medians and ranges
Ctrough	Summary statistics to assess attainment of steady state: geometric means and coefficients of variation; plots vs time by dose

Abbreviations: AI_AUC, AUC Accumulation Index; AI_Cmax, Cmax Accumulation Index; AI_Ctau, Ctau Accumulation Index; AUC(0-T), area under the plasma serum concentration-time curve from time zero to time of last quantifiable concentration; AUC(TAU), area under the serum concentration-time curve in 1 dosing interval; CLT, total body clearance; Css-avg, average serum concentration over a dosing interval (AUC[TAU]/tau) at steady state; Ctau, observed serum concentration at the end of a dosing interval; Tmax, Time of maximum observed plasma serum concentration; Ctrough, trough observed serum concentrations (this includes pre-dose concentrations [C0] and Ctau).

Note: PK time-concentration data may be pooled with data from other studies for PPK analysis, which will be presented in a separate report.

10.3.4 Immunogenicity Analyses

Endpoint	Statistical Analysis Methods
Incidence of ADA to BMS-986253, nivolumab, or ipilimumab administrated in combination Baseline ADA-positive participant is defined as a participant who has an ADA detected sample at baseline. ADA-positive participant is a participant with at least 1 ADA-positive sample relative to baseline after initiation of the treatment	Frequency distribution of baseline ADA-positive participants and ADA-positive participants after initiation of the treatment; summary of ADA peak titer, ADA onset and duration, summary of select AEs by ADA status, summary of BOR by ADA status

Abbreviation: ADA, anti-drug antibody; AE, adverse event; BOR, best overall response.

10.3.5 Biomarker Analyses

Endpoint	Statistical Analysis Methods
Summary measures of absolute values of serum IL-8, and change (or percent change) from baseline in serum IL-8	Summary statistics by planned study day and cohort; Plots of the time course of biomarkers, geometric mean of the ratio of post-baseline IL-8 and corresponding CI.

Abbreviations: CI, confidence interval; IL-8, interleukin-8.

10.3.6 ECG Analyses

All ECG data analyses including summaries of each ECG parameter, frequency distribution of participants' maximum values/changes, and scatter plots will be performed following the current practice of ECG data analysis. Concentration-response analysis may be performed using the mixed

effect model, if appropriate and applicable. The details of ECG data analysis will be provided in the Statistical Analysis Plan (SAP).

10.3.7 Other Analyses

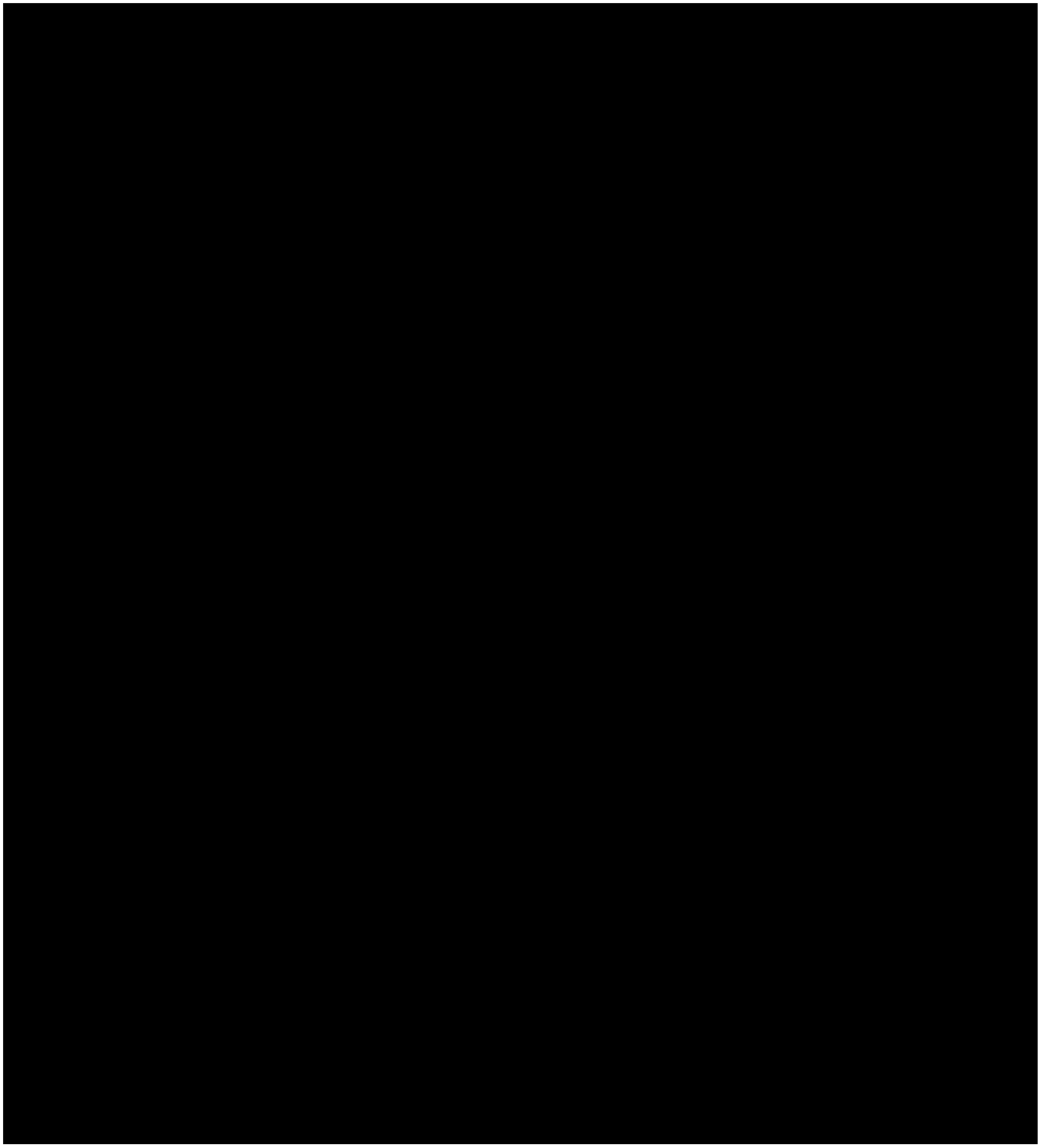
[redacted] PFS for a participant is defined as the time from the first dosing date to the date of first objectively documented disease progression or death due to any cause, whichever occurs first. [redacted] OS is defined as the time between the date of first dose and the date of death due to any cause. For participants who are alive, their survival time will be censored at the date of last contact date (or "last known alive date"). OSR at 1 year and 2 years will be analyzed similarly to PFSR. The PPK and pharmacodynamic analyses may be presented separately from the main clinical study report.

10.3.8 Interim Analyses

10.3.8.1 Part 1

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

[redacted]



11 REFERENCES

[1] Hoos A. Development of immuno-oncology drugs - from CTLA4 to PD1 to the next generations. Nat Rev Drug Discov 2016 Apr;15(4):235-47.

[2] Sharma P, Hu-Lieskovan S, Wargo JA, et al. Primary, Adaptive, and Acquired Resistance to Cancer Immunotherapy. Cell. 2017 Feb 9;168(4):707-723.

[3] Sanmamed MF, Carranza-Rua O, Alfaro C, et al. Serum interleukin-8 reflects tumor burden and treatment response across malignancies of multiple tissue origins. Clin Cancer Res 2014;20(22):5697-707.

[4] Russo RC, Garcia CC, Teixeira MM, et al. The CXCL8/IL-8 chemokine family and its receptors in inflammatory diseases. Expert Rev Clin Immunol. 2014 May;10(5):593-619.

[5] Boekholdt SM, Peters RJ, Hack CE, et al. IL-8 plasma concentrations and the risk of future coronary artery disease in apparently healthy men and women: the EPIC-Norfolk prospective population study. Arterioscler Thromb Vasc Biol. 2004 Aug;24(8):1503-8.

[6] Hoffmann E, Dittrich-Breiholz O, Holtmann H, et al. Multiple control of interleukin-8 gene expression. J Leukoc Biol. 2002 Nov;72(5):847-55.

[7] Pine SR, Mechanic LE, Enewold L, et al. Increased levels of circulating interleukin 6, interleukin 8, C-reactive protein, and risk of lung cancer. J Natl Cancer Inst. 2011 Jul 20;103(14):1112-22.

[8] Rody A, Karn T, Liedtke C, et al. A clinically relevant gene signature in triple negative and basal-like breast cancer. Breast Cancer Res. 2011;13(5):R97.

[9] Lurje G, Zhang W, Schultheis AM, et al. Polymorphisms in VEGF and IL-8 predict tumor recurrence in stage III colon cancer. Ann Oncol. 2008;19:1734–41.

[10] Sharma J, Gray KP, Nakabayashi M, et al. Use of elevated baseline IL-8, CCL-2, and TNFα to predict for shorter overall survival (OS) in men with metastatic prostate cancer initiating androgen-deprivation therapy (ADT). Journal of Clinical Oncology 30, no. 5_suppl. 2012 Feb;13-13.

[11] Chuntharapai A, Lee J, Hebert CA, et al. Monoclonal antibodies detect different distribution patterns of IL-8 receptor A and IL-8 receptor B on human peripheral blood leukocytes. J. Immunol. 1994;153(4):5682–5688.

[12] David JM, Dominguez C, Hamilton DH, et al. The IL-8/IL-8R axis: a double agent in tumor immune resistance. Vaccines (Basel). 2016;4(3):pil. E22.

[13] Alfaro C, Teijeira A, Oñate C, et al. Tumor-Produced Interleukin-8 Attracts Human Myeloid-Derived Suppressor Cells and Elicits Extrusion of Neutrophil Extracellular Traps (NETs). Clin Cancer Res. 2016 Aug 1;22(15):3924-36.

[14] Fernando RI, Castillo MD, Litzinger M, et al. IL-8 signaling plays a critical role in the epithelial-mesenchymal transition of human carcinoma cells. Cancer Res. 2011;71(15):5296-306.

[15] Charafe-Jauffret E, et al. Breast cancer cell lines contain functional cancer stem cells with metastatic capacity and a distinct molecular signature. Cancer Res. 2009, 69, 1302–1313.

[16] Hwang WL, Yang MH, Tsai ML, et al. SNAIL regulates interleukin-8 expression, stem cell-like activity, and tumorigenicity of human colorectal carcinoma cells. Gastroenterology. 2011;141(1):279-91, 291.e1-5.

[17] Tang KH, Ma S, Lee TK, et al. CD133(+) liver tumor-initiating cells promote tumor angiogenesis, growth, and self-renewal through neurotensin/interleukin-8/CXCL1 signaling. Hepatology. 2012;55(3):807-20.

[18] Ning Y, Manegold PC, Hong YK, et al. Interleukin-8 is associated with proliferation, migration, angiogenesis and chemosensitivity in vitro and in vivo in colon cancer cell line models. Int J Cancer. 2011;128(9):2038-49.

[19] Ascierto ML, Makohon-Moore A, Lipson EJ, et al. Transcriptional mechanisms of resistance to anti-PD-1 therapy. Clin Cancer Res. 2017;23(12):3168-3180.

[20] Sanmamed MF, Perez-Garcia JL, Schalper KA, et al. Changes in serum interleukin-8 (IL-8) levels reflect and predict response to anti-PD-1 treatment in melanoma and non-small cell lung cancer patients. Ann Oncol 2017;208:1988-95.

[21] Schalper KA, Carleton M, Zhou M, et al. Elevated serum interleukin-8 is associated with enhanced intratumor neutrophils and reduced clinical benefit of immune-checkpoint inhibitors. Nature Medicine. 2020;26:688-692.

[22] Asfaha S, Dubeykovskiy AN, Tomita H, et al. Mice that express human interleukin-8 have increased mobilization of immature myeloid cells, which exacerbates inflammation and accelerates colon carcinogenesis. Gastroenterology. 2013;144(1):155-66.

[23] Yuen KC, Liu L-F, Gupta V, et al. High systemic and tumor-associated IL-8 correlates with reduced clinical benefit of PD-L1 blockade. Nature Medicine. 2020;26:693-698.

[24] BMS-986253 Investigator Brochure Version 8. Bristol Myers Squibb Company, 2023. Document Control No. 930106282.

[25] Bilusic M, Heery CR, Collins JM, et al. Phase I trial of HuMax-IL-8 (BMS-986253), an anti-IL-8 monoclonal antibody, in patients with metastatic or unresectable solid tumors. Journal ImmunoTherapy of Cancer. 2019;7(240):1-8.

[26] BMS-936558 Investigator Brochure Version 20. Bristol Myers Squibb Company, 2021. Document Control No. 930128344.

[27] BMS-734016 Investigator Brochure, Version 24. Bristol Myers Squibb Company, 2021. Document Control No. 930017531.

[28] Chen Y, Shi M, Yu GZ, et al. Interleukin-8, a promising predictor for prognosis of pancreatic cancer. World J Gastroenterol. 2012;18(10):1123-9.

[29] Chen JJ, Yao PL, Yuan A, et al. Up-regulation of tumor interleukin-8 expression by infiltrating macrophages: its correlation with tumor angiogenesis and patient survival in non-small cell lung cancer. Clin Cancer Res. 2003;9(2):729-37.

[30] Zhu YM, Webster SJ, Flower D, et al. Interleukin-8/CXCL8 is a growth factor for human lung cancer cells. Br J Cancer. 2004;91(11):1970-6.

[31] Spira A, Beane JE, Shah V, et al. Airway epithelial gene expression in the diagnostic evaluation of smokers with suspect lung cancer. Nat Med. 2007;13(3):361-6.

[32] Skov L, Beurskens FJ, Zachariae CO, et al. IL-8 as antibody therapeutic target in inflammatory diseases: reduction of clinical activity in palmoplantar pustulosis. J Immunol, 2008;181(1):669-79.

[33] Marvel D, Gabrilovich DI. Myeloid-derived suppressor cells in the tumor microenvironment: expect the unexpected. J Clin Invest. 2015 Sep;125(9):3356-64.

[34] Kumar V, Patel S, Tcyganov E, et al. The Nature of Myeloid-Derived Suppressor Cells in the Tumor Microenvironment. Trends Immunol. 2016 Mar;37(3):208-220.

[35] Highfill SL, Cui Y, Giles AJ, et al. Disruption of CXCR2-mediated MDSC tumor trafficking enhances anti-PD1 efficacy. Sci Transl Med. 2014 May 21;6(237):237ra67.

[36] Steele CW, Karim SA, Leach JDG, et al. CXCR2 Inhibition Profoundly Suppresses Metastases and Augments Immunotherapy in Pancreatic Ductal Adenocarcinoma. Cancer Cell. 2016 Jun 13;29(6):832-845.

[37] Curran MA, Montalvo W, Yagita H, et al. PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors. Proc Natl Acad Sci USA 2010;107:4275-80.

[38] Benoy IH, Salgado R, Van Dam P, et al. Increased serum interleukin-8 in patients with early and metastatic breast cancer correlates with early dissemination and survival. Clin Cancer Res 2004;10:7157-62.

[39] Xiao YC, Yang ZB, Cheng XS, et al. CXCL8, overexpressed in colorectal cancer, enhances the resistance of colorectal cancer cells to anoikis. Cancer Lett 2015;361:22–32.

[40] Fang Y, Saiyin H, Zhao X, et al. IL-8-positive tumor-infiltrating inflammatory cells are a novel prognostic marker in pancreatic ductal adenocarcinoma patients. Pancreas 2016;45(5):671-8.

[41] Li XP, Yang XY, Biskup E, et al. Co-expression of CXCL8 and HIF-1α is associated with metastasis and poor prognosis in hepatocellular carcinoma. Oncotarget 2015;6(26):22880-9.

[42] Akiba J, Yano H, Ogasawara S, et al. Expression and function of interleukin-8 in human hepatocellular carcinoma. Int J Oncol 2001;18(2):257-64.

[43] Welling TH, Fu S, Wan S et al. Elevated serum IL-8 is associated with the presence of hepatocellular carcinoma and independently predicts survival. Cancer Invest 2012;30(10):689-97.

[44] Fu X, Dai Z, Song K, et al. Macrophage-secreted IL-8 induces epithelial-mesenchymal transition in hepatocellular carcinoma cells by activating the JAK2/STAT3/Snail pathway. Int J Oncol 2015;46:587-96.

[45] Diaz-Montero CM, Salem ML, Nishimura MI, et al. Increased circulating myeloid-derived suppressor cells correlate with clinical cancer stage, metastatic tumor burden, and doxorubicin-cyclophosphamide chemotherapy. Cancer Immunol Immunother 2009;58(1):49-59.

[46] Gentzler R, Hall R, Kunk PR, et al. Beyond melanoma: inhibiting the PD-1/PD-L1 pathway in solid tumors. Immunotherapy 2016;8(5):583-600.

[47] Olson DJ, Eroglu Z, Brockstein B, et al. Pembrolizumab plus ipilimumab following anti-PD-1/L1 failure in melanoma. J Clin Oncol 2021;39:2647-55.

[48] Pires da Silva I, Ahmed T, Reijers ILM, et al. Ipilimumab alone or ipilimumab plus anti-PD-1 therapy in patients with metastatic melanoma resistant to anti-PD-(L)1 monotherapy: a multicentre, retrospective, cohort study. Lancet Oncol 2021;22:836-47.

[49] National Comprehensive Cancer Network. Melanoma: Cutaneous Version 2.2021. Available from: URL: https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf

[50] Michielin O, van Akkooi ACJ, Ascierto PA, et al.; ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. Ann Oncol 2019;30:1884-1901.

[51] Patrinely, JR, Baker, LX, Davis, EJ, et al. Oucomes after progression of disease with anti-PD-1/PD-L1 therapy for patients with advanced melanoma. Cancer 2020;126:3448-55.

[52] Diem S, Kasenda B, Spain L, et al. Serum lactate dehydrogenase as an early marker for outcome in patients treated with anti-PD-1 therapy in metastatic melanoma. Br J Cancer 2016;114(3); 256-61.

[53] Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med 2019;381:1535-46.

[54] Ribas A, Hamid O, Daud A, et al. Association of pembrolizumab with tumor response and survival among patients with advanced melanoma. JAMA 2016;315(15):1600-9.

[55] Spigel DR, McLeod M, Hussein MA. Randomized results of fixed-duration (1-yr) vs continuous nivolumab in patients (pts) with advanced non-small cell lung cancer (NSCLC) (Abstract 1297O) 2017, Ann Oncol 2017;28(Suppl 5):461.

[redacted]

[60] Wang DD, Zhang S, Zhao H, et al. Fixed dosing versus body size-based dosing of monoclonal antibodies in adult clinical trials. J Clin Pharmacol 2009;49(9):1012-24.

[61] Bai S, Jorga K, Xin Y, et al. A guide to rational dosing of monoclonal antibodies. Clin Pharmacokinet 2012;51(2):119-35.

[62] Hay KA, Hanafi LA, Li D, et al. Kinetics and biomarkers of severe cytokine release syndrome after CD19 chimeric antigen receptor-modified T-cell therapy. Blood 2017;130:2295-306.

[63] Ceschi A, Noseda R, Palin K, et al. Immune checkpoint inhibitor-related cytokine release syndrome: analysis of WHO global pharmacovigilance database. Front Pharmacol 2020;11:557.

[64] Carter SJ, Tattersall RS, Ramanan AV. Macrophage activation syndrome in adults: recent advances in pathophysiology, diagnosis and treatment. Rheumatology 2019;58:5-17. doi: 10.1093/rheumatology/key006. PMID: 29481673.

[65] Retamozo S, Brito-Zerón P, Sisó-Almirall A, et al. Haemophagocytic syndrome and COVID-19. Clin Rheumatol 2021;40:1233-44. doi: 10.1007/s10067-020-05569-4. PMID: 33389315; PMCID: PMC7778844.

[66] Mohamed Jiffry MZ, Ahmed-Khan M, Vargas J, et al. Hemophagocytic Lymphohistiocytosis in a Patient With Post-acute COVID-19 Infection. Cureus 2022;14:e31451. doi: 10.7759/cureus.31451. PMID: 36523678; PMCID: PMC9747112.

[67] Karakike E, Giamarellos-Bourboulis EJ. Macrophage Activation-Like Syndrome: A Distinct Entity Leading to Early Death in Sepsis. Front Immunol 2019;31:10-55. doi: 10.3389/fimmu.2019.00055. PMID: 30766533; PMCID: PMC6365431.

[68] Noseda R, Bertoli R, Müller L, et al. Haemophagocytic lymphohistiocytosis in patients treated with immune checkpoint inhibitors: Analysis of WHO global database of individual case safety reports. J ImmunoTher Cancer 2019;7:117.

[69] Nivolumab (BMS-936558). Response to the Pharmacovigilance Risk Assessment Committee (PRAC) signal assessment report on haemophagocytic lymphohistiocytosis (HLH) with Nivolumab (OPDIVO); dated 03-Oct-2019. Bristol-Myers Squibb. Response document dated 26-Nov-2019. Document Control No. 930146897.

