Official Title of Study:

A Phase 3, Open Label, Randomized, Non-Inferiority Pharmacokinetic Study of Nivolumab Subcutaneous (Nivo SC) Versus Intravenous (Nivo IV) Administration in Participants With Stage IIIA/B/C/D or Stage IV Adjuvant Melanoma Following Complete Resection

NCT Number: NCT05297565

Document Date (Date in which document was last revised): 25 May 2023

CLINICAL PROTOCOL CA2096GE

A Phase 3, Open Label, Randomized, Non-Inferiority Pharmacokinetic Study of Nivolumab Subcutaneous (Nivo SC) Versus Intravenous (Nivo IV) Administration in Participants with Stage IIIA/B/C/D or Stage IV Adjuvant Melanoma Following Complete Resection

(CheckMate-6GE: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 6GE)

Brief Title:
A Pharmacokinetic Study of Nivolumab Subcutaneous vs Intravenous Administration in Participants with Stage IIIA/B/C/D or Stage IV Melanoma Following Complete Resection

Protocol Amendment 01
Incorporates Administrative Letters 01, 02, and 03

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IND: 150,904
EudraCT/EU Trial Number: 2021-003208-42
UTN: U1111-1266-6116

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Protocol Amendment 01	25-May-2023	• Bristol-Myers Squibb has made a strategic decision to terminate the CA2096GE trial. This decision was not related to any safety concerns. Study recruitment has closed and treatment of ongoing, active participants will continue per Protocol Amendment 01. Changes implemented in this amendment aim to alleviate participant and site burden and include updates to sample collection, study procedures, and study design. • Pharmacokinetic (PK) co-primary endpoints, and secondary endpoints have been removed. Efficacy, patient-reported outcomes (PROs), and biomarker analyses will not be completed. Samples already collected for PK and immunogenicity assessments will be analyzed bioanalytically for nivolumab concentrations and anti-drug antibodies (ADAs) and reported as listings. Further collections for PK, ADAs, biomarkers, and PROs will be discontinued. Only safety assessments will be conducted. • [redacted] • Balanced the frequency of clinic visits between treatment arms. • [redacted]
[redacted]		
Original Protocol	30-Sep-2021	N/A

OVERALL RATIONALE FOR GLOBAL PROTOCOL AMENDMENT 01:

Bristol-Myers Squibb (BMS) has made a strategic decision to terminate the CA2096GE trial. This decision was not related to any safety concerns. Study recruitment has closed; treatment and follow-up of ongoing active participants will continue per Protocol Amendment 01. Changes implemented in this amendment aim to alleviate participant and site burden and include updates to sample collection, study procedures, and study design.

Pharmacokinetic (PK) co-primary endpoints, and secondary endpoints have been removed. Efficacy, patient-reported outcomes (PROs), and biomarker analyses will not be completed. Samples already collected for PK and immunogenicity assessments will be analyzed bioanalytically for nivolumab concentrations and anti-drug antibodies (ADAs) and reported as listings. Further collections for PK, ADAs, biomarkers, and PROs will be discontinued. Only safety assessments will be conducted.

[redacted]

Changes were made to balance the frequency of clinic visits between Part 1 Arm A and Part 1 Arm B. Participants in Part 1 Arm A will now have assessments in the clinic every 4 weeks (Q4W), beginning on Cycle 5, Day 1.

[redacted]

[redacted]

Other edits were made throughout the protocol to fix minor errors, add clarity, and improve consistency and alignment. The Summary was updated to reflect changes in the amendment.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 01

Section Number & Title	Description of Change	Brief Rationale
Title Page	Updated title.	Per Administrative Letter 02.
Table 2-1: Screening Procedural Outline (CA2096GE) [redacted] Table 2-2: On Study Treatment Procedural Outline (Arm A) [redacted] (CA2096GE) Table 2-3: On Study Treatment Procedural Outline (Arm B) (Nivo IV) (CA2096GE) [redacted] Section 3.1.1: Research Hypotheses Table 4-1: Objectives & Endpoints Section 5.1: Overall Design	• Marked as not applicable per Protocol Amendment 01. [redacted] • Removed PK, efficacy, PRO, IMG, and biomarker analyses.	To reflect study procedures that are no longer applicable due to trial termination.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 01