[70] Ramos-Casals M, Brito-Zerón P, López-Guillermo A, et al. Adult haemophagocytic syndrome. Lancet 2014; 26;383:1503-16. doi: 10.1016/S0140-6736(13)61048-X. Epub 2013 Nov 27. Erratum in: Lancet. 2014 Apr 26;383(9927):1464. PMID: 24290661.

[71] Lehmberg K, Nichols KE, Henter JI, Girschikofsky M, Greenwood T, Jordan M, Kumar A, Minkov M, La Rosée P, Weitzman S; Study Group on Hemophagocytic Lymphohistiocytosis Subtypes of the Histiocyte Society. Consensus recommendations for the diagnosis and management of hemophagocytic lymphohistiocytosis associated with malignancies. Haematologica. 2015 Aug;100(8):997-1004. doi: 10.3324/haematol.2015.123562. PMID: 26314082; PMCID: PMC5004414.

[72] Fardet L, Galicier L, Lambotte O, Marzac C, Aumont C, Chahwan D, Coppo P, Hejblum G. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. Arthritis Rheumatol. 2014 Sep;66(9):2613-20. doi: 10.1002/art.38690. PMID: 24782338. (available from http://saintantoine.aphp.fr/score/)

[redacted]

12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
[redacted]	[redacted]
ADA	anti-drug antibody
AE	adverse event
AFP	alpha fetoprotein
AI	accumulation index
AI_AUC	AUC Accumulation Index; ratio of AUC(TAU) at steady state to AUC(TAU) after the first dose
AI_Cmax	Cmax Accumulation Index; ratio of Cmax at steady state to Cmax after the first dose
AI_Ctau	Ctau Accumulation Index; ratio of Ctau at steady state to Ctau after the first dose
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the serum concentration-time curve
AUC(0-T)	area under the concentration-time curve from time zero to the time of last quantifiable concentration
AUC(TAU)	area under the serum concentration-time curve in 1 dosing interval
BICR	blinded independent central review
[redacted]	[redacted]
BMS	Bristol Myers Squibb
BOR	best overall response
BP	blood pressure
BRAF	proto-oncogene B-Raf
C	Cycle
Cavgss	average steady-state concentration
CBC	complete blood count
CD8	cluster of differentiation 8
CFR	Code of Federal Regulations
CI	confidence interval

Term	Definition
[redacted]	[redacted]
CLT	total body clearance
Cmax	maximum observed plasma concentration
[redacted]	[redacted]
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CR	complete response
CRC	colorectal cancer
CrCl	creatinine clearance
CRF	case report form, paper or electronic
CSC	cancer stem cell
Css-avg	average serum concentration over a dosing interval (AUC[TAU]/tau) at steady state
CT	computed tomography
Ctau	observed serum concentration at the end of a dosing interval
CTC	common terminology criteria
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
Ctrough	trough observed serum concentrations
CXCR1/2	C-X-C chemokine receptor type 1/2
CxDx	Cycle x Day x
d	days
D	Day
DILI	drug-induced liver injury
dL	deciliter
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response

Term	Definition
EBV	Epstein-Barr virus
EC	Ethics Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	Electronic Data Capture
eg	exempli gratia
EGFR	epidermal growth factor receptor
EMT	epithelial mesenchymal transition
EOI	end of infusion
EOT	end of treatment
FDA	Food and Drug Administration
FPFV	first patient first visit
FSH	follicle-stimulating hormone
FU	follow-up
g	gram
GPVE	Global Pharmacovigilance and Epidemiology
HCC	hepatocellular carcinoma
HER2	human epidermal growth factor receptor 2
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HLH	hemophagocytic lymphohistiocytosis
HPV	human papillomavirus
Hr, hr	hour
HR	hazard ratio
IB	Investigator's Brochure
[redacted]	[redacted]
[redacted]	[redacted]
ICF	informed consent form

Term	Definition
ICI	immune checkpoint inhibitor
IFN-γ	interferon gamma
Ig	immunoglobulin
IgG1κ	immunoglobulin G1 kappa
IHC	immunohistochemistry
IL-8	interleukin-8
IMAR	immune-mediated adverse reaction
IMG	immunogenicity
IMP	Investigational Medicinal Product
I-O	immuno-oncology
IP	Investigational Product
irAE	immune-related adverse event
[redacted]	[redacted]
IRT	Interactive Response Technology
iu	international unit
ius	intrauterine hormone releasing system
IV	intravenous
IVIG	intravenous immunoglobulin
kg	kilogram
[redacted]	[redacted]
L	liter
LAM	lactational amenorrhea method
LDH	lactate dehydrogenase
LPLV	last patient last visit
mAb	monoclonal antibody
MALS	macrophage activation-like syndrome
MAS	macrophage activation syndrome
MDSC	myeloid-derived suppressor cells
mg	milligram
[redacted]	[redacted]

Term	Definition
min	minute
mL	milliliter
MLH1	MutL homolog 1
MM	medical monitor
MMR	measles, mumps, rubella
[redacted]	[redacted]
MR	medical research
mRECIST	modified Response Evaluation Criteria in Solid Tumors
MRI	magnetic resonance imaging
msec	millisecond
MSH2	MutS Homolog 2
MSH6	MutS Homolog 6
MSI	microsatellite instability status
MSI-H	microsatellite instability-high
MSS	microsatellite stable
MTD	maximum tolerated dose
µg	microgram
N	number of participants or observations
NCI	National Cancer Institute
Nivo	nivolumab
NK	natural killer
NLR	neutrophil-to-leukocyte ratio
[redacted]	[redacted]
Non-IMP	noninvestigational Medicinal Product
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed cell death 1

Term	Definition
p-DILI	potential drug-induced liver injury
PD-L1	programmed death ligand-1
PD-L2	programmed death ligand-2
PE	physical examination
PET	positron emission tomography
PFS	progression-free survival
PFSR	progression-free survival rate
PID	patient identifier number
PK	pharmacokinetic(s)
pMMR	mismatch repair proficient
[redacted]	[redacted]
PMS2	protein homolog 2, mismatch repair system component
PPK	population pharmacokinetics
PR	partial response
PT	Preferred Term
Q	quartile
Q12W	every 12 weeks
Q2W	every 2 weeks
Q3W	every 3 weeks
Q4W	every 4 weeks
Q8W	every 8 weeks
[redacted]	[redacted]
QXW	every X weeks
R	randomized
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
ROS1	c-ros oncogene 1
RP2D	recommended Phase 2 dose
RSI	Reference Safety Information

Term	Definition
RT	reverse transcriptase
S	sequential assignment
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCCHN	squamous cell carcinoma of the head and neck
SD	standard deviation
sIL-8	serum interleukin 8
SMT	Safety Management Team
SOC	System Organ Class
SpO2	percentage of blood saturation
SUSAR	Suspected, Unexpected Serious Adverse Reaction
T3	triiodothyronine
T4	thyroxine
[redacted]	[redacted]
TAU	dosing interval
[redacted]	[redacted]
[redacted]	[redacted]
Tmax	time of maximum observed plasma serum concentration
TMB	tumor mutational burden
[redacted]	[redacted]
TNBC	triple-negative breast cancer
TRAE	treatment-related adverse event
TSH	thyroid-stimulating hormone
UCC	urothelial cancer
ULN	upper limit of normal
US	United States [of America]
WOCBP	women of childbearing potential
WNOCBP	women **not** of childbearing potential
WS	World-wide Patient Safety

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

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

REGULATORY AND ETHICAL CONSIDERATIONS

This study will be conducted in accordance with:

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

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

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

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

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

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

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

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

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

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

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

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

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

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

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

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

FINANCIAL DISCLOSURE

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

INFORMED CONSENT PROCESS

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

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

The investigator or his/her representative must:

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

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

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

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

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

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

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

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

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

BMS COMMITMENT TO DIVERSITY IN CLINICAL TRIALS

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

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

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

DATA PROTECTION, DATA PRIVACY, AND DATA SECURITY

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

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

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

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

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

SOURCE DOCUMENTS

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

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

- The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definitions of what constitutes source data can be found in ICH E6 GCP.

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 TREATMENT RECORDS

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

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

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

CASE REPORT FORMS

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents, or the discrepancies must be

explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

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

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

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

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

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

MONITORING

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

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

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

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

RECORDS RETENTION

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

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

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

RETURN OF STUDY TREATMENT

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

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

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

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

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

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

It is, however, the investigator's or designee's responsibility to arrange for disposal of all empty study treatment containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The return of full or partially used study treatments supplied by BMS or its vendors will be arranged by the responsible Study Monitor.

STUDY AND SITE START AND CLOSURE

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

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

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

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

- Discontinuation of further study intervention development

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

DISSEMINATION OF CLINICAL STUDY DATA

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

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
- Involvement in trial design
- Other criteria (as determined by the study team)

SCIENTIFIC PUBLICATIONS

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

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

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

1) Substantial intellectual contribution to the conception or design of the work; or the acquisition of data (ie, evaluable participants with quality data), analysis, or interpretation of data for the work (eg, problem solving, advice, evaluation, insights and conclusion); AND
2) Drafting the work or revising it critically for important intellectual content; AND
3) Final approval of the version to be published; AND
4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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

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

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

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

ADVERSE EVENTS

Adverse Event Definition:

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

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

Events Meeting the AE Definition

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

Events NOT Meeting the AE Definition

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

DEFINITION OF SAE

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

SERIOUS ADVERSE EVENTS

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

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

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

EVALUATING AES AND SAES

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure 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**

All SAEs and AEs will be assessed using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03.

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 User Dependent *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.

- 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 7.9.1 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 7.9.1 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 ECOG PERFORMANCE STATUS

These scales and criteria are used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. They are included here for health care professionals to access.

ECOG PERFORMANCE STATUS*

Grade	ECOG
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 self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol.:

Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

APPENDIX 6 MANAGEMENT ALGORITHMS FOR STUDIES UNDER CTCAE VERSION 4.0

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

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

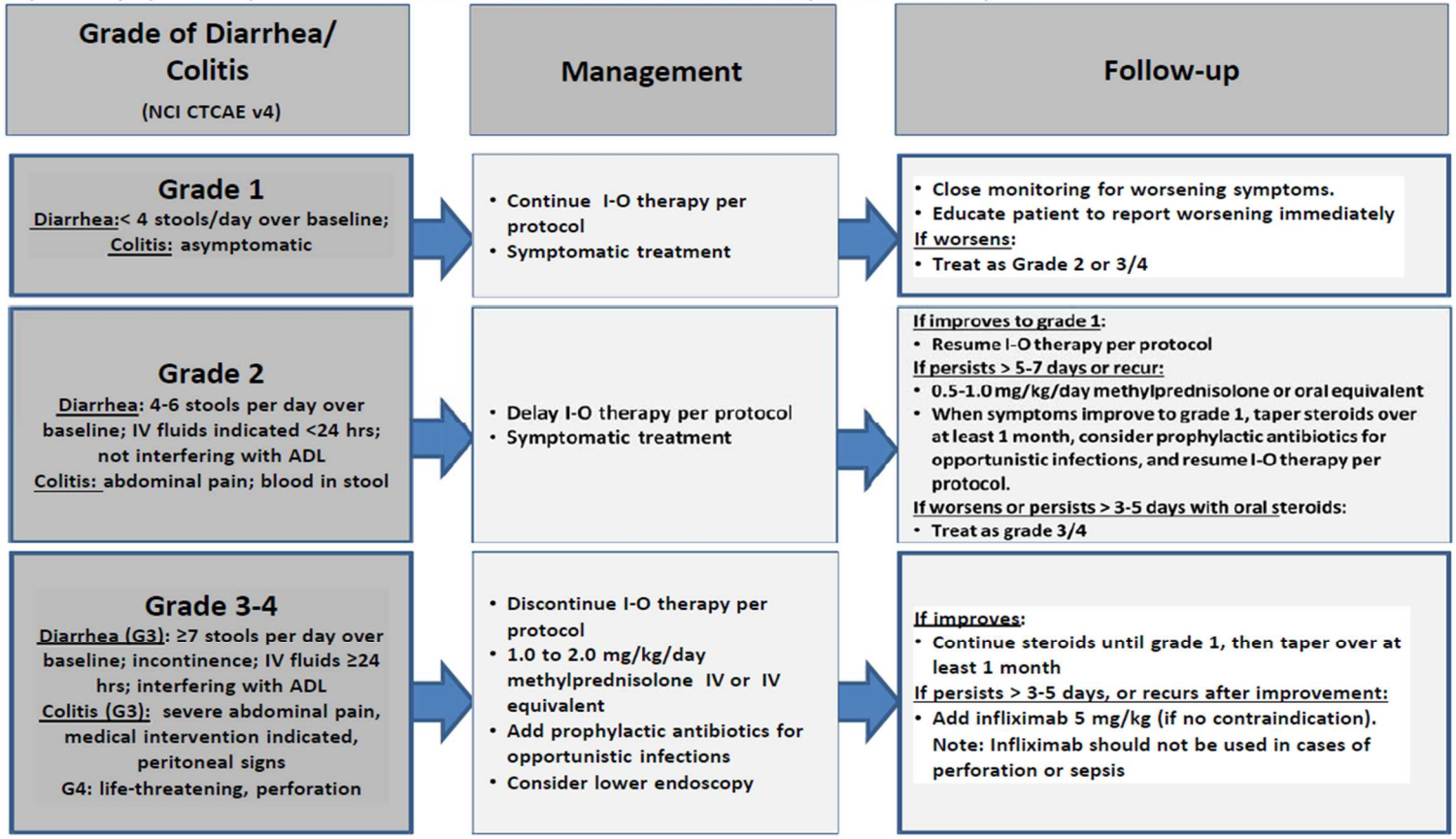
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the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

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

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

GI Adverse Event Management Algorithm

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

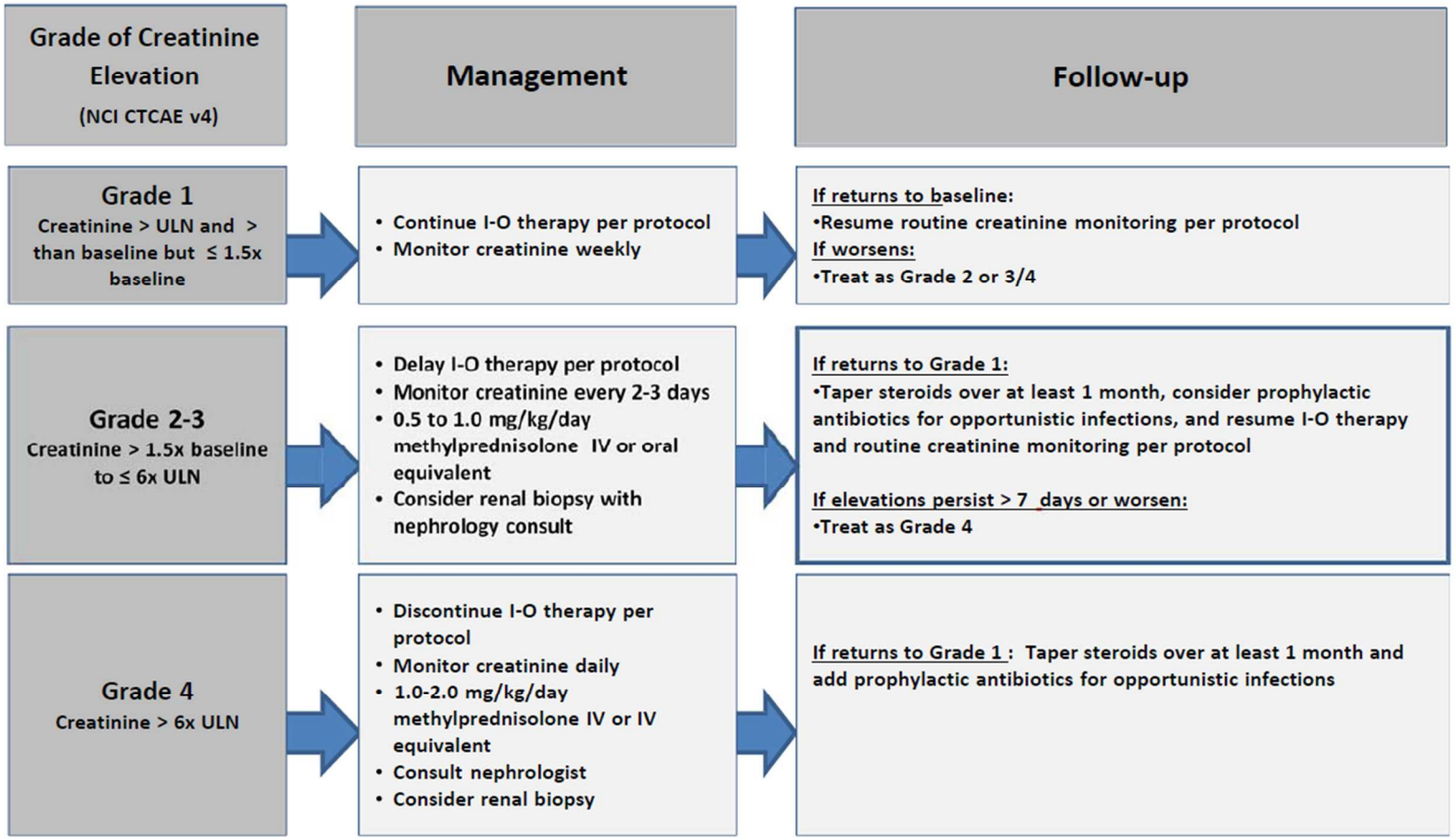


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

28-Sep-2020

Renal Adverse Event Management Algorithm

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

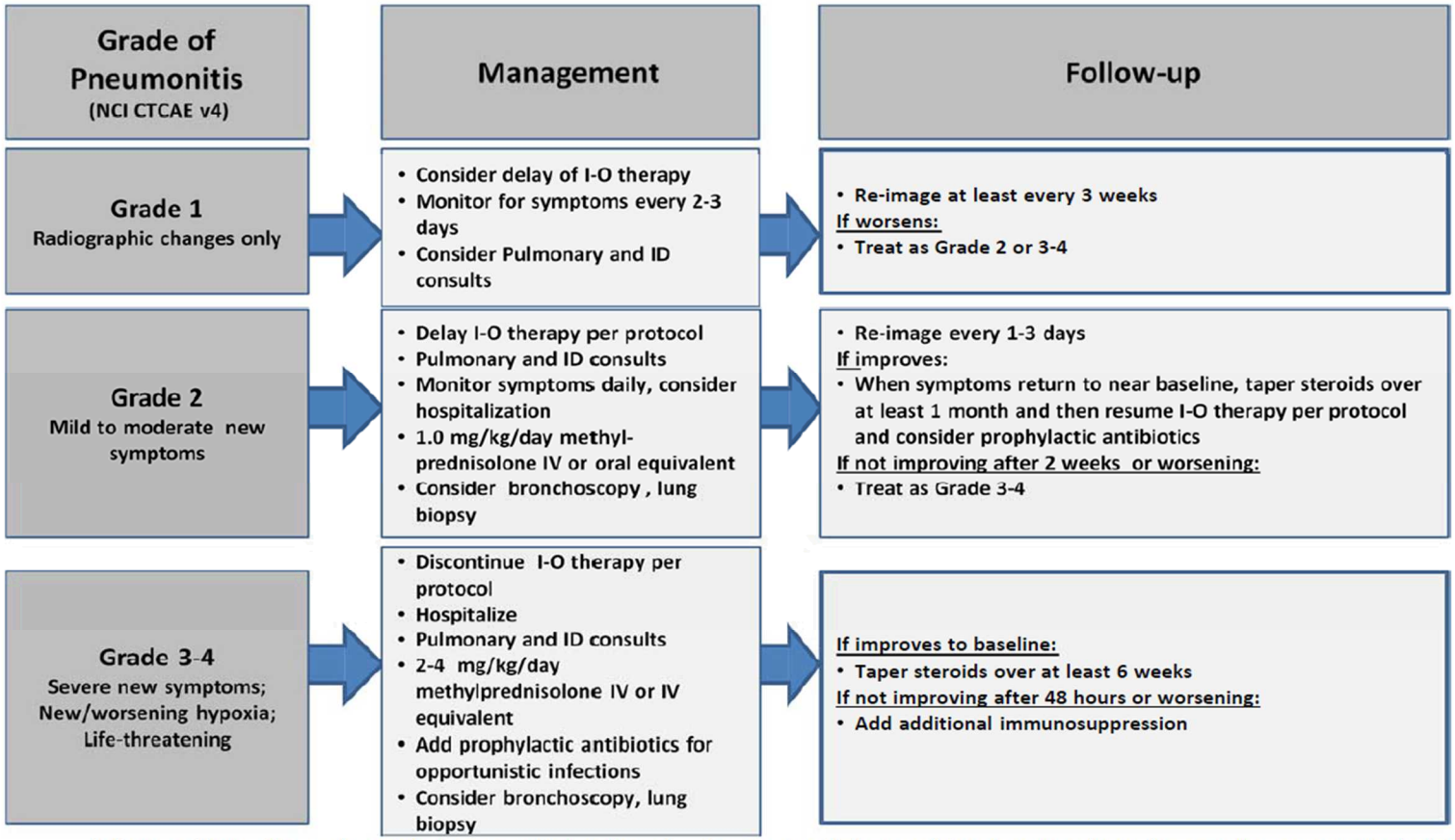


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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.

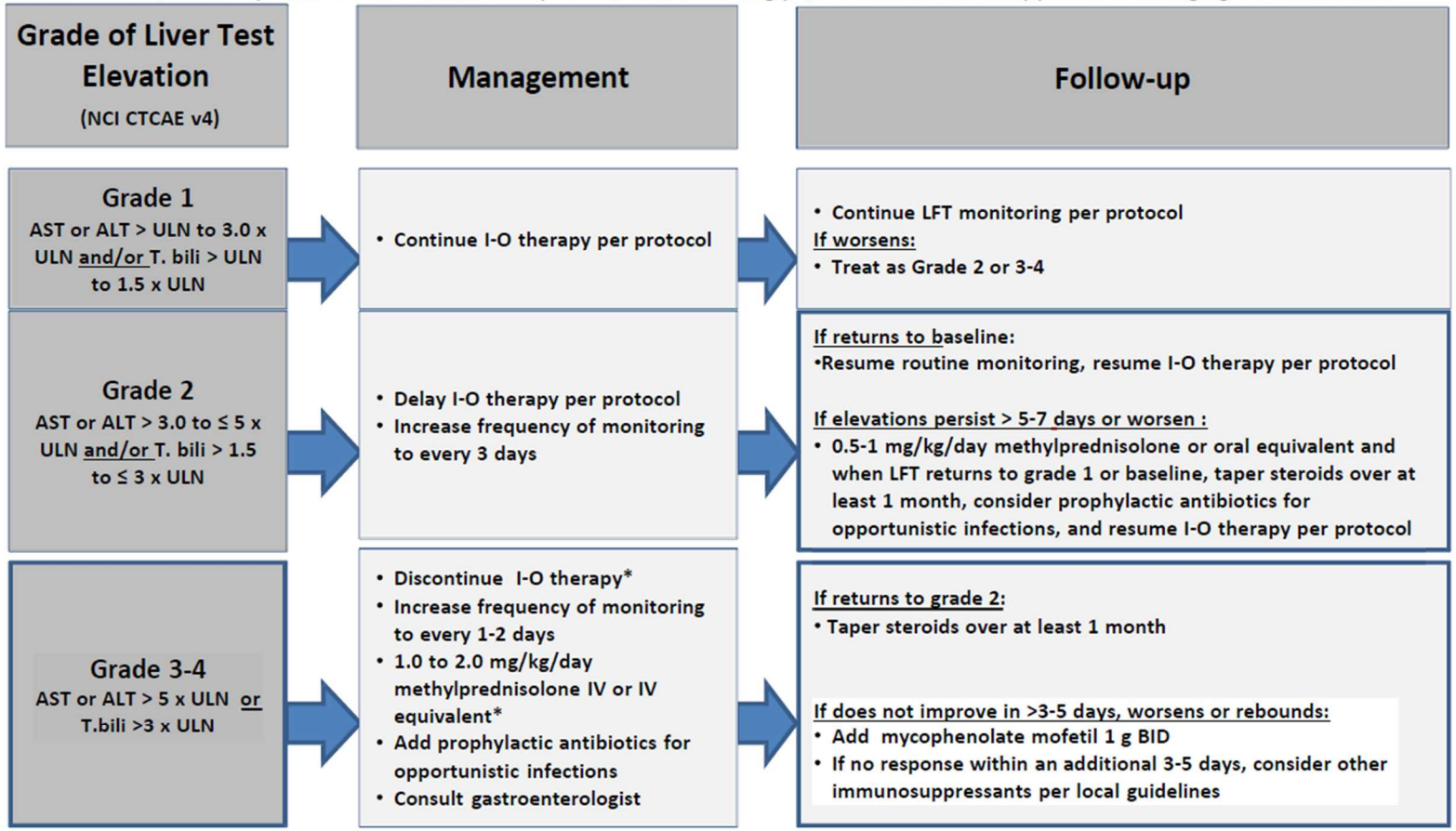


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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.



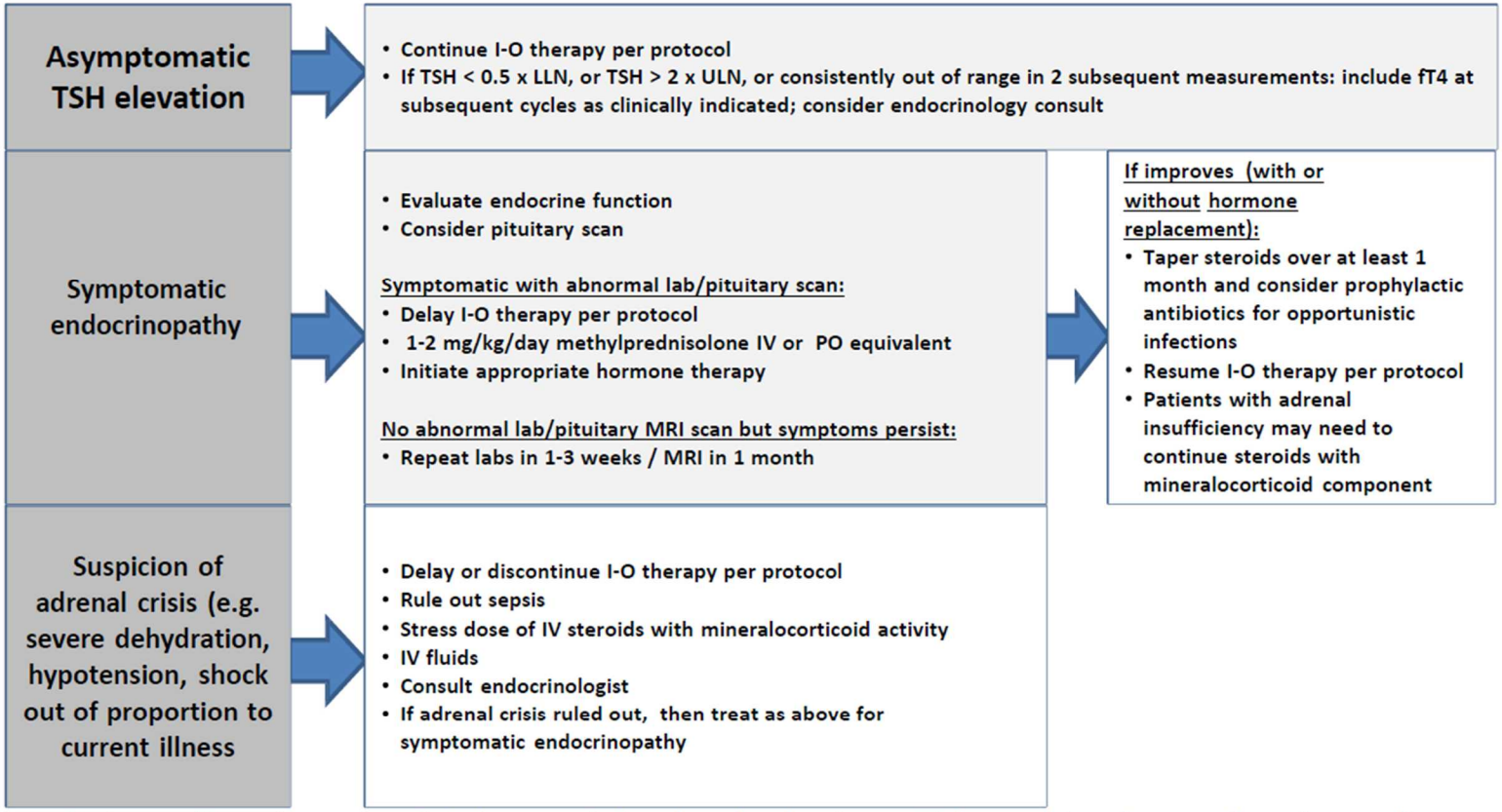
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

*The recommended starting dose for grade 4 hepatitis 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.

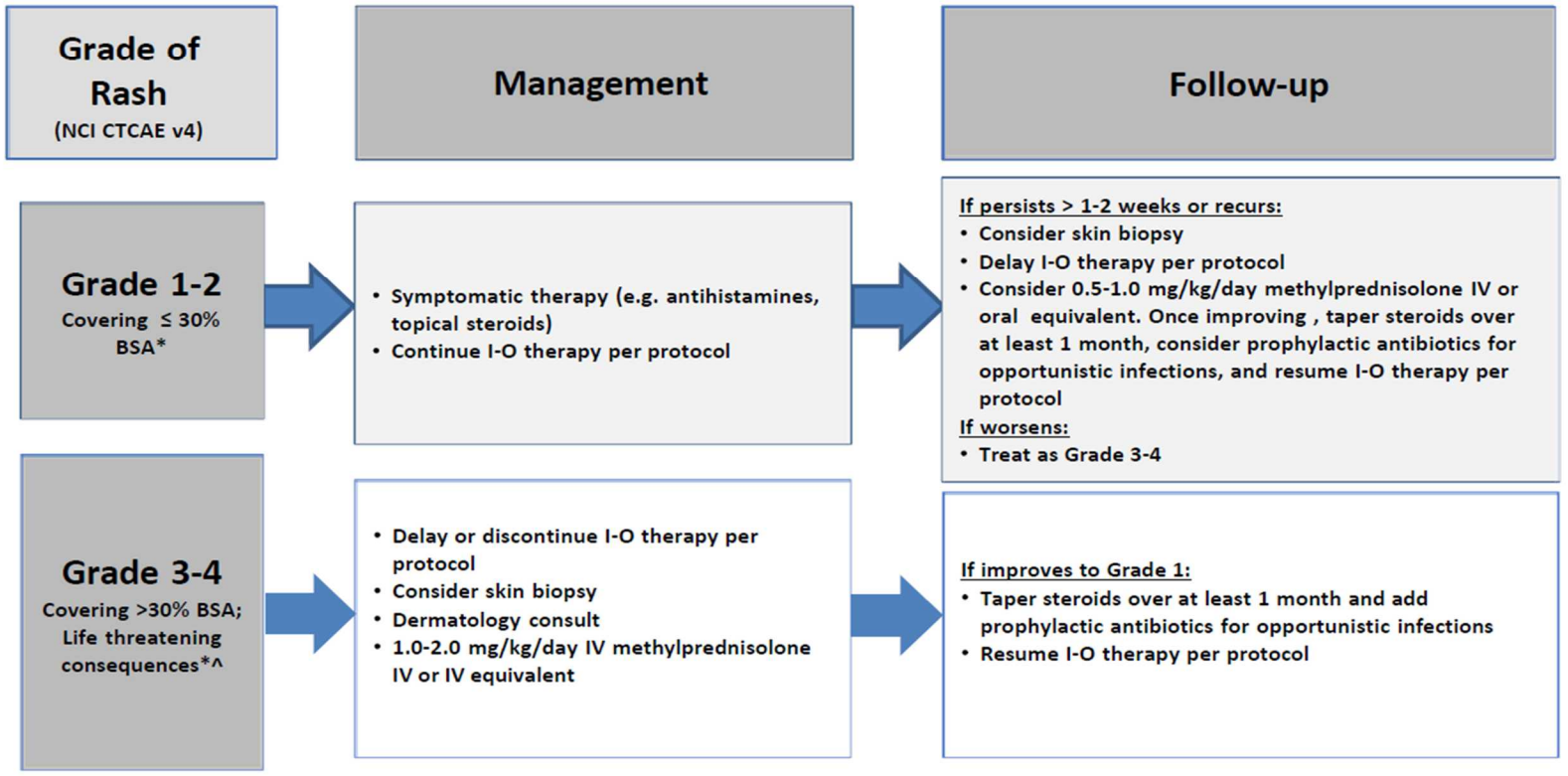


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

*Refer to NCI CTCAE v4 for term-specific grading criteria.

^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

28-Sep-2020

Neurological Adverse Event Management Algorithm

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

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

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

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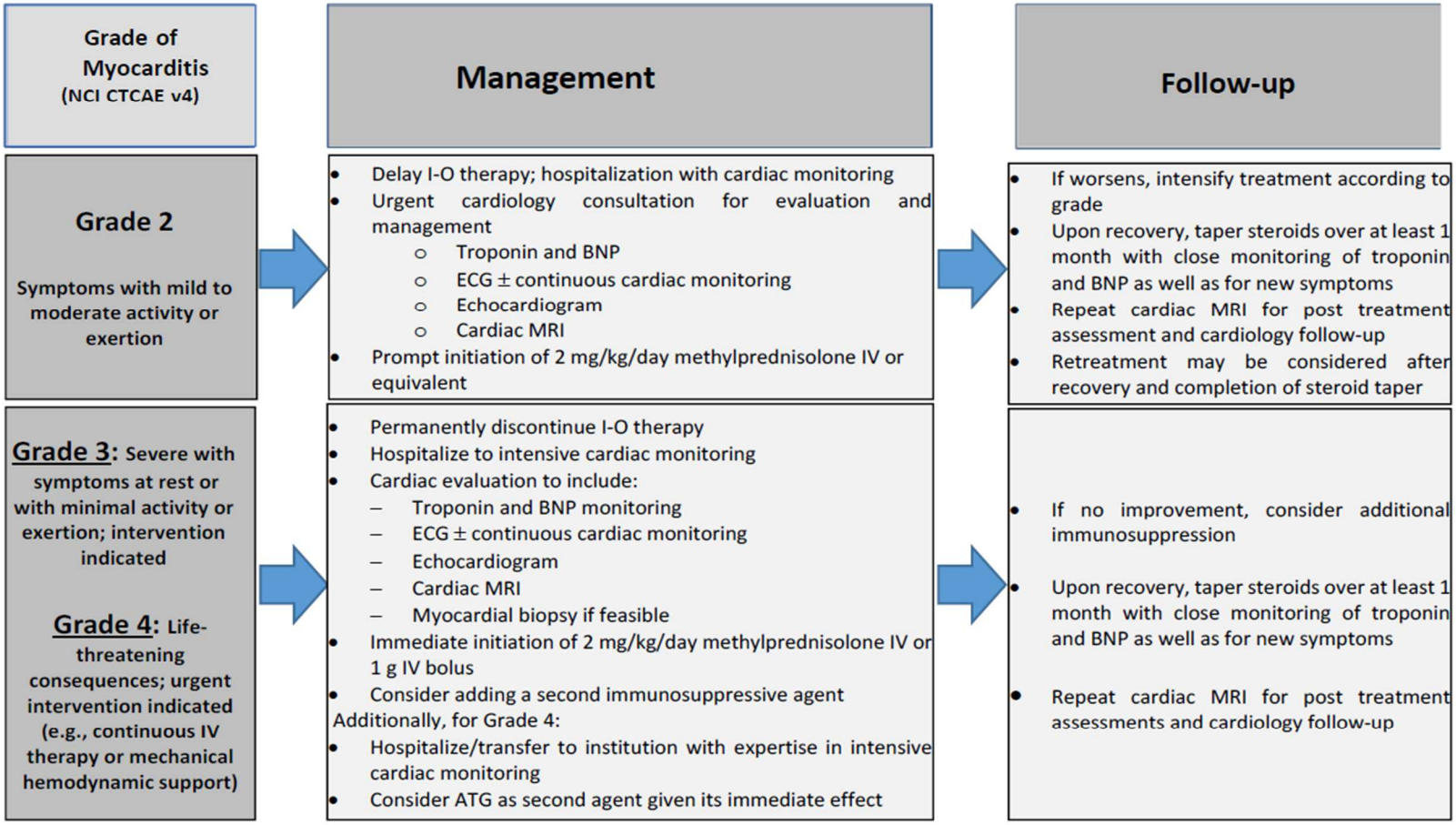
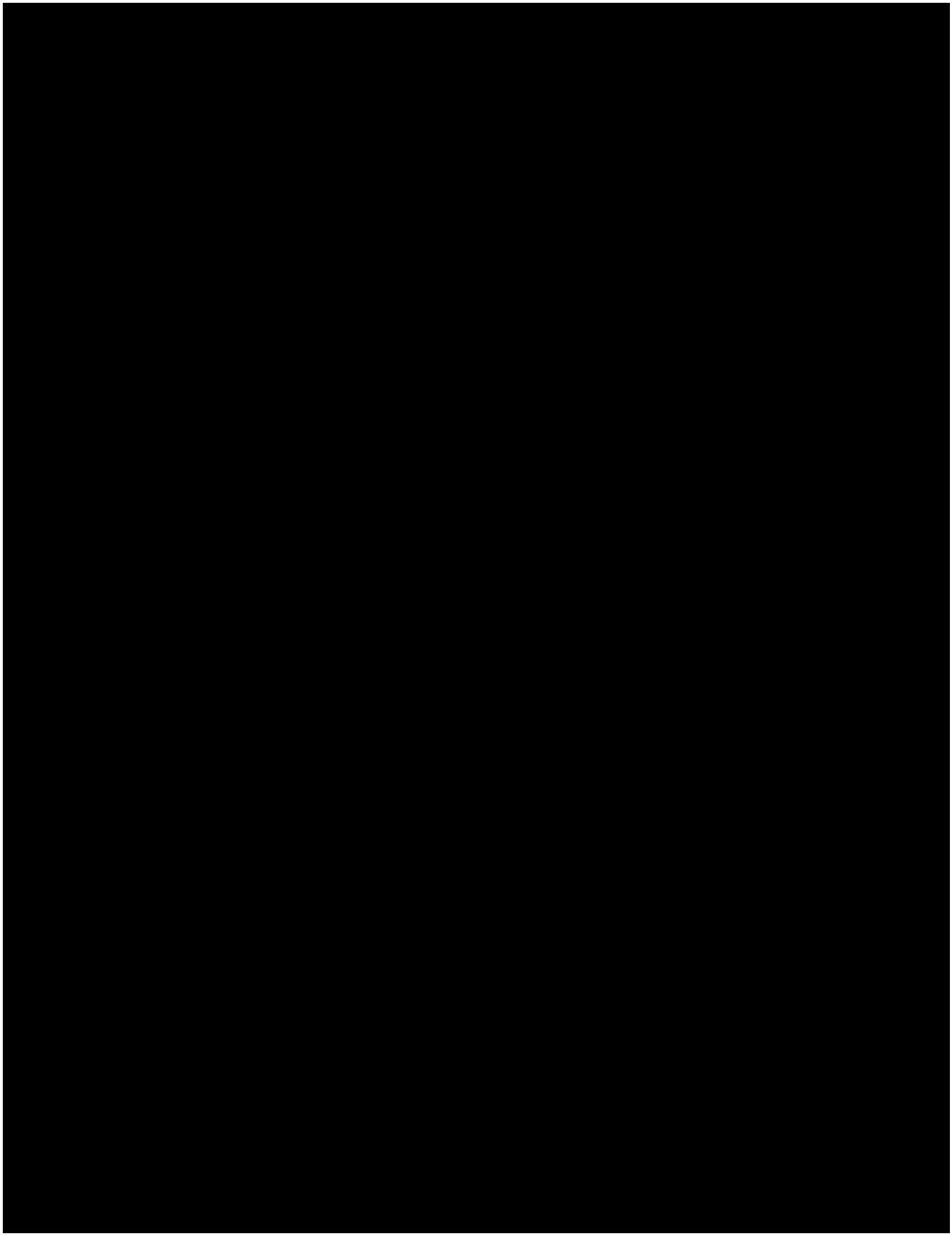
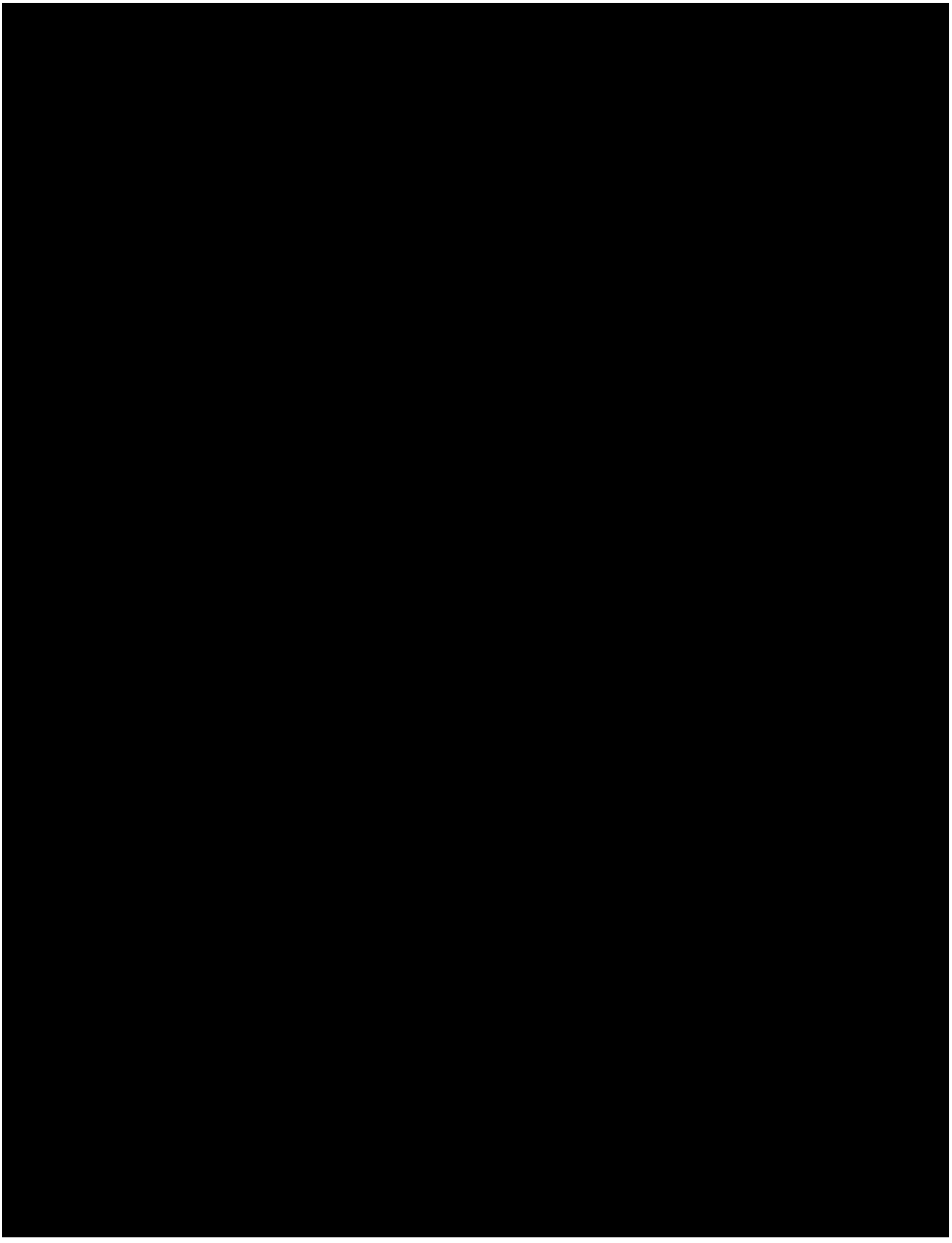
Myocarditis Adverse Event Management Algorithm