Section Number & Title	Description of Change	Brief Rationale
Section 5.1.1: Screening Period [redacted] [redacted] Section 5.4.2: Rationale for Part 1 Endpoints and Non-Inferiority Margin [redacted] Section 5.4.6: Rationale for Inclusion of Clinical Outcome Assessments/PROs (Part 1) [redacted] Section 6.1: Inclusion Criteria Section 6.2: Exclusion Criteria [redacted] Section 6.4: Screen Failures Table 7.1-1: Study Interventions Section 8.1.2: Post-study Intervention Study Follow-up Section 9.1.4.1: FACT-G7 (Part 1 Only) Section 9.1.4.2: EQ-5D-5L (Part 1 Only) Section 9.1.4.3: Modified CTSQ (Part 1 Only) Section 9.1.4.4: Modified TASQ (Part 1 Only) Section 9.1.4.5: SIAQ (Part 1 Only) [redacted] Section 9.5: Pharmacokinetics Section 9.5.1: Pharmacokinetics and Anti-Drug Antibody Sample Collection and Processing Section 9.8: Biomarkers Section 9.9: Additional Research Section 9.11: Health Economics OR Medical Resource Utilization and Health Economics Section 10: Statistical Considerations Section 10.1: Statistical Hypotheses [redacted] Section 10.4.2.1: Part 1 PK Co-Primary Endpoints [redacted] Section 10.4.3: Secondary Endpoint(s) Section 10.4.6.1: Exposure-Response Analyses Section 10.4.6.2: Immunogenicity Analyses Section 10.4.6.3: Outcomes Research		

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 10.4.6.4: Biomarkers Section 10.4.7.1: Part 1 [redacted]		
Table 2-2: On Study Treatment Procedural Outline (Arm A) [redacted] (CA2096GE)	[redacted]	To balance the frequency of physical examinations.
Table 2-2: On Study Treatment Procedural Outline (Arm A) [redacted] (CA2096GE) Section 5.1.2.1: Randomized Study Cohort	[redacted]	To provide clarification.
Table 2-2: On Study Treatment Procedural Outline (Arm A) [redacted] (CA2096GE) Table 2-3: On Study Treatment Procedural Outline (Arm B) (Nivo IV) (CA2096GE) Table 2-5: Follow-up Assessments (CA2096GE) Section 9.1.1: Efficacy Assessment for the Study Section 9.1.2: Imaging Assessment for the Study Section 9.1.3.1: Investigator Assessment of Recurrence	Updated details about frequency of imaging, body parts to undergo imaging, and requirements of imaging.	To ensure consistency with updates made throughout the protocol.
Table 2-2: On Study Treatment Procedural Outline (Arm A) [redacted] (CA2096GE) Section 7.4.5.1: Systemic Reactions Occurring In-clinic	[redacted]	To provide additional safety guidance.
Table 2-2: On Study Treatment Procedural Outline (Arm A) [redacted] (CA2096GE) Section 5.1: Overall Design Section 5.1.2: Treatment Period Section 5.1.2.1: Randomized Study Cohort Section 9.2.5: Pregnancy [redacted]	[redacted]	[redacted]