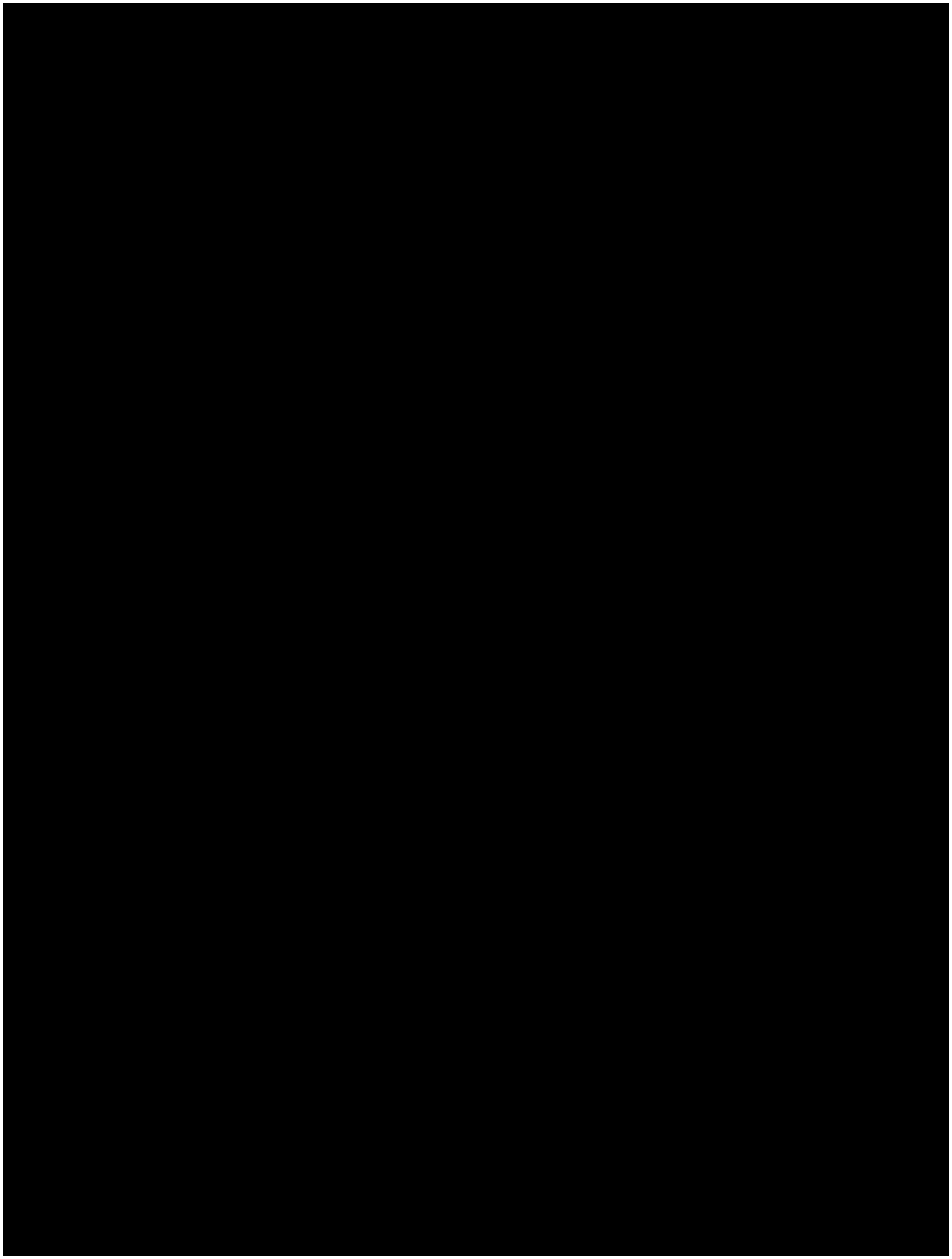


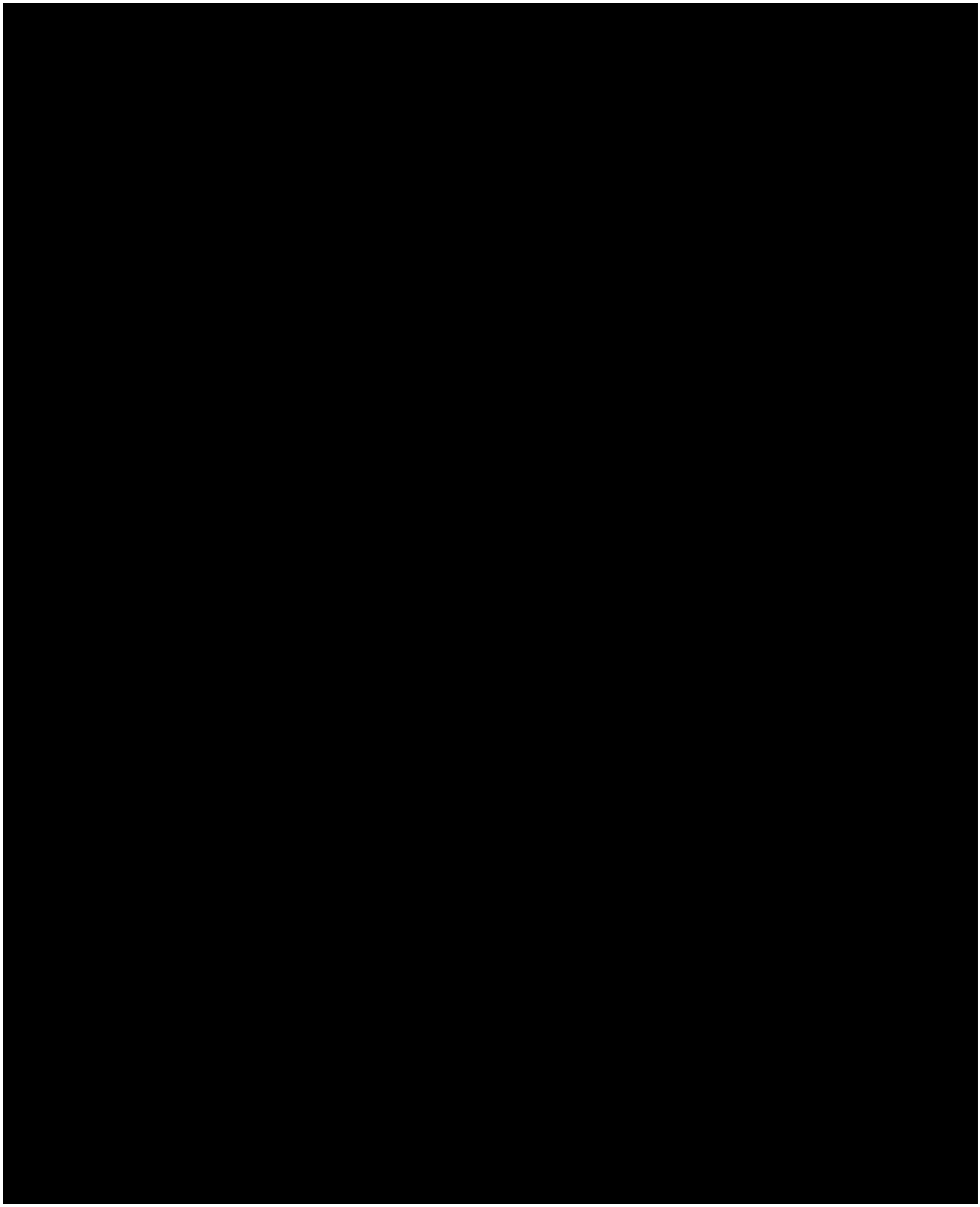
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

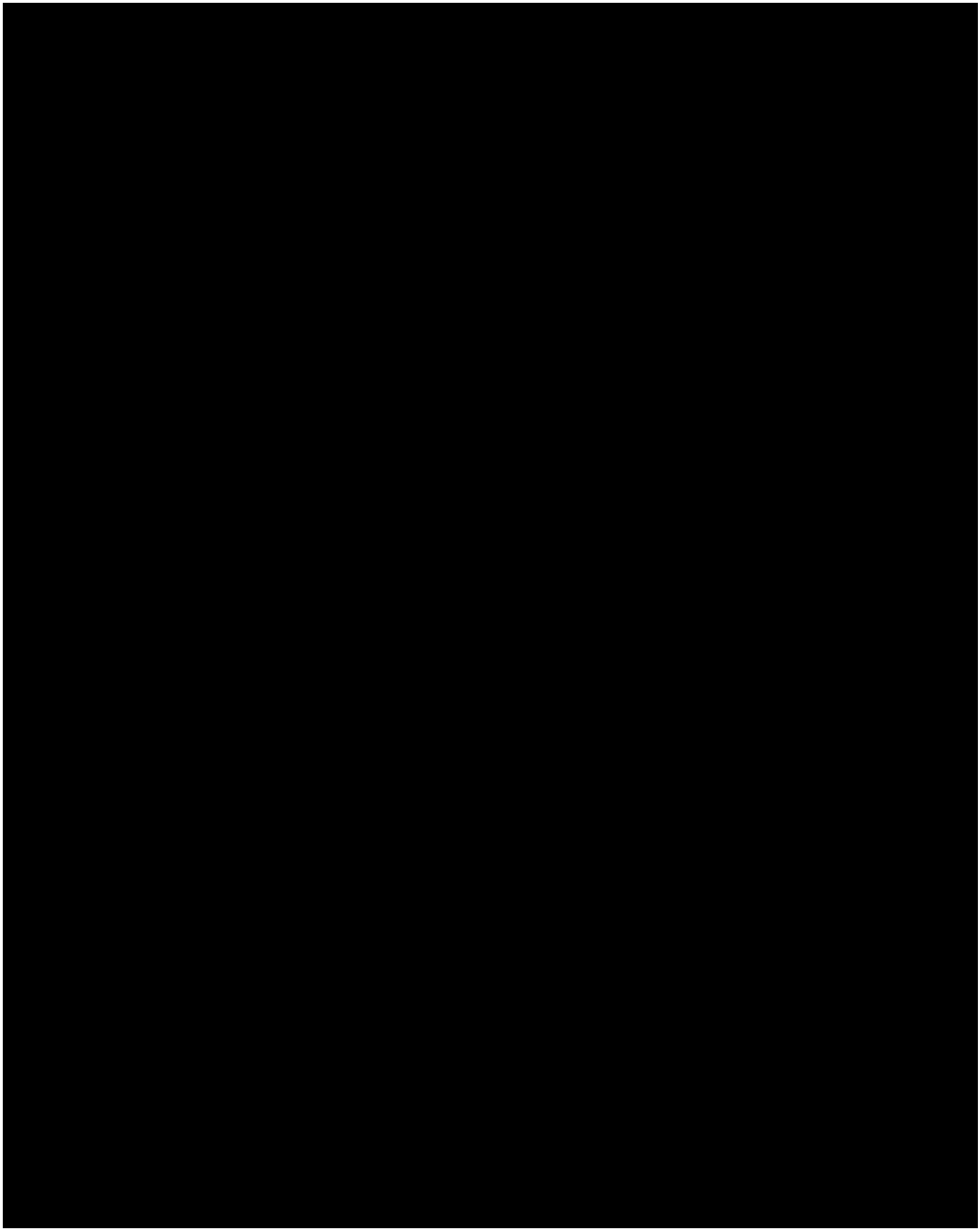
28-Sep-2020

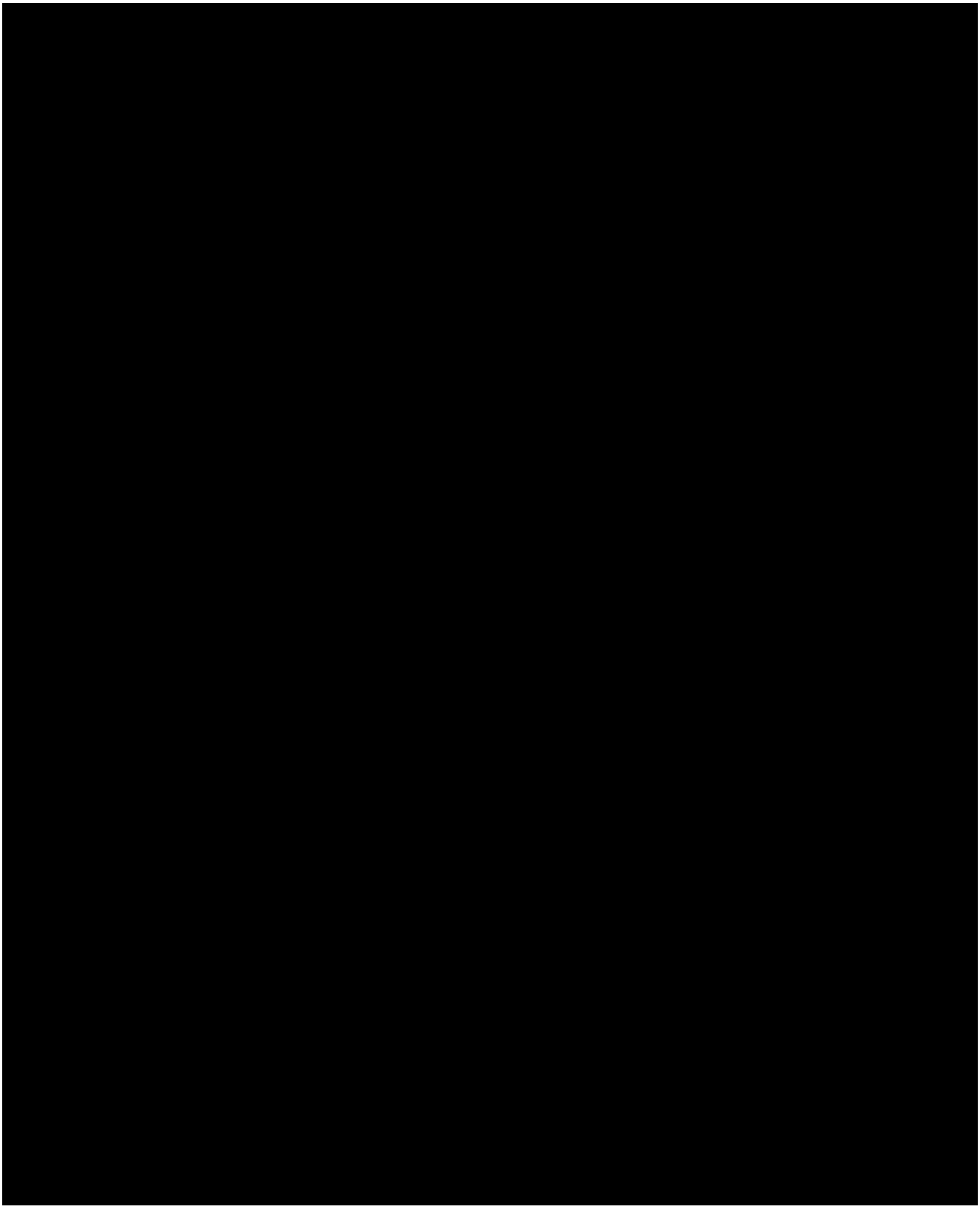


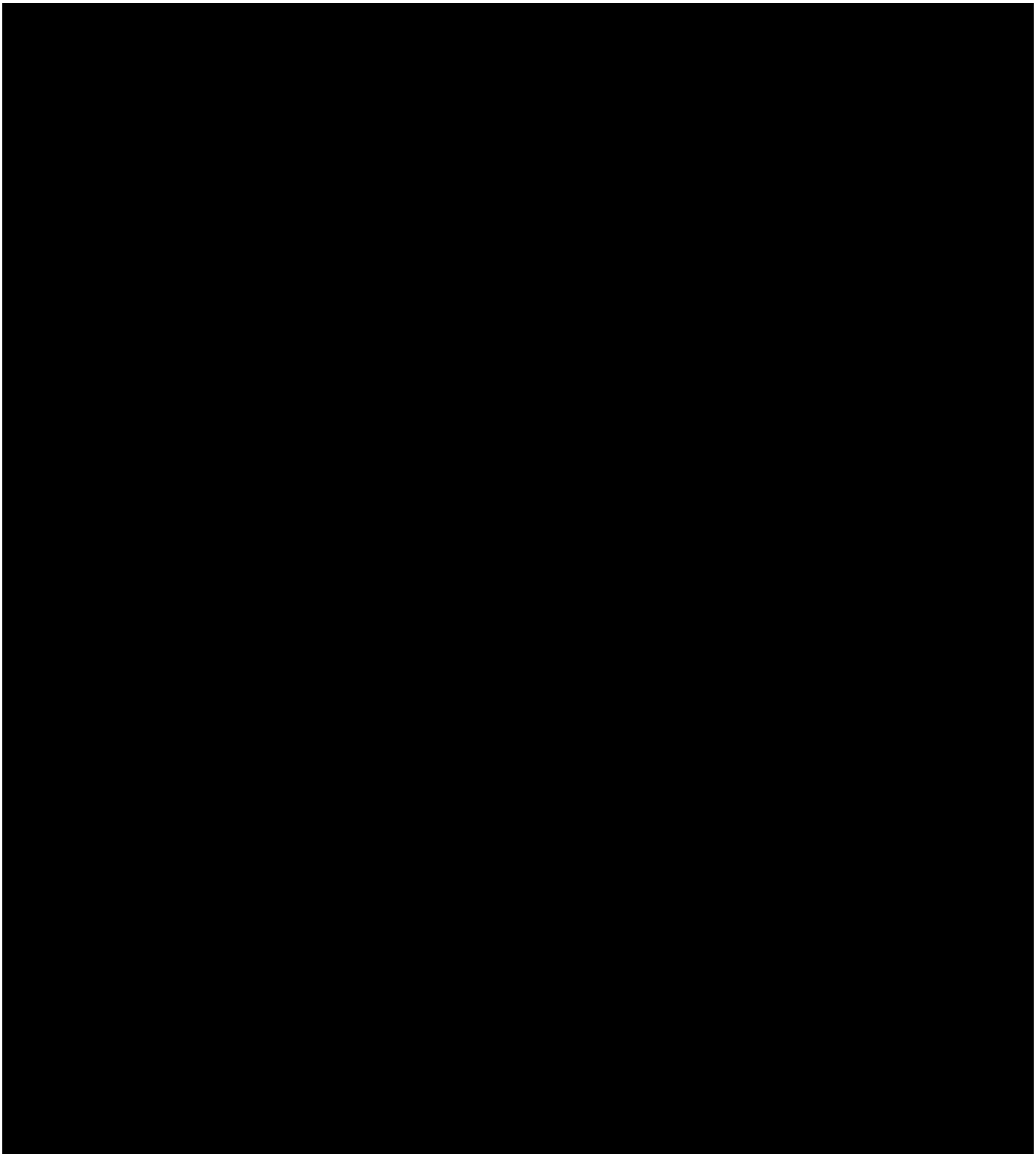


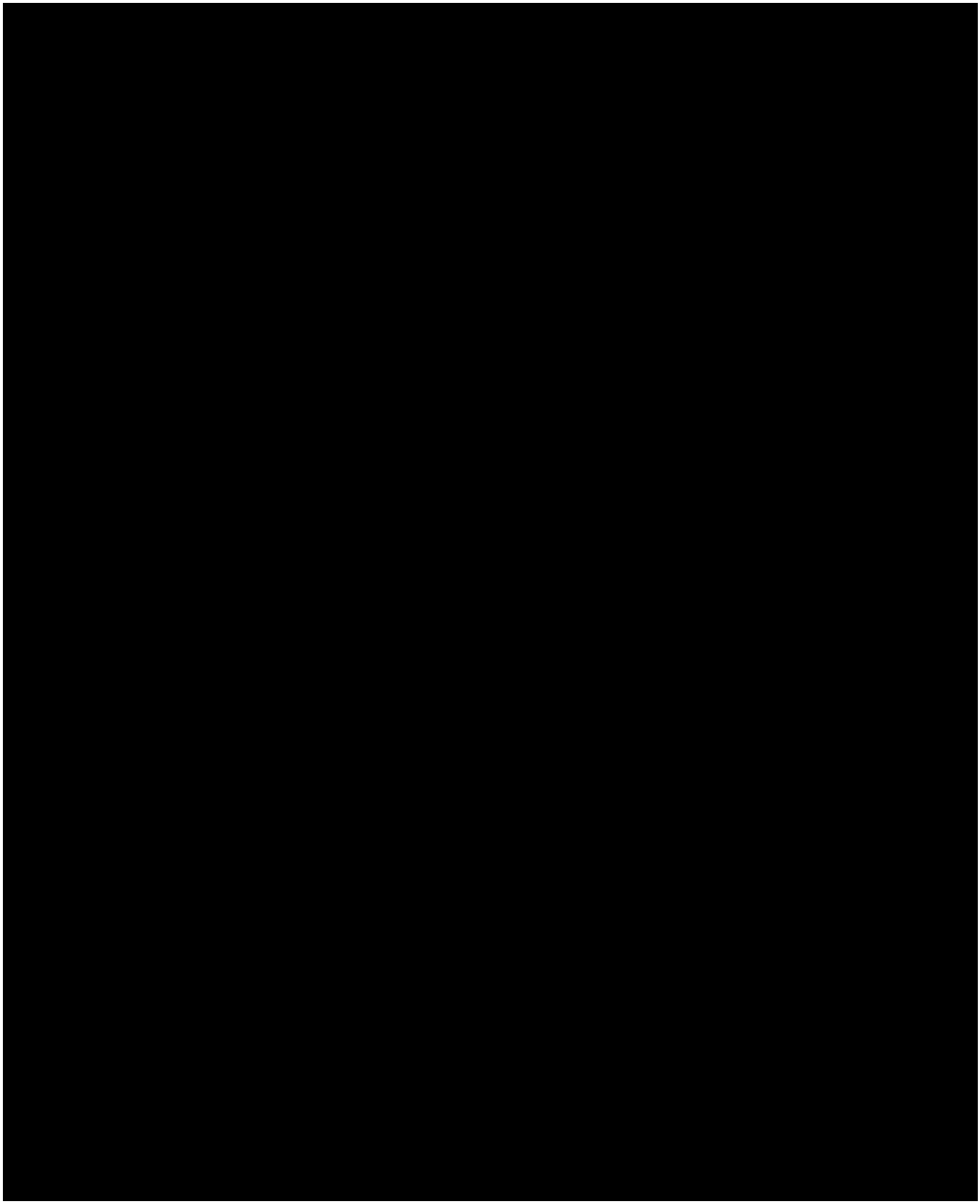












APPENDIX 8 RESPONSE EVALUATION CRITERIA IN SOLID TUMORS GUIDELINES (VERSION 1.1) WITH BMS MODIFICATIONS

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 5.3.2-1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline. When patients have non-measurable (therefore non-target) disease only, Table 5.3.2-2 is to be used.

Table 5.3.2-1: Time Point Response: Patients With Target (± Non-Target) Disease

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

Table 5.3.2-1: Time Point Response: Patients With Target (± Non-Target) Disease			
Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**
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 5.3.2-2: Time Point Response: Patients with Non-target Disease Only		
Non-Target Lesions	**New Lesions**	**Overall Response**
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
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 5.3.3-1. When SD is believed to be best response, it must meet the protocol specified minimum time from the date of first treatment or randomization date.

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

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

Table 5.3.3-1: Best Overall Response (Confirmation of CR and PR Required)		
Overall Response First Time Point	**Overall Response Subsequent Time Point**	**Best Overall Response**
CR	CR	CR
CR	PR	SD, PD OR PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
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 9 CHILD-PUGH SCORE

Score	Points
Child-Pugh A	5 - 6
Child-Pugh B	7 - 9
Child-Pugh C	> 9

Scoring

	Score		
Measure	1 Point	2 Points	3 Points
Ascites	Absent	Slight	Moderate
Serum bilirubin (mg/dl)	< 2.0	2.0 - 3.0	> 3.0
Serum albumin (g/dl)	> 3.5	2.8 - 3.5	< 2.8
PT prolongation or INR	< 4 sec < 1.7	4 - 6 sec 1.7 - 2.3	> 6 sec > 2.3
Encephalopathy grade	None	1 - 2	3 - 4

Abbreviations: INR = International normalized ratio; PT = prothrombin time.

Encephalopathy Grading

Encephalopathy Grade	Clinical Definition
Grade 0	Normal consciousness, personality, and neurological examination
Grade 1	Restless, sleep disturbed, irritable/agitated, tremor, and impaired handwriting
Grade 2	Lethargic, time-disoriented, inappropriate, asterixis, and ataxia
Grade 3	Somnolent, stuporous, place-disoriented, hyperactive reflexes, and rigidity
Grade 4	Unarousable coma, no personality/behavior, decerebrate

APPENDIX 10 NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION

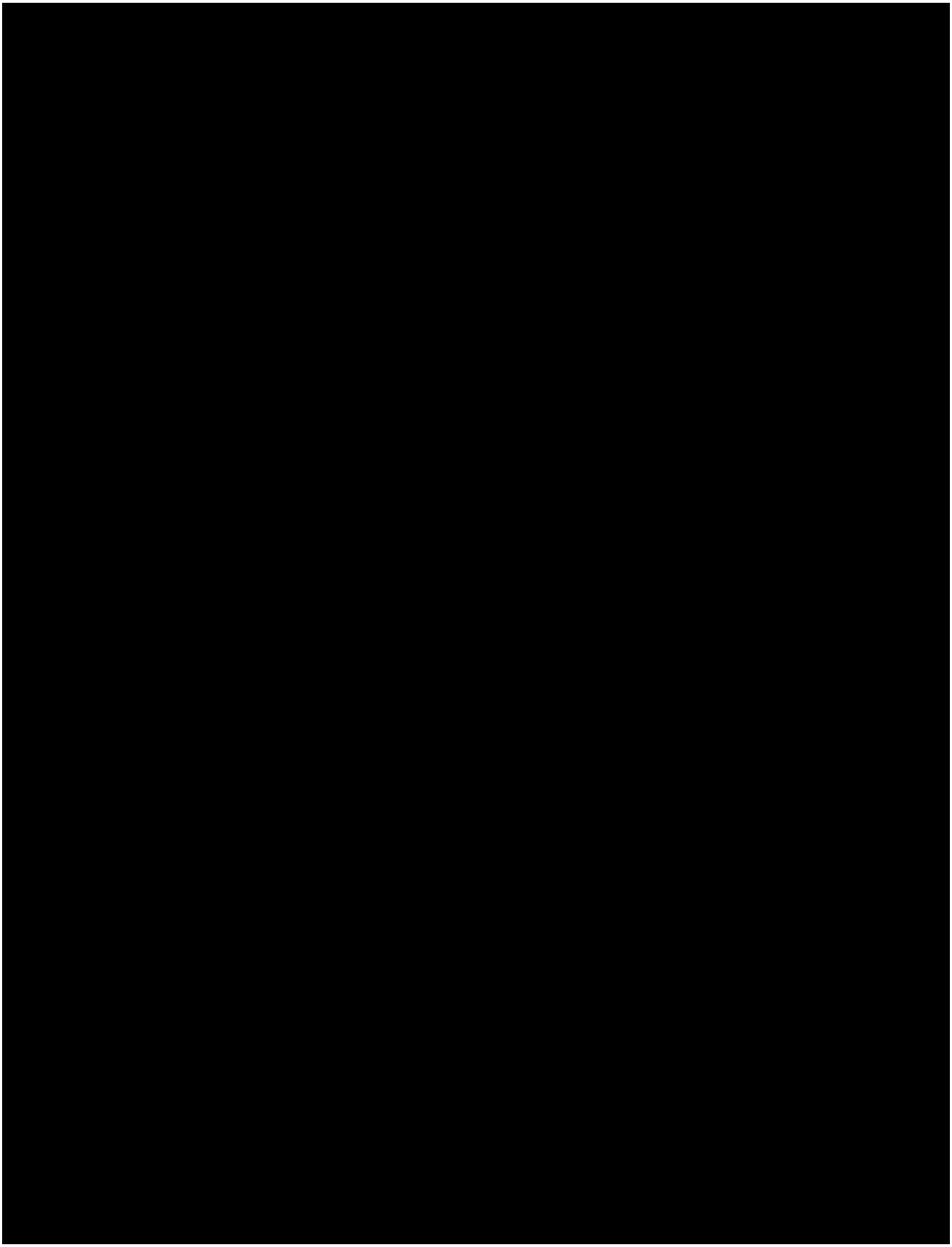
NYHA Class	Patients with Cardiac Disease (Description of Heart Failure Related Symptoms)
Class I (Mild)	Patients with cardiac disease but without resulting in limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation (rapid or pounding heart beat), dyspnea (shortness of breath), or anginal pain (chest pain).
Class II (Mild)	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain
Class III (Moderate)	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV (Severe)	Patients with cardiac disease resulting in the inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

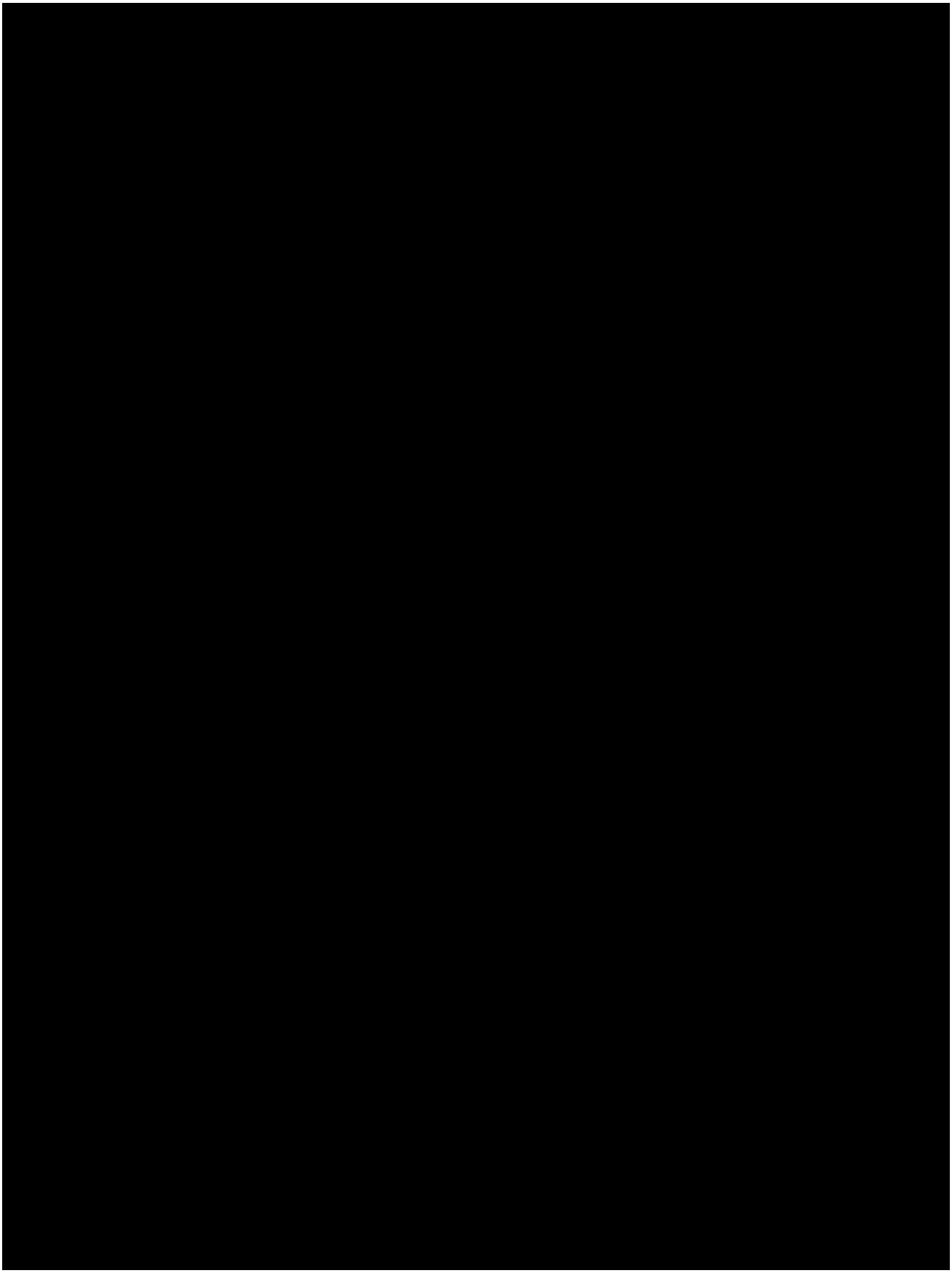
Reference: The Criteria Committee of the New York Heart Association. *Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels*. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256.

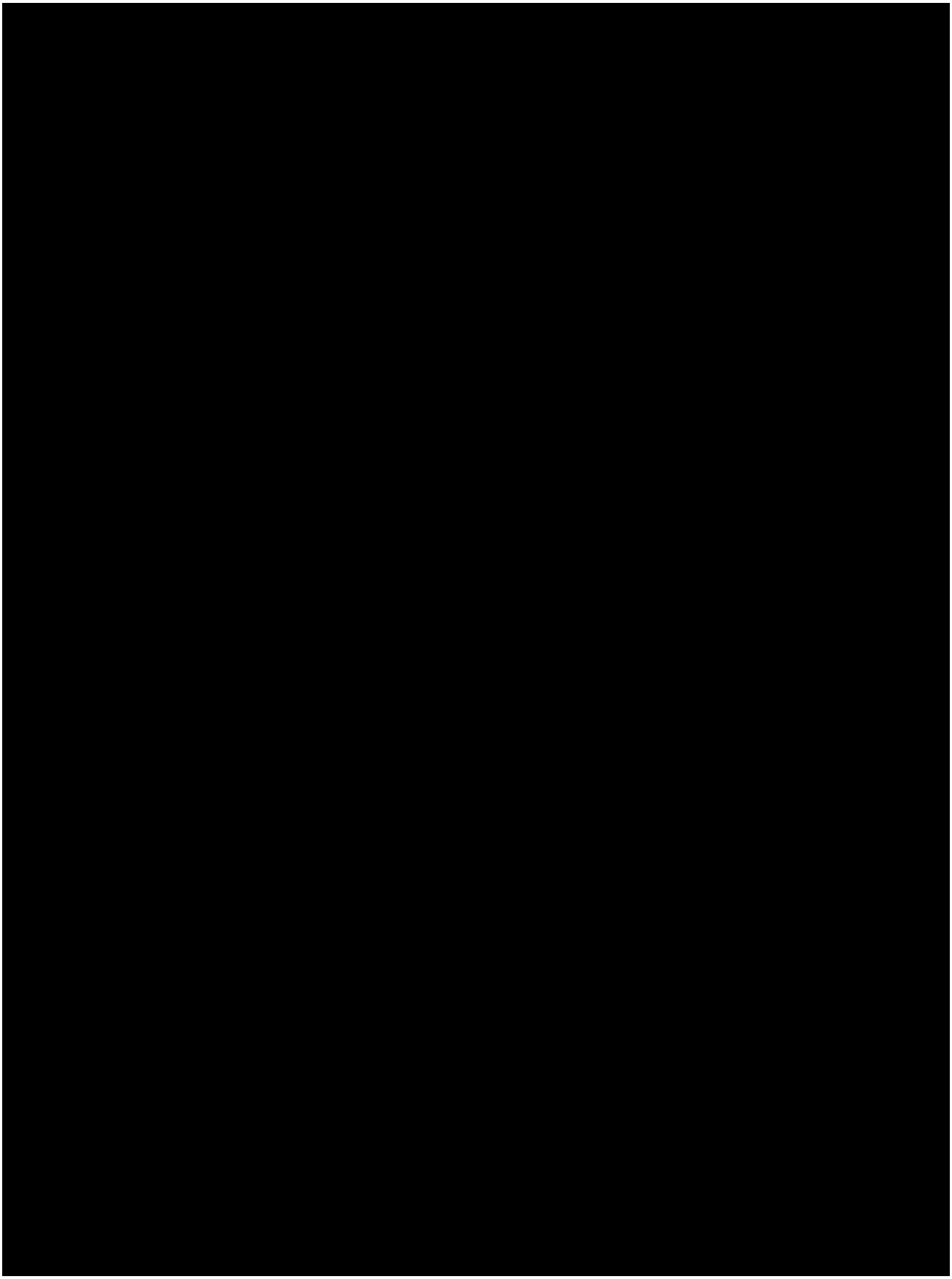
APPENDIX 11 COUNTRY SPECIFIC AMENDMENTS

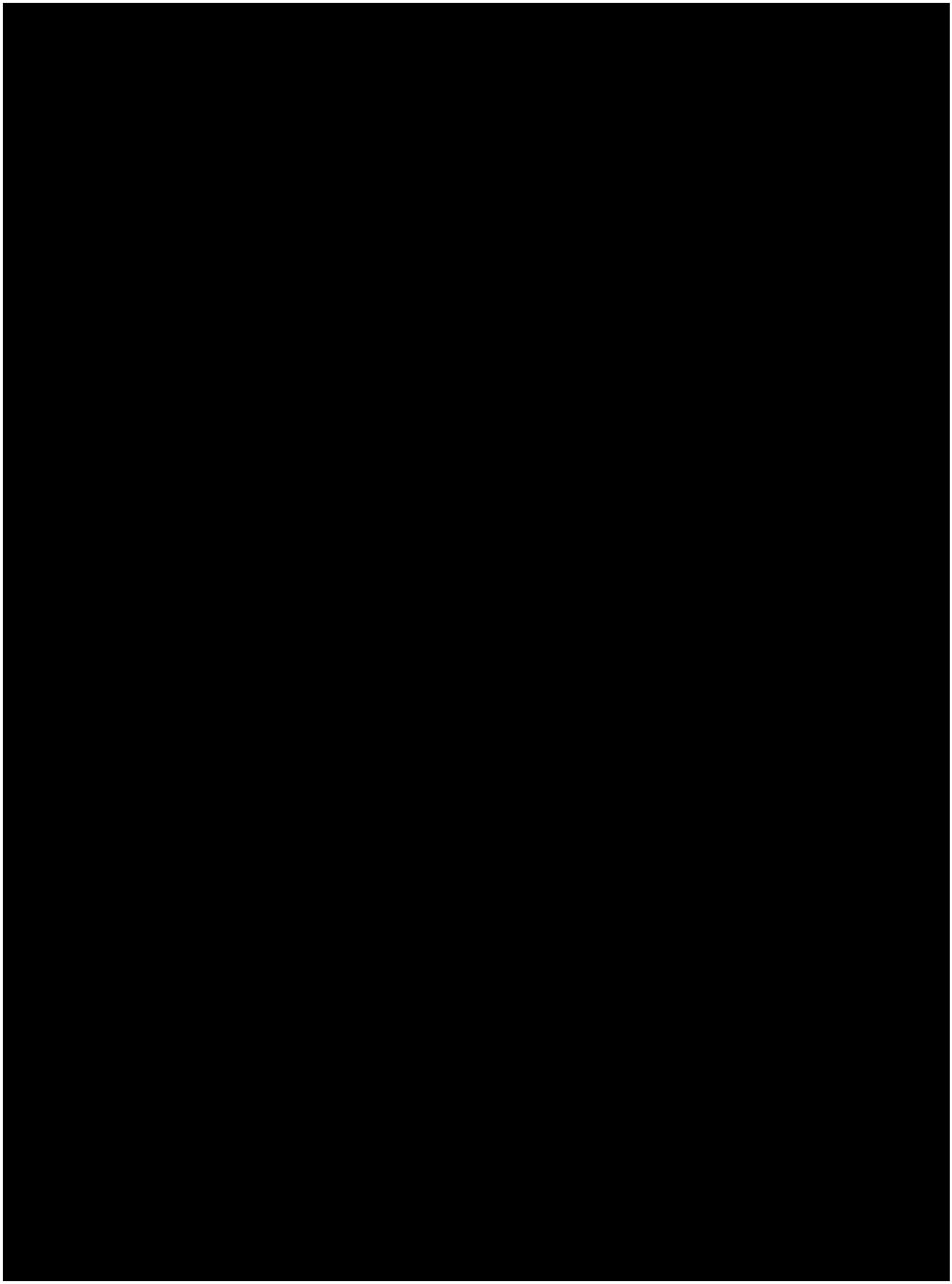
Germany and Any Other Countries Where Exclusion of HIV Positive Participants Is Locally Mandated

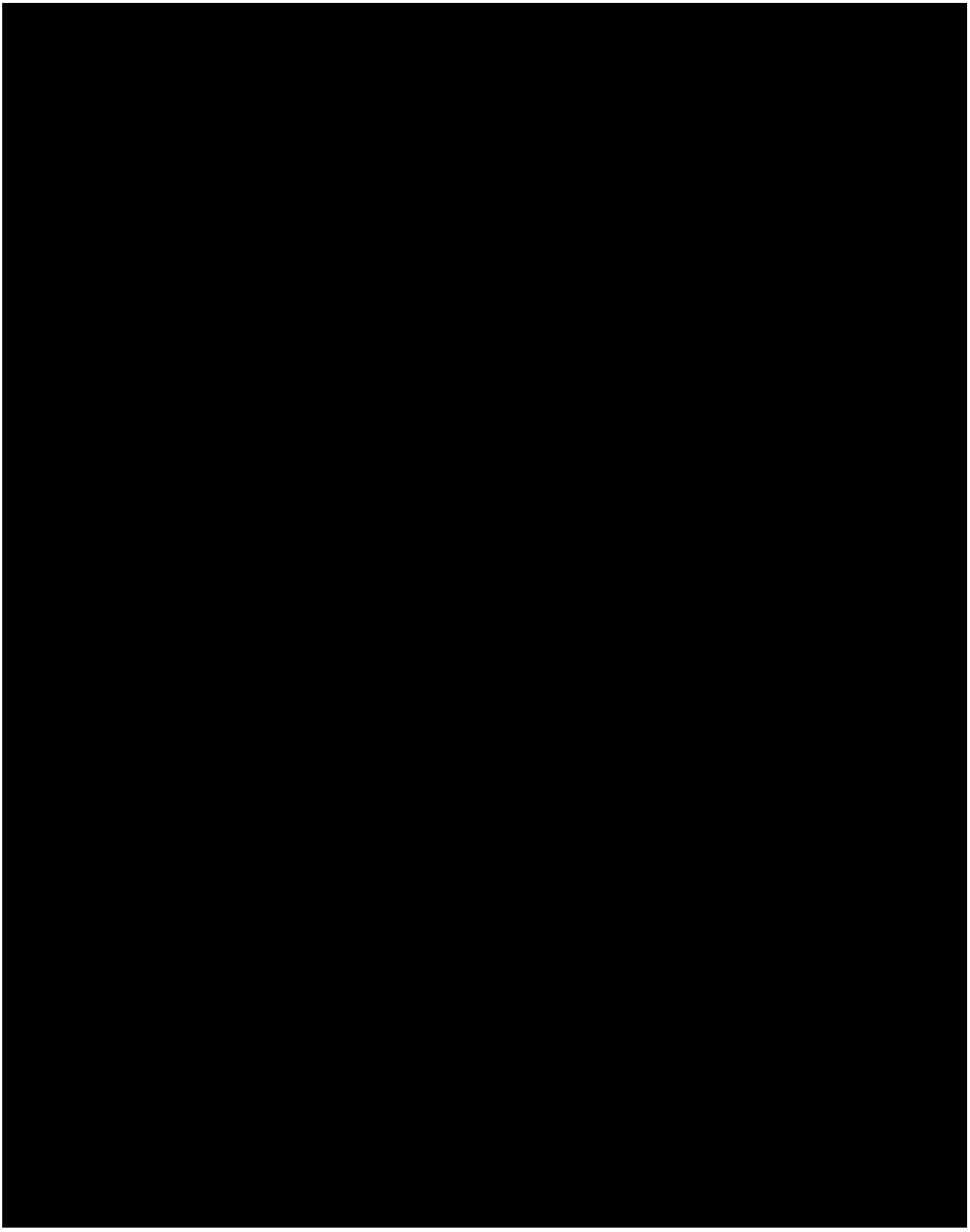
	Country-specific language
Section 6.2 Exclusion Criteria, Exclusion criterion 3) e)	"Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)"to be replaced with "Positive test for HIV".

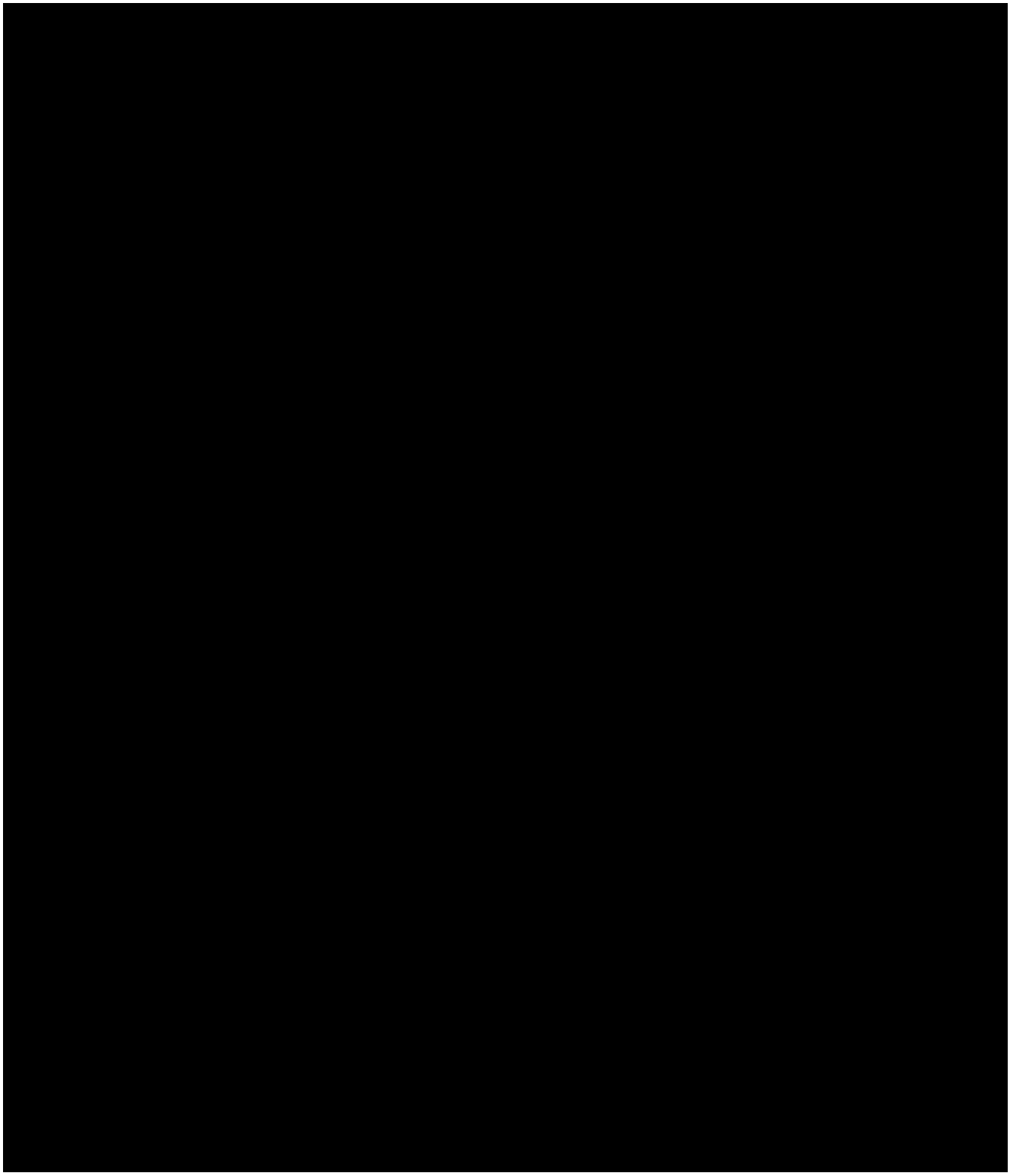


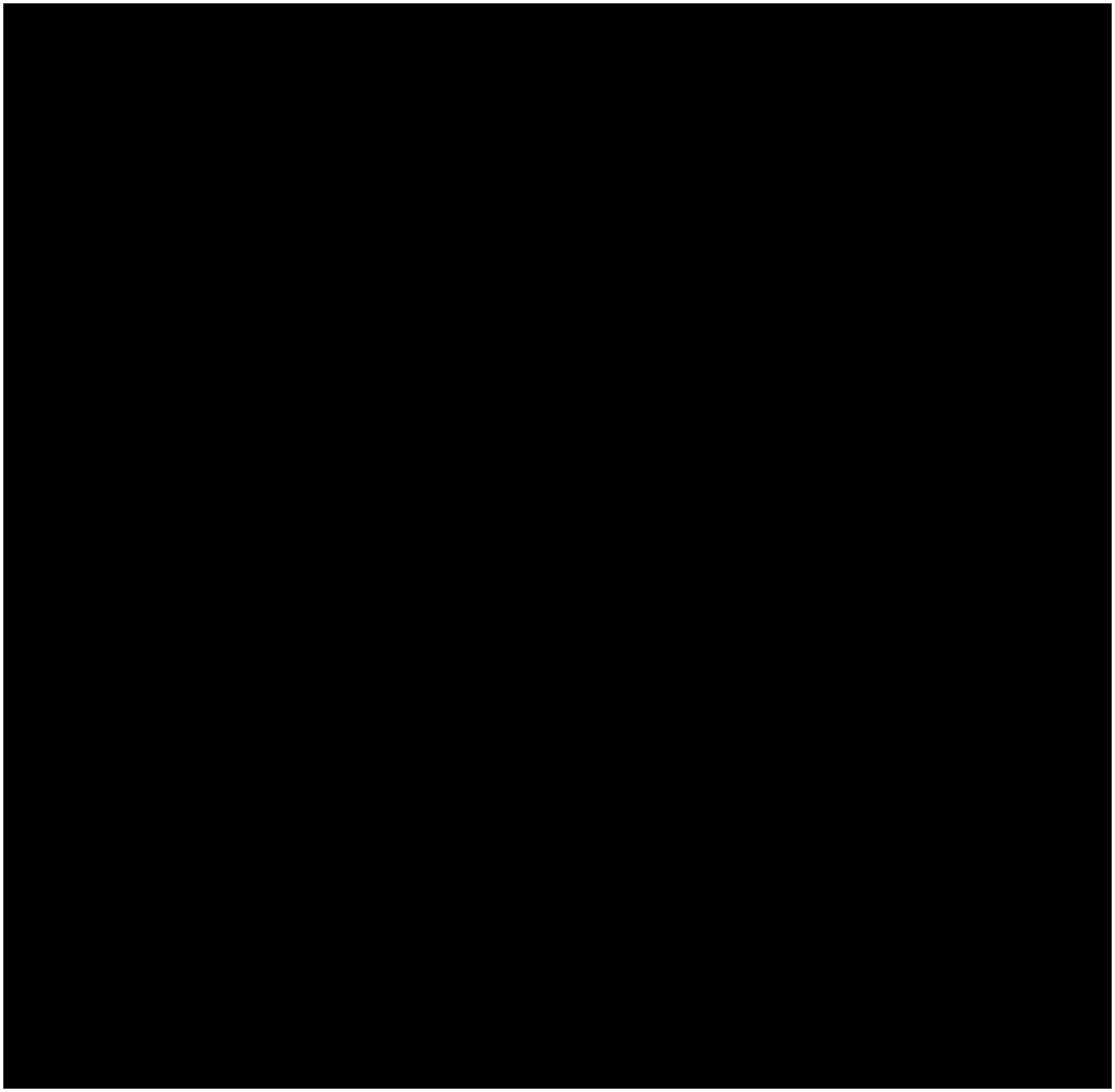












APPENDIX 13 PROTOCOL AMENDMENT SUMMARY OF CHANGE HISTORY

Overall Rationale for Protocol Amendment 06, 17-May-2023

[redacted]

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-2: Screening Procedural Outline (All Study Phases) Table 2-5: On-treatment Procedural Outline [redacted] Table 2-6: On-treatment Procedural Outline (Part 1C and Part 2 - BMS-986253 Q2W and Nivolumab and Ipilimumab Q3W) Table 2-7: Safety Follow-up Procedural Outline Section 3.3.1: Safety Monitoring on Study Treatment Table 4-2: Objectives and Endpoints - Part 2 Section 9.2.3: Follow-up of Adverse Events and Serious Adverse Events	Removed severe acute respiratory syndrome coronavirus 2 serology testing.	To align with revised Bristol-Myers Squibb Company (BMS) guidelines.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 9.8: Biomarkers [redacted]		
Table 2-2: Screening Procedural Outline (All Study Phases)	Removed fasting requirement.	Fasting is no longer a requirement as it is not clinically necessary.
Table 2-2: Screening Procedural Outline (All Study Phases) Table 2-3: On-treatment Procedural Outline (Part 1A and Cohorts 1B1 through 1B3 - BMS-986253 Q4W and Nivolumab Q4W) Table 2-4: On-treatment Procedural Outline (Cohorts 1B4 through 1B6 - BMS-986253 Q2W and Nivolumab Q4W) Table 2-5: On-treatment Procedural Outline [redacted] Table 2-6: On-treatment Procedural Outline (Part 1C and Part 2 - BMS-986253 Q2W and Nivolumab and Ipilimumab Q3W) Table 2-7: Safety Follow-up Procedural Outline	Added serious adverse event reporting requirements. Clarified adverse event reporting.	Clarification and alignment throughout the protocol.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 9.2.1: Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information		
Table 2-2: Screening Procedural Outline (All Study Phases) Section 5.1.2: Screening Period Section 6.1: Inclusion Criteria [redacted]	[redacted] Clarified biopsy language. Revised inclusion criteria for pre-treatment biopsy for participants enrolled in Part 2.	To ensure data quality. To improve study accessibility for participants in Part 2.
Table 2-2: Screening Procedural Outline (All Study Phases)	Specified timing of image acquisition.	Clarification.
Table 2-3: On-treatment Procedural Outline (Part 1A and Cohorts 1B1 through 1B3 - BMS-986253 Q4W and Nivolumab Q4W) Table 2-4: On-treatment Procedural Outline (Cohorts 1B4 through 1B6- BMS-986253 Q2W and Nivolumab Q4W) Table 2-5: On-treatment Procedural Outline [redacted] Table 2-6: On-treatment Procedural Outline (Part 1C and Part 2 - BMS-986253 Q2W and Nivolumab and Ipilimumab Q3W) Section 5.1.1: Follow-up Section 5.1.5.1: Safety Follow-up Period	Specified end of treatment (EOT) definition. For participants who do not complete all scheduled cycles of therapy, the EOT visit will be the next visit following the last study dose. If the EOT visit occurs 30 days or more after receipt of the last dose, then the EOT visit and Follow-up 1 visit can be completed at the same time.	Clarification.
Table 2-7: Safety Follow-up Procedural Outline Section 5.1.5.3: Survival Follow-up Period	Clarified language for survival follow-up and safety follow-up.	To maintain alignment throughout the protocol.
Section 5.1: Overall Design Section 10.1.2: Part 1C	Added information about Cohort 1C1 and the impact of that data on Cohort 1C2.	To confirm the safety and evaluate the efficacy of the triplet regimen in participants with MSS and/or pMMR CRC.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
	Added justification to open Part 1C2 for enrollment of approximately up to 10 participants with CRC.	
Section 5.1: Overall Design Figure 5.1-2: Study Design Part 1 Figure 5.1-3: Study Design Part 2 Section 5.5.2: Rationale for Part 1B Dosing Schedules and Maximum Administered Dose Section 5.5.4: Rationale for Nivolumab Dose Selection Section 5.5.5: Rationale for Ipilimumab Dose Selection Section 5.5.6: Rationale for Part 2 Dosing Schedules and Maximum Administered Dose/RP2D Section 7.4: Method of Treatment Assignment and Stratification Table 7.3-1: Dose, Frequency, Infusion Time, and Sequence of IPs [redacted]	• Updated study designs with the number of participants enrolled as of publication of Protocol Amendment 06. • Identified the MTD/MAD of BMS-986253 as 3600 mg every 2 weeks (Q2W) • [redacted] [redacted] • Updated Study Design Part 2 to reflect the RP2D. • Added a new section.	To justify the selection of the RP2D for Part 2.
Section 5.1: Overall Design Figure 5.1-2: Study Design: Part 1	Updated the number of participants for Part A Cohort 1B1 [redacted]	Part A Cohort 1B1 enrolled a total of [redacted] participants.
Section 5.1.2: Screening Period	Added "Repeat serum IL-8 testing will not be required if the previous sample was obtained within 42 days of study treatment initiation."	Clarification
Section 6.1: Inclusion Criteria	Clarified inclusion criterion 2) a) that participants must have radiographically measurable disease. Added criterion 2) c) xii) (4) (a) with palliative radiation considerations. Updated criterion 2 a) for screening [redacted] requirements. Updated criterion 2) c) vi) (2) with microsatellite instability status or mismatch repair information.	To clarify the inclusion criteria and improve readability.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 6.2: Exclusion Criteria [redacted] Section 7.6.8: Hemophagocytic Lymphohistiocytosis (HLH) Section 7.6.8.1: HLH Management Approaches	Added exclusion criterion 3) i): History of HLH/macrophage activation syndrome (MAS). Added exclusion criterion 3) j): diseases related to chronic Epstein-Barr virus infections. Added HLH as a dose-limiting toxicity that requires treatment discontinuation Added new sections with background information about HLH and management of HLH.	[redacted]
Table 7.3-1: Dose, Frequency, Infusion Time, and Sequence of IPs	Added footnote h to specify the infusion time.	Clarification and to maintain alignment throughout the protocol.
Section 7.4: Method of Treatment Assignment and Stratification	Corrected an error in the description of assigning the participant identifier number. Removed description of replacing participants.	Correction. Participants will not be replaced in this way.
[redacted]		
Section 10.3.4: Immunogenicity Analyses	Added "summary of anti-drug antibody (ADA) peak titer, ADA onset and duration, summary of select adverse events, by ADA status, summary of best overall response by ADA status."	To align with the updated immunogenicity statistical analysis plan.
Appendix 2: Study Governance Considerations	Added sections: • BMS Commitment to Diversity in Clinical Trials • Data Protection, Data Privacy, and Data Security	To align with BMS commitment to diversity in clinical trials. To comply with the European Union Clinical Trials Regulation requirement.

Overall Rationale For Protocol Amendment 05, 17-Feb-2022

Protocol Amendment 05 [redacted] Although there have been no such events to date, management guidelines for potential cytokine release syndrome (CRS) and myocarditis are added [redacted]

Criteria regarding prior use of targeted therapy in participants with [redacted] melanoma is also updated to accommodate prioritization of combination immunotherapy when appropriate, with added justification provided for the use of combination ipilimumab and nivolumab in Part 2 based on newly published data.

Several other changes are made to improve clarity and readability and to update guidance regarding coronavirus disease 2019 (COVID-19) and COVID-19 vaccines.

Updates were made to align with the 2021 editions of the nivolumab Investigator Brochure (Version 20, Document Control No. 930128344), the ipilimumab Investigator Brochure (Version 24, Document Control No. 930017531), and the BMS-986253 Investigator Brochure (Version 6, Document Control No. 930106282).

This amendment incorporates the changes from the approved Administrative Letter 05, which are detailed in the Document History but not listed in the Summary of Key Changes below.

Changes made to align the Summary (formerly Synopsis) with updates made to the Body.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 05

Section Number & Title	Description of Change	Brief Rationale
Title Page	Updated name and title of study personnel. Corrected contact information and added European BMS address.	To reflect the updates in study team personnel and contact information.
Section 2: Schedule of Activities	Removed Table 2-6: On-treatment Procedural Outline Part 2 for BMS-986253 Q3W Schedule: BMS-986253 or Placebo Q3W, Nivolumab Q3W, and Ipilimumab Q3W (x 4 doses). Subsequent tables are renumbered to account for this deletion.	BMS-986253 will be administered every 2 weeks (Q2W) in Part 2, therefore this table is not needed.
Section 5.1: Overall Design	Clarified the current status of the study (ongoing vs already enrolled cohorts). [redacted]	To clarify the study design.
Figure 5.1-2: Study Design: Part 1	Updated figure to reflect Part 1 study design.	To reflect changes to the study design.
Table 2-2: Screening Procedural Outline (All Study Phases) Section 5.1.1 Pre-Screening Period (Applicable for Part 1 Only)	Clarified timepoint from IL-8 results by central laboratory and signature of the main informed consent.	To clarify the enrollment process.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 05

Section Number & Title	Description of Change	Brief Rationale
Section 5.1.5.2: Response Follow-up Period	Clarified imaging collection during the follow-up period in Part 2 of the study.	To clarify when imaging procedures are required during the follow-up period.
Section 5.4.8: Rationale for Treatment of Post-PD-(L)1 Melanoma in Part 2	Updated to include new references and current treatment guidelines.	To provide additional rationale for nivolumab and ipilimumab combination as control arm for Part 2.
Section 5.5.2: Rationale for Part 1B Dosing Schedules and Maximum Administered Dose	[redacted]	
Section 6.1: Inclusion Criteria	Inclusion criteria were added or updated for: 2) c) i): Non-small cell lung carcinoma is no longer enrolling per Protocol Amendment 04. 2) c) ii) 2): Reintroduced the following criteria for RCC participants with a clear cell component: Must have received and progressed/been intolerant of (or not be a candidate for) an anti-angiogenic therapy (eg, including but limited to bevacizumab, axitinib, cabozantinib, pazopanib, sorafenib, sunitinib and tivozanib). 2) c) iii) 4) a: BRAF-mutated participants must have received (or not be a candidate for) BRAF inhibitor treatment, or declined targeted therapy after having been provided adequate information to make an informed decision. 2) c) vi) 4) Microsatellite Stable Colorectal cancer participants with epidermal growth factor receptor (EGFR)-expressing RAS wildtype tumors must have received (or not be a candidate for) EGFR directed therapy (eg, cetuximab). 2) c) xii) 3) a: If participant has a [redacted] they must have received (or not be a candidate for) BRAF inhibitor treatment, or declined targeted therapy after having been provided adequate information to make an informed decision. Removed wording for the non-applicable inclusion criteria.	[redacted] to update language regarding prior use of targeted therapy in participants with [redacted] melanoma to accommodate prioritization of immunotherapy when appropriate.
Table 7.3-1: Dose, Frequency, Infusion Time and Sequence of IPs	Updated table.	To reflect the current study design and dose schedule for Part 2 (Q2W).
[redacted]		

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 05

Section Number & Title	Description of Change	Brief Rationale
[redacted] Section 7.6.5: Exceptions to Permanent Discontinuation Criteria	Updated list of exceptions, including Grade 3 CRS that returns to Grade 1 in < 6 hours. Removed information not applicable in this section which belongs in Section 8.1: Discontinuation from Study Treatment	To align with the Bristol-Myers Squibb (BMS) Protocol Model Document.
Section 7.6.7: Management of Cytokine Release Syndrome (CRS)	Added a new section regarding management of CRS.	[redacted]
Section 7.10.1: Palliative Local Therapy	Updated wording for Part 2 palliative radiation.	To clarify when participants in part 2 may receive palliative radiation.
Section 7.11 Treatment After the End of the Study	Updated wording regarding treatment after the end of study for participants receiving clinical benefit	To clarify that participants receiving clinical benefit could be treated beyond 3 years after consultation with the Medical Monitor.
Table 9.1.4-1: Laboratory Tests	Removed occult blood stool testing (colorectal cancer [CRC] participants at screening only) and gamma-glutamyl transferase test for all participants. In addition, some laboratory tests are only needed at screening for Part 2.	To remove participant assessments that do not add clinical value.
Section 9.4.1: Imaging Assessment for the Study	Clarified imaging collection during the follow-up period in Part 2 of the study.	To clarify when imaging procedures are required during the follow-up period.
[redacted]		

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 05

Section Number & Title	Description of Change	Brief Rationale
[redacted]		
Section 10.1.3: Part 2	Updated Part 2 statistical section.	To provide additional details regarding primary objective in Part 2.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 05

Section Number & Title	Description of Change	Brief Rationale
[redacted]		
Appendices 1-4	Updated Appendix 1, Appendix 2, Appendix 3, and Appendix 4.	To align with BMS global standards.
Appendix 6: Management Algorithms for Studies Under CTCAE Version 4.0	Appendix 6 was updated.	To align with IB Version 19, Addendum 01, for nivolumab.
Entire document	Additional corrections and editorial or formatting changes, where appropriate.	To provide clarity.

Overall Rationale for Protocol Amendment 04: 23-Nov-2020

Based on interim analysis of Part 1 (as described in BMS-986253 IB version 05, March 2020) the following key revisions to the protocol were made:

The maximum administered dose of BMS-986253 was increased to 3600 mg Q2W (in combination with nivolumab 480 mg Q4W in Cohort 1B6). Based on safety data from Cohorts 1A, and 1B1-1B5, BMS-986253 plus nivolumab was well tolerated at BMS-986253 2400 mg Q2W + nivolumab 480 mg Q4W (Cohort 1B4), and dose-dependent AEs were not identified based on available data. Furthermore, dose and frequency-dependent-free serum IL-8 suppression was observed, with robust suppression at 2400 mg Q2W + nivolumab 480 mg Q4W. Additionally, based on PK/PD modeling, higher doses of BMS-986253 may improve serum IL-8 suppression. For the aforementioned reasons, the maximum administered dose of BMS-986253 in Part 1B will be 3600 mg Q2W (in combination with nivolumab 480 mg Q4W in Cohort 1B6); Cohort 1B6 will include a safety lead-in with 4 participants.

[redacted]

Evaluation of the triplet combination of BMS-986253 plus nivolumab plus ipilimumab was added to the protocol. Combining immunotherapeutic agents with different mechanisms of action offers the possibility of synergistic response. The combination of nivolumab and ipilimumab is approved in several cancers, including RCC, melanoma, NSCLC, and MSI-high CRC. Baseline serum IL-8 levels correlate with prognosis in patients treated with anti-PD-1 therapy, including melanoma patients, treated with a combination of nivolumab and ipilimumab on CA224067. Adding BMS-986253, a fully human mAb against IL-8, to nivolumab plus ipilimumab could improve clinical outcomes.

Change Part 2 from a dose expansion phase to a double-blind, randomized investigation of BMS-986253 plus nivolumab plus ipilimumab versus nivolumab plus ipilimumab in advanced melanoma study. [redacted] There are currently no approved agents for patients with melanoma who have progressed on prior anti-PD-(L)1 therapy. However, based on retrospective analyses and prospective Phase II data on pembrolizumab and ipilimumab in patients who have progressed on anti-PD-1 therapy (NCT02743819), the combination of nivolumab plus ipilimumab (plus placebo) was chosen for the control arm.

In addition, treatment duration was increased from 2 years to 3 years, and some sections were added or updated to align the protocol wording with the most recent Protocol Model Document.

Summary of Key Changes for Protocol Amendment 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 1 Synopsis	Updated to incorporate changes from revision 4	
Section 2 Schedule of Activities	Table 2-1 Modified Prescreening requirements for Part 1 and removed Prescreening requirements for Part 2.	Part 1: Prescreening is required as serum IL-8 levels impact cohort eligibility. Parts 1A and 1B require participants to have a [redacted] to guide PD evaluation and dose selection. Part 1C allows participants with any serum IL-8 level to enroll, since the main goal is to generate safety data for BMS-986253 plus nivolumab plus ipilimumab. Part 2: Prescreening is not required. Participants with any serum IL-8 level may participate to allow for generation of data to support a future patient selection strategy.
	Table 2-2 Added serology for SARS-CoV-2 to required assessments during the screening period Added MRI of the brain for all participants in Part 2	To align with revised objectives and endpoints To rule out evidence of progression for brain metastases
	[redacted]	Table added to align with the current protocol design
	Added Table 2-6 including the required assessments during the treatment period for Part 2 if BMS-986253 Q3W is used.	Table added to align with the current protocol design
	Added Table 2-7 including the required assessments during the treatment period for Part 2 if BMS-986253 Q2W is used.	Table added to align with the current protocol design
	Table 2-8. Added serology for SARS-CoV-2 to required assessments during the follow-up period	To align with revised objectives and endpoints
Section 3 Introduction	Updated introduction to the study	To reflect current study design
Section 3.1 Study Rationale Section 3.2.1 BMS-986253	Added combination of nivolumab and ipilimumab	To reflect current study design
Section 3.2.2 Nivolumab	Updated nivolumab background	Updated to reflect updated latest version of the nivolumab IB.
Section 3.2.3 Ipilimumab	Added section	To provide information of new investigational product added to this study
Section 3.2.4 Nivolumab plus Ipilimumab	Added section	To provide safety information regarding nivolumab plus ipilimumab treatment

Summary of Key Changes for Protocol Amendment 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 3.3 Benefit /Risk Assessment	Updated information for combination BMS-986253 + nivolumab. Added benefit /risk assessment for the combination of BMS-986253 + nivolumab + ipilimumab, and safety profile of ipilimumab monotherapy and modified safety of BMS-986253	To reflect updated study design and safety data presented in latest versions of the BMS-986253, nivolumab and ipilimumab IBs.
Section 4 Table 4-1 Objectives and Endpoints-Part 1	Added the triplet combination to objectives and endpoints and added specific objectives for ipilimumab	To incorporate changes related to the evaluation of the triplet combination of BMS-986253 plus nivolumab plus ipilimumab in Part 1.
Section 4 Table 4-2 Objectives and Endpoints-Part 2	Added and modified objectives and endpoints for double-blinded melanoma participants	To reflect change in Part 2 study design, and add objectives related to SARS-CoV-2.
Section 5.1 Overall Design	Added Cohort 1B6: 3600 mg BMS-986253 Q2W + nivolumab Q4W [redacted] Modified tumor types to be included in Part 1B. [redacted] Added Part 1C (Cohorts 1C1 [redacted] safety evaluation of BMS-986253 plus nivolumab plus ipilimumab Added tumor types allowed to be enrolled in Part 1C Changed Part 2 from a single-arm expansion in multiple tumor types to a double-blind, randomized study in advanced melanoma in participants who have progressed on anti-PD-(L)1 therapy.	Safety was confirmed for 2400 mg [redacted] Q2W + nivo Q4W, and MTD has not been reached. A higher dose of BMS-986253 may offer better serum IL-8 suppression. To allow for ease in scheduling for the triplet combination with ipilimumab and nivolumab, which are given at a Q3W schedule for the first 12 weeks of treatment. Based on preliminary clinical activity from interim analysis of Part 1 data A new triplet combination BMS-986253 plus nivolumab plus ipilimumab will be explored to evaluate the safety and to determine the RP2D for Part 2. To reflect current study design Based on interim analysis of Part 1, there was evidence of early clinical activity in melanoma
[redacted]		

Summary of Key Changes for Protocol Amendment 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Figure 5.1-2 Study Design: Part 1	Updated figure to reflect Part 1 study design	To reflect changes to the study design.
Figure 5.1-3 Study Design: Part 2	Added figure for Part 2	To reflect changes to the study design.
Section 5.1.1 Prescreening Period (applicable for Part 1A only)	Modified Prescreening requirements for Part 1 and removed Prescreening requirements for Part 2.	See Rationale for Table 2-1.
Section 5.1.2 Screening Period	Updated assignment to a Study Part during the screening period	To align with the current study design, as Part 2 is double-blind, randomized study
Section 5.1.3 Treatment Period	Added schedules for study procedures in Cohort [redacted], Part 1C, and Part 2. Increased treatment duration from 2 to 3 years.	To align study with updated study design. To allow participants who continue to derive clinical benefit after 2 years of treatment (CR, PR, SD), to continue treatment for an extra 1 year on study, since BMS-986253 is blocking a cytokine produced by the tumor.
Section 5.1.6 Data Monitoring Committee and Other External Committees	Added independent Data Monitoring Committee in Part 2	Part 2 is double-blinded and an independent Data Monitoring Committee will help to monitor the patient safety while the study team is blinded
[redacted]		
Section 5.4.4 Rationale for Combination of BMS-986253, Ipilimumab, and Nivolumab	New section added	To provide the rationale for triplet combination of BMS-986253, nivolumab, and ipilimumab
Section 5.4.5 Rationale for Testing Different Doses in Parallel in Part 1	Modified section to include Part 1C	To reflect the current study design.
Section 5.4.8 Rationale for Treatment of Post-PD-(L)1 Melanoma in Part 2	Added section	To reflect the current study design
Section 5.4.9 Rationale for Stratification in Part 2	Added section	To reflect the current study design

Summary of Key Changes for Protocol Amendment 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.5.2 Rationale for Part 1B Dosing Schedules and Maximum Administered Dose	Updated and renamed section "Rationale for assessing Q2W dosing" [redacted]	To align with the current study design and provide rationale for BMS-986253 MAD and schedules.
Section 5.5.4 Rationale for Nivolumab Dose Selection	Updated and renamed section from "Rationale for Nivolumab 30-minute infusion"	To align with the current study design and provide rationale for nivolumab dose selection. Nivolumab is approved to be administered for 30 min, for all doses used on study.
Section 5.5.5 Rationale for Ipilimumab Dose Selection	Added section	To reflect the current study design
Section 6.1 Inclusion Criteria	Modified inclusion criterion to remove tumor types in Part 2 (to include melanoma only) and add tumor types (HCC and CRC) to Part 1C. 2c i) Modified criteria so that NSCLC cannot be enrolled in Cohorts 1B6 and [redacted] 2c v) Removed criteria for triple negative breast cancer 2c vi) Modified criteria for CRC, which will be included in Part 1C (originally in Part 2) 2c vii) Removed criteria for pancreatic ductal adenocarcinoma 2c viii) Modified criteria for HCC, which will be included in Part 1C (originally in Part 2) 2c xii) Added information for Melanoma Part 2 inclusion criteria	To align the type of participant and target disease characteristics with the current study design
	3a. Modified criteria to so that only participants in Parts 1A and 1B are required to have baseline [redacted]	To reflect study design changes -- see above (Prescreening changes)
Section 6.2 Exclusion Criteria	1b. Added that participants with leptomeningeal metastases will be excluded. 3g and 3h. Added SARS-CoV-2 language regarding receipt of a SARS-CoV-2 vaccine within 14 days of C1D1 and participants with SARS-CoV-2 infection at baseline.	To clarify exclusion criteria around CNS metastases To exclude participants who have previously received a SARS-CoV-2 vaccine within 14 days of C1D1 and participants with prior SARS-CoV-2 infection, symptoms must have completely resolved and based on investigator assessment in consultation with the clinical trial physician, there are no

Summary of Key Changes for Protocol Amendment 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
	3e. Clarified wording for participants requiring adrenal replacement steroid treatment 3e v) 3) Modified exclusion criteria for HCC	sequelae that would place the participant at a higher risk of receiving investigational treatment. To allow participants using adrenal replacement steroid doses > 10 mg daily prednisone equivalent in the absence of active autoimmune disease To align the type of participant and target disease characteristics with the current study design
Section 6.4.1 Restesting During Screening or Lead-In Period	Added language for SARS-CoV-2 infection	To allow for participants to be rescreened if they develop suspected or confirmed symptomatic SARS-CoV-2 infection
Section 7.1 Treatments Administered	Added ipilimumab and placebo [redacted] sodium chloride for injection or [redacted] dextrose for injection) to treatments and updated BMS-986253 and nivolumab product descriptions	To reflect the current study design
Section 7.2 Handling and Dispensing	Added information on how to handle/dispense/infuse placebo	To reflect the current study design
Section 7.3 Schedule of Dose for Each Investigational Product	Added treatment sequence and administration time for each study part. Updated Table 7.3-1 Dose, Frequency, Infusion, Time and Sequence of IPs	To reflect the current study design
Section 7.4 Method of Treatment Assignment	Added information for Part 1C and Part 2 [redacted]	To reflect the current study design To facilitate the parallel enrolment in Part 1
Section 7.5 Blinding	Added Part 2 blinding information	To reflect the current study design
Section 7.6. Dose Modification	Added ipilimumab	To reflect the current study design
Section 7.6.1 Dose-limiting Toxicities	Clarified discontinuation due to dose-limiting toxicities	To reflect the current study design
Section 7.6.3 Dose Delays Due to Toxicities	Added information regarding toxicity reevaluation and tumor assessment during delays due to toxicities	To clarify assessments and reevaluation of toxicity during dose delays due to toxicities
Section 7.6.4 Criteria to Resume Treatment	Added information regarding criteria for resuming treatment Added guidance for resuming treatment after COVID-19 infection	To clarify the criteria for resuming treatment Addition of standard language for BMS protocol due to COVID-19

Summary of Key Changes for Protocol Amendment 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 7.6.6 Management of Drug-related Infusion Reactions	Added ipilimumab.	To reflect the current study design
Section 8.1 Discontinuation from Study Treatment	Updated required language and added specific information related to the study	This section was updated to align with the most recent Protocol Model Document and to reflect the current study design
Section 8.2 Discontinuation from the Study	Updated section	This section was updated to align with the most recent Protocol Model Document
Section 9.2.2 Method of Detecting AEs and SAEs	Deleted sentence "In order to prevent reporting bias, participants should not be questioned regarding the specific occurrence of one or more AEs"	This section was updated to align with the most recent Protocol Model Document
Section 9.3 Overdose	Added ipilimumab	To reflect current study design
Section 9.4 Efficacy Assessments	Added combination nivolumab and ipilimumab	To reflect current study design
Section 9.4.1 Imaging Assessment for the Study	Specified how to handle unscheduled CT/MRI images	To aid in assessment of efficacy
Section 9.4.2 BICR Confirmation of Progression (Part 2)	Added section	To aid in assessment of efficacy in Part 2
Section 9.5 Pharmacokinetics and Immunogenicity Assessments	[redacted]	To reflect the current study design for PK and immunogenicity assessments
Section 9.8.1 Serum IL-8 Levels for Participant Selection	Updated serum IL-8 requirements for Parts 1 and 2 [redacted]	To reflect the current study design for biomarker samples. Minimize procedures for participants

[redacted]

Summary of Key Changes for Protocol Amendment 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 10.1 Sample Size Determination	Divided into Subsection 10.1.1, for Parts 1A and 1B, Subsection 10.1.2, for Part 1C, and Subsection 10.1.3, for Part 2 Added sample size justification for Part 1C, and changed sample size justification for Part 2	To reflect the current study design
Section 10.3.1 Efficacy Analyses	Added Table 10.3.1-2: Part 2 Efficacy Analysis	To align primary endpoint efficacy analysis with the current study design
[redacted]		

Overall Rationale for Revised Protocol 03: 10-Jul-2019

The purpose of this revised protocol is to expand enrollment in Part 1 to allow further assessment of pharmacodynamic changes in the tumor microenvironment at a specific dosing regimen, if warranted. The maximum number of treated participants in Part 1 was increased from approximately [redacted] The presentation of the objectives and endpoints have been changed [redacted] Lastly, inclusion criteria for participants within Part 1 have been modified. The tumor types in Part 1 have not changed; however, modifications of the inclusion criteria define a more homogeneous population within those tumor types (restricted to participants who progressed on or within 3 months of anti-PD[L]1-based therapy) to aid in additional pharmacodynamic analysis. The synopsis has been updated to reflect the changes below and minor typographical and formatting errors have been corrected.

Summary of Key Changes for Revised Protocol 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 2 Schedule of Activities	Table 2-2: Updated instructions for HPV testing; Added stool collection to schedule of assessments.	To clarify acceptable methods for establishing HPV status in participants with oropharyngeal squamous cell carcinoma of the head and neck (SCCHN) To clarify screening schedule for stool sample collection
Section 2 Schedule of Activities	Table 2-3: Notes on ECG testing now refer to C1D1 and C4D1. Added EOT pregnancy test to schedule of assessments	To clarify instructions for PK time-matched ECGs To add EOT pregnancy testing
Section 2 Schedule of Activities	Table 2-4: Notes on ECG testing now refer to C1D1 and C4D1.	To clarify instructions for PK time-matched ECGs.
Section 3-3 Benefit/Risk Assessment	The following text added: Based on preliminary safety data from this study presented in the BMS-986253 IB, an increase in immune mediated adverse reactions with the combination of BMS-986253 and nivolumab compared with nivolumab monotherapy is not expected.	To reflect updated safety data presented in latest version of the IB.
Section 4 Objectives and Endpoints	Objectives and endpoints for Part 1 and Part 2 are presented in separate tables.	[redacted] OBJECTIVES HAVE NOT BEEN CHANGED; only the presentation is altered.

Summary of Key Changes for Revised Protocol 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.1 Overall Design	Added dose levels of BMS-986253 for Cohorts B4 and B5; Added the following text: Additional exploration of a specific dosing regimen may be warranted, in which case a maximum of approximately [redacted] additional participants will be assigned to a dosing regimen of interest in Part 1B. A maximum of approximately [redacted] participants will be dosed in Part 1. Updated study design figure to include Cohorts B4, B5, and B6. Updated figure caption to include potential pharmacodynamic dosing group and safety lead-in for 2400 mg BMS-986253 Q2W + Nivo 480 mg Q4W dosing regimen.	Dose levels for Cohorts B4 and B5 have been identified and so were added to the protocol. Other changes made to reflect changes to the study design.
Section 5.2 Number of Participants	Number of participants updated	To reflect addition of patients for pharmacodynamic assessment
Section 5.4.5 Rationale for Assessing Q2W Dosing	New section added.	To provide a rationale for Q24 dosing [redacted]
Section 6.1 Inclusion Criteria	Criterion 2.a i has been added	To clarify criteria for selecting target lesions for inclusion
Section 6.1 Inclusion Criteria	Changes to IC criteria for NSCLC participants: IC 2 c i (6) and IC 2 c i (8) removed IC 2 c i (9) added.	To further refine eligibility criteria based on baseline disease characteristics and previous treatment with anti-cancer therapies.
Section 6.1 Inclusion Criteria	Changes to IC criteria for renal cell carcinoma participants: IC 2 c ii (2) and IC 2 c ii (4) removed IC 2 c ii (5) added.	To further refine eligibility criteria based on baseline disease characteristics and previous treatment with anti-cancer therapies.
Section 6.1 Inclusion Criteria	Changes to IC criteria melanoma participants: IC 2 c iii (1) a added IC 2 c iii (3) removed IC 2 c iii (5) added.	To further refine eligibility criteria based on baseline disease characteristics and previous treatment with anti-cancer therapies.
Section 6.1 Inclusion Criteria	Changes to IC criteria for urothelial carcinoma participants: IC 2 c x (5) removed IC 2 c x (6) added.	To further refine eligibility criteria based on baseline disease characteristics and previous treatment with anti-cancer therapies.

Summary of Key Changes for Revised Protocol 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 6.1 Inclusion Criteria	Changes to IC criteria SCCHN participants: IC 2 c xi (5) modified IC 2 c xi (6) removed IC 2 c xi (7) added.	To further refine eligibility criteria based on baseline disease characteristics and previous treatment with anti-cancer therapies.
Section 6.1 Inclusion Criteria	IC 4 f: The following text added: In addition, male participants must be willing to refrain from sperm donation during this time	[redacted]
Section 6.1 Inclusion Criteria	IC 4 g removed	Duplicate text
Section 6.2 Exclusion Criteria	EC 5 a: The following text (**bolded**) added: Note: under certain specific circumstances **and only in countries where local regulation permit** a person who has been imprisoned may be included or permitted to continue as a participant.	To align with BMS global standards
Section 7.3 Schedule of Dose for Each Investigational Product	The following text added: For both nivolumab and BMS-986253, participants may be dosed within a ±2 day window. Premedications are not recommended.	To clarify minimum dosing interval for nivolumab and BMS-986253
Section 7.4 Method of Treatment Assignment	Number of subjects updated and rationale for additional participants for pharmacodynamic assessment added	To align with changes in study design
Section 9.1.3	The following text added (**bold**): All ECG tests will be performed in triplicate for Cycles 1 and 4 (ie, 1 ECG test equals 3 consecutive individual 12 lead ECGs performed **at least 5 minutes apart**).	To clarify ECG collection on Cycles 1 and 4
Section 8.2.1 Study Termination	The following text added: BMS reserves the right to terminate the study at any time for reasons including but not limited to the following: safety concerns, termination of drug development, lack of efficacy, and lack of meeting study objectives/endpoints	[redacted]
Section 9.5 Pharmacokinetics and Immunogenicity Assessments	Footnotes [redacted] updated	To clarify instructions for end-of-infusion sample collection
Section 9.8 Biomarkers	Table 9.8-1 updated	To clarify pretreatment sample collection

Summary of Key Changes for Revised Protocol 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 9.8.5 Methods to detect HPV status of SCCHN originating in the Oropharynx	New section added	To clarify acceptable methods for establishing HPV status in participants with oropharyngeal squamous cell carcinoma of the head and neck (SCCHN)
Section 10.1 Sample Size Determination	Sample size updated; rationale for sample size of pharmacodynamic assessment group added.	To support potential additional participants for pharmacodynamic assessment
Appendix 2	Updated definition of serious breach	To align with BMS global standards

Overall Rationale for Revised Protocol 02: 02-Nov-2018

There are several reasons for this protocol revision. The study design is being modified for participants enrolling in Part 1B to provide flexibility to explore additional dosing regimens. In addition, we would like to clarify and amend procedures related to collection of SAEs during the Pre-Screen Period. All participants will be entered into IRT and receive a unique subject ID after signing the Pre-Screen ICF. SAEs related to the pre-screen blood draw will be collected and followed until resolution or stabilization. The inclusion criteria are also being modified to allow certain PD-(L)1 naive participants with NSCLC, RCC, SCCHN, and UCC into the study. Lastly, we would like to include guidance on palliative treatments that occur during the study period.

Summary of key changes for Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Synopsis	• Text in Synopsis updated	Synopsis was updated to reflect the changes made in the protocol
Section 2 Schedule of Activities; Section 5 Study Design;	• New "Table 2-1 - Prescreening Procedural Outline (All Study Phases)" and "Section 5.1.1 Pre-Screening Period" have been added for Pre-screening visits. • All the preceding tables in Section 2 have new numbering due to addition of this Table 2-1. • Table 2-2 - Screening Procedural Outline: – Procedures (Informed Consent, IRT [redacted]) have been re-arranged in the table. – IL-8 serum procedure has been removed from the Screening table as it is now listed under Table 2-1 Prescreening Procedural. – Notes section under human papillomavirus status of tumor for SCCHN of the oropharynx has been updated. • All the preceding sections in Section 5 have new numbering due to addition of this new Section 5.1.1.	To clarify and update Pre-Screening Procedures.
Section 2, Schedule of Activities	• On-treatment Procedural Outline table is now presented in two separate tables as listed below: • Table 2-3 On-treatment Procedural Outline (BMS-986253 Q4W and Nivolumab Q4W) • Table 2-4 On-treatment Procedural Outline (BMS-986253 Q2W and Nivolumab Q4W)	Based on safety, PD, and PK data evaluation, we may explore additional dosing regimens for BMS-986253. Time points were changed to accommodate exploration of Q2W dosing of BMS-986253.

Summary of key changes for Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 2, Schedule of Activities; Table 2-5 Safety Follow-Up Procedural Outline	• Pharmacokinetic Assessments has been added under Procedure.	To clarify procedures
Section 3.1 Study Rationale; Section 5.1.4 Window Visits; Section 7.4 Method of Treatment Assignment; Section 9.1.4 Clinical Safety Laboratory Assessments; Section 10.3.5 Biomarker Analyses	• Clarifying details have been added in these sections and text has been updated	Clarification of text
Section 5.1, Overall Design; Section 10.1, Sample Size Determination	• Clarifying details have been added and text has been updated under overall design for participants enrolling in Part 1B. The study design schema has been updated to reflect the change.	Based on review of safety, PD, and PK data we may close current treatment arms and/or explore additional dosing regimens for BMS-986253
• Section 5.1.3 Treatment Period; • Table 2-3 On-treatment Procedural Outline (BMS-986253 Q4W and Nivolumab Q4W); • Table 2-4 On-treatment Procedural Outline (BMS-986253 Q2W and Nivolumab Q4W); • Section 9.8.2.1.3 Tumor-Based Biomarkers	• Sections and tables have been updated to modify [redacted] to be collected at 5 weeks (± 3 days) at Cycle 2 Day 8 (± 3 days) after first dose.	Based on safety, PD, and PK data evaluation, we may explore additional dosing regimens for BMS-986253. Time points were changed to accommodate exploration of Q2W dosing of BMS-986253
Section 5.2 Number of Participants; Section 10.1 Sample Size Determination	• Total number of participants have been updated [redacted] as the number of participants for Part 1 (dose-finding phase) are now [redacted]	Based on review of safety, PD, and PK data we may close current treatment arms and/or explore additional dosing regimens for BMS-986253
Section 5.5.2, Rationale for Dose Selection and Dosing Schedule	• Text for Part 1B table-note has been updated.	Based on review of safety, PD, and PK data we may close current treatment arms and/or explore additional dosing regimens for BMS-986253

Summary of key changes for Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 6.1 Inclusion Criteria	• Criteria 2) c) i) (2), 2) c) i) (4), 2) c) ii) (1), 2) c) iv), 2) c) x) (2), and 2) c) xi) (2) are not applicable after implementation of this revised protocol 02 and ***"Not applicable as per revised protocol 02"*** has been added in the beginning of each listed criteria.	Inclusion criteria are expanding to include specific IO naive populations
	• Criteria 2) c) has been modified as below: • "The following tumor histologies will be permitted except for participants with **CNS metastases as the only site of active disease. All participants must have received, and then progressed, relapsed, or been intolerant to at least 1 standard treatment regimen in the advanced or metastatic setting according to tumor type. Part 1 will include patients with NSCLC, RCC, melanoma, HNSCC, and UCC. Part 2 will include patients with NSCLC, RCC, melanoma, TNBC, colorectal cancer, HCC, and PDAC**".	The phrase in the bold was added as a clarification of text
	• Criteria 2) c) i) (5) has been modified as below: 1) "Epidermal growth factor receptor **(EGFR),** anaplastic lymphoma kinase **(ALK), and ROS1 mutational status must be known for patients with lung adenocarcinoma."**	
	• New eligibility criteria under NSCLC, RCC, UCC, and SCCHN have been added as listed below: • NSCLC: Criteria 2) c) i) (6), 2) c) i) (7), 2) c) i) (8), • RCC: Criteria 2) c) ii) (3), 2) c) ii) (4), • UCC: Criteria 2) c) x) (5), • SCCHN: Criteria 2) c) xi) (6)	Inclusion criteria are expanding to include specific IO naive populations
	• Criteria 2) c) iii) (3) has been modified as below: 2) "Must have had radiologically documented progressive or recurrent disease either during or after completion of anti-PD-(L)1 **therapy (administered** as monotherapy or **as part** of a combination). No more than one	The phrase in the bold was added as a clarification of text

Summary of key changes for Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
	intervening systemic therapy is permitted between anti-PD-(L)1 treatment and enrollment on this trial."	
	• Criteria 2) c) vii) (2) has been modified as below: 3) "Participants must have received and progressed **on or** been intolerant to (not candidates for) **at least 1 line** of standard of care **treatment**."	
	• Criteria 2) c) viii) (1) has been modified as below: 4) **"Participants cannot be** eligible for liver transplant at the time of inclusion. For participants who progressed after locoregional therapy, locoregional therapy for HCC must be completed at least 4 weeks prior to the baseline scan. All acute toxic effects of any prior local treatment must have resolved to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03 Grade > 1 or been deemed irreversible."	
	• Criteria 2) c) viii) (2) has been modified as below: 5) "**Participants may either have histologically or radiologically confirmed HCC**. **Participants with** a radiological diagnosis may be enrolled for screening in the study but histological confirmation is mandatory prior to initiation of study therapy."	
	• Criteria 4) g) has been modified to remove "Azoospermic males are exempt from contraceptive requirements".	This modification was made since sperm counts are not performed on this study.
Section 6.2 Exclusion Criteria; Section 7.9.1 Prohibited and/or Restricted Treatments	• Criteria 3) e) ix) has been modified as below: 6) "Receipt of a live/attenuated vaccine within 30 days of first treatment." 7) Additional bullet 4 has been added.	The modification was made to comply with the current BMS standards for studies using nivolumab. This restriction is based on theoretical risk of adverse effects for nivolumab and not on clinical or safety data. The administration of live vaccines is contraindicated in patients receiving BMS-986253 treatment.

Summary of key changes for Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 7.1 Treatment Administered	• Table 7.1-1 has been updated for additional potency for BMS-986253 100 mg/mL.	This has been modified due to a change in drug supply.
Section 7.3 Schedule of Dose for Each Investigational Product	• Clarifying details about infusion of BMS-986253 administered at Q2W have been added and Table 7.3-1 has been updated with these details. • Additional table-note has been added explaining infusion time for 2,400 mg BMS-986253.	[redacted] we may explore additional dosing regimens for BMS-986253.
Section 7.5 Blinding	Text in this section has been revised and clarification about access to IRT treatment codes has been added.	To meet new BMS standards on randomization and blinding
[redacted]		
Section 7.10.1 Palliative Local Therapy	New section added	To add guidelines for palliative therapy during the study
Section 9.2.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information	Text under this section has been modified and clarifying details about collecting serious adverse events after the participant sign the pre-screen ICF and the main ICF has been updated.	We are now going to collect related SAEs from Pre-Screening, and follow them until resolution. These related SAEs will now be collected electronically per new guidelines.
Section 9.4.1 Imaging Assessment for the Study; Table 2-2 Screening Procedural Outline; • Table 2-3 On-treatment Procedural Outline (BMS-986253 Q4W and Nivolumab Q4W); • Table 2-4 On-treatment Procedural Outline (BMS-986253 Q2W and Nivolumab Q4W); Table 2-5 Safety Follow-Up Procedural Outline	• Text has been modified to update the period for acquiring images to 28 days. • Text under Section 9.4.1 and within Tables 2-2 through 2-5 have been revised to align across these sections.	Update in section 9.4 was to correct an error in the text. All other changes were made to reflect changes in study design.

Summary of key changes for Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 9.5 Pharmacokinetics and Immunogenicity Assessments	• The text in this section has been modified by adding clarifying details for collection of pharmacokinetics and immunogenicity assessment data from participants enrolled in the study. Additional time points have been added to [redacted] • Title for subsection 9.5.1 was removed as Section 9.5 title already contains "Immunogenicity".	Updates were made to reflect change of collection from C3 to C4 to better characterize BMS-986253 exposure at steady state.
Section 9.8 Biomarkers	[redacted]	Updates were made to reflect changes in study design, and so biomarker collection correlates with imaging
Section 9.8.2.1.2 Whole blood Gene Expression	• New section has been added	We may use gene expression data to assess changes in immune cells in the blood.
Section 10.3 Statistical Analysis; Appendix 3: Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow Up and Reporting; Appendix 6 Management Algorithms	• Text under section 10.3 and appendices have been updated	Updates were made to align with the recent BMS protocol model document
Appendix 4 Women of Childbearing Potential Definitions and Methods of Contraception	Text under "Contraception Guidance for Female Participants of Child Bearing Potential" for relevant systemic exposure for female participants has been corrected to 5 months.	The update was made to correct a typographical error regarding number of months in the previous protocol version.
Appendix 11 Country Specific Amendment	New appendix added	Appendix was added to specify HIV country-specific requirements for Germany.
All	Minor formatting and typographical corrections	Minor, therefore have not been summarized

Overall Rationale for the Revised Protocol 01, 13-Mar-2018

The primary reasons for these changes are to expand enrollment in Part 1 to include advanced Squamous cell carcinoma of the head and Neck (SCCHN) and Urothelial cancer (UCC) participants, modify eligibility criteria for participants with NSCLC, RCC, TNBC, HCC, CRC, and modify the sampling schedule for pharmacodynamic assessment. Additional revisions have been made to align the protocol with respect to these changes. . Additionally, the revised protocol incorporates Administrative Letters 01 and 02 which correct typographical errors in the numbering of inclusion and exclusion criteria.

Summary of key changes of Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Synopsis	Synopsis was updated	Synopsis was updated to reflect the changes made in the protocol
Section 2, Table 2-1 Screening Procedural Outline	[redacted]	
	Body imaging added to Tumor Type Assessment along with details in notes section for participant with SCCHN, HCC and TNBC.	Alignment with standard Imaging protocol language. Indication specific imaging added for SCCHN, HCC, and TNBC
	Notes section was updated for IL-8 Serum	Clarification to the requirement of a prescreening test for serum IL-8 to determine eligibility
	Laboratory test for human papillomavirus status of tumor for SCCHN of the oropharynx was added	Inclusion of SCCHN and requirement to determine HPV status for stratification purpose.
Section 2, Table 2-2 On-treatment Procedural Outline	Eastern Cooperative Oncology Group (ECOG) Performance Status was added on Day 1 of each cycle	The test was unintentionally omitted from the On-treatment study table. ECOG is used to monitor a participant's daily living abilities and is important to assess while on treatment.
	[redacted]	
	Revised the ECG notes column to indicate when time matched ECGs are to be taken in Part 1 and Part 2 of the study	The notes column was updated to clarify during which cycles time matched ECGs are taken in Part 1 of the study and to clarify ECGs are taken only pre-dose in Part 2 of the study
	Weight collection was added	Required but accidentally omitted in the previous version.

Summary of key changes of Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
	A clarifying note was added to the notes column for Vital Signs and Oxygen Saturations	The notes column was updated to clarify that post-dose vital signs are required after BMS 986253 dosing AND after Nivolumab dosing
	Tumor Imaging changed to Body Imaging and additional details on CT/MRI scan locations. Additional details for participant with SCCHN, HCC and TNBC were added	Alignment with standard Imaging protocol language. Indication specific imaging added for SCCHN, HCC, and TNBC
Section 2, Table 2-3 Safety Follow-up Procedural Outline	Tumor Imaging changed to Body Imaging. Additional details for participants with SCCHN, HCC and TNBC were added	Alignment with standard Imaging protocol language. Indication specific imaging added for SCCHN, HCC, and TNBC
Section 2, Table 2-3 Safety Follow-up Procedural Outline and Section 5.1 Overall Design	Clarifying note was added to Assessment of Participant Survival Status regarding time frame and length of follow up.	The notes column was updated to include a specific time frame of every 12 weeks for 2 years for participant survival status.
Section 4, Table 4-1 Objectives and Endpoints	[redacted]	[redacted]
	ORR, mDOR, and PFSR [redacted] by BICR was added as an endpoint	
Section 5.1 Overall Design [redacted]	Limit of quantitation (LLOQ) of IL-8 defined [redacted]	Precision to the definition of Serum IL-8 level for the eligibility in the study.
Section 5.1.2 Treatment period	[redacted]	
Section 5.1.2 Treatment period and Section 9.8, Table 9.8.1-1	Added collection of stool sample during screening, on treatment and at progression	To explore the potential effect of the gut microbiome to the therapy.
Section 6.1 Inclusion Criteria	Clarifying detail added for prior therapy to include standard of care chemotherapy for non-small cell lung carcinoma, renal cell carcinoma, triple negative breast cancer, colorectal cancer and pancreatic ductal adenocarcinoma.	To resolve discrepancies of inclusion criteria with the current standard therapies.

Summary of key changes of Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
	For patients with melanoma criteria change to include no more than one intervening systemic therapy is permitted between anti-PD-(L)1 treatment and enrollment on this trial.	To resolve discrepancies of inclusion criteria with the current standard therapies.
Applicable in section 6.1 Inclusion criteria and throughout	Permitted tumor histologies was updated to include urothelial carcinoma and squamous cell carcinoma head and neck	Adding tumor type to explore the role of IL-8 in post-PD1 resistance
Section 7.9.2 7.9.2 Other Restrictions and Precautions	Corrected the allowed dose of inhaled, topical and adrenal replacement steroids from > 10 mg to ≤ 10 mg	To correct a typographical error regarding the allowed steroid dose
Section 8.1.1 Treatment Beyond Progression	Additional information regarding required re-consent with an ICF to continue treatment beyond progression was added	Alignment with standard protocol template language
Section 8.1.1.1 Discontinuation Due to Further Progression	This section was removed and the information added to section 8.1.1	To reduce repetition
Section 9.1.4, Table 9.1.4-1 Laboratory Tests	Added alanine aminotransferase (ALT) to the list of laboratory tests	ALT was mistakenly omitted from the original protocol and should be included
Section 9.4 Efficacy Assessments	Additional detail provided about change in tumor response and measurement will be assessed using RECIST v1.1 criteria. [redacted]	To clarify that RECIST v1.1 is to be performed by the Investigator [redacted]
Section 9.4.1 Imaging Assessment for the Study	Clarifying information added for time frame to acquire images	To ensure accuracy
[redacted]		
Section 9.8 Biomarkers	Clarifying details added to biomarkers description	To ensure accuracy with the clinical plan
[redacted]		
Appendix # 4	Relevant systemic exposure for male participants updated to 7 months	To correct a typographical error regarding number of months

Summary of key changes of Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Appendix # 7	Appendix 07 was updated.	Fixed incorrect dose that was presented in the graph. Corrected graph and corresponding table were presented.
Appendix # 8	Appendix 8 was updated	Appendix was updated to include RECIST criteria with BMS modifications
All	Minor formatting and typographical corrections	Minor, therefore have not been summarized