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-2: On Study Treatment Procedural Outline (Arm A) [redacted] (CA2096GE)	• [redacted] • Updated table notes to provide more details about procedures. • [redacted] • Removed "infusion"-related adverse events (AEs). • [redacted] •	To provide consistency with updates made throughout the protocol.
Table 2-2: On Study Treatment Procedural Outline (Arm A) [redacted] (CA2096GE) Table 2-3: On Study Treatment Procedural Outline (Arm B) (Nivo IV) (CA2096GE) Table 2-5: Follow-up Assessments (CA2096GE)	• Deleted "Targeted" from physical examination • Deleted references to [redacted] • Added "Physical examination, including targeted physical examination for detection of disease recurrence."	To clarify that target physical examination refers specifically to detection of disease recurrence. [redacted]
Table 2-3: On Study Treatment Procedural Outline (Arm B) (Nivo IV) (CA2096GE)	• Updated footnote a.	To provide clarification and consistency with updates made throughout the protocol.
Table 2-5: Follow-up Assessments (CA2096GE) Section 5.1.3: Follow-Up Period Section 5.3: End of Study Definition Section 8.1.2: Post-study Intervention Study Follow-up	Removed Survival Follow-up.	Due to trial termination, survival follow-up has been removed to alleviate participant and site burden.
Table 2-5: Follow-up Assessments (CA2096GE) Section 3.3.3: Nivolumab Overall Benefit/Risk Conclusion Section 9.2: Adverse Events	[redacted]	[redacted]
Section 3: Introduction	[redacted]	To reflect the strategy of the Sponsor to terminate the study.
Section 3.1: Study Rationale	Added overall rationale for Protocol Amendment 01.	To describe the decision to terminate the CA2096GE trial.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
	Deleted language that states Arm A versus Arm B will be subjected to statistical hypothesis testing.	It is no longer possible to perform hypothesis testing due to limited number of participants in the study due to study termination.
Section 3.2: Background Section 5.5.6: Safety/IMG with Nivo SC + rHuPH20 Section 5.6.2: Clinical Pharmacology of Recombinant Human Hyaluronidase PH20	Included additional background information.	To include latest data from the nivolumab Investigator's Brochure v5.0.
Section 3.3: Benefit/Risk Assessment	Added details about SC administration of nivolumab coformulated with recombinant human hyaluronidase PH20 enzyme (rHuPH20).	To provide additional safety guidance.
Section 3.3: Benefit/Risk Assessment Section 3.3.3: Nivolumab Overall Benefit/Risk Conclusion Section 5.1.4: Data Monitoring Committee and Other Committees	Updated Data Monitoring Committee (DMC) and Study Steering Committee (SSC) language.	To align with the current requirements of the DMC and SSC following study termination.
Section 4: Objectives and Endpoints Table 4-1: Objectives and Endpoints Section 10.4.2: Primary Endpoint(s) Table 10.4.2-1: Primary Endpoint Section 10.4.5: Other Safety Analysis	Updated objectives and endpoints as well as removed the main estimands. Safety is now the primary objective.	To reflect the current status of analyses that will and will no longer be conducted.
Section 5.1: Overall Design Section 5.2: Number of Participants	Updated the number of participants.	To reflect the current status of number of participants based on study termination.
Figure 5.1-1: Study Design Schema	Updated the Study Design Schema.	To align with updates to the study design.
Section 5.1: Overall Design Section 5.1.2.1: Randomized Study Cohort	Changed "expected" to "required" regarding in-clinic visits for participants in the Nivo [redacted] arm.	To provide clarification.
Section 5.1.2: Treatment Period Section 8.1.3: Study Treatment Beyond Recurrence	Removed: "In certain circumstances, participants with recurrence of disease but with otherwise stable or improved performance and clinical status may continue to be treated in the event of a perceived benefit per the investigator. Investigator must contact the Sponsor for approval" and deleted relevant Section 8.1.3.	There will not be treatment beyond progression.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.1.2.1: Randomized Study Cohort [redacted]	[redacted] Added Section 5.1.2.3 to clarify participant decision for opting out and investigator criteria for opting out. Added a flowchart to illustrate opt-out. Clarified that participants are unable to transfer between Arm A and Arm B. [redacted]	To provide clarification.
Figure 5.5.3-1: Predicted Nivolumab Exposures by Dose, Route of Administration, and Body Weight Tertiles for Base Case Bioavailability (70%) in Adjuvant Melanoma Figure 5.5.3-2: Predicted Nivolumab Exposures by Dose, Route of Administration, and Body Weight Tertiles for Worse Case Bioavailability (60%) in Adjuvant Melanoma	Added figures.	These were inadvertently left out of the original protocol. Added to correct the error.
Section 5.5.4: Rationale for Switch from Q2W to Q4W (Arm B [IV])	Added a new section.	To reduce participant burden.
Section 5.5.5: Rationale for Continued Adjuvant Therapy for Participants Who Are Diagnosed with Melanoma in Situ During Study Treatment	Added a new section.	To clarify continued adjuvant therapy for participants who are diagnosed with melanoma in situ during study treatment.
Section 6.1: Inclusion Criteria Section 9.2: Adverse Events Appendix 2: Study Governance Considerations	Removed participants' use of a legally accepted representative to sign the informed consent form.	Legally acceptable representatives are no longer allowed under global Protocol Amendment 01.
Section 6.2: Exclusion Criteria	Removed phrase "while enrolled on study" from criterion 3) k) i).	Administrative edit.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 7.1.2: Study Treatment Details for [redacted] with rHuPH20	[redacted]	To provide further clarification.
[redacted]	[redacted]	[redacted]
Section 7.6: Treatment Compliance	Added out-of-window dosing. Added text to ensure participants are given instructions on how to proceed in case of out-of-window dosing.	To provide additional safety guidance.
Section 9.11: Health Economics OR Medical Resource Utilization and Health Economics	Removed collection of Healthcare Resource Use data.	To mitigate burden on study sites.
Section 9.1.3.3: Definitions	• Excluded malignant melanoma in situ in defining recurrence as appearance of new melanoma lesions. • Updated definitions for recurrences and added new definitions.	• To clarify recurrence definition. • To provide further clarification.
Section 9.1.4: Health Outcomes Assessments	Added paragraph that PRO data collection is being removed; however, the data may be used internally at some point in the future.	To clarify that the data may be used at some point in the future to help develop PRO strategies in future clinical trials.
[redacted]	[redacted]	[redacted].
Section 10.2: Sample Size Determination	Updated language describing the aim of the study.	To reflect that safety is the only primary objective.
Section 10.3: Analyses Sets	Revised descriptions for analysis sets and populations.	To simplify the text.
Section 10.4.2: Primary Endpoint(s) Section 10.4.5: Other Safety Analysis	Moved language in Section 10.4.5 to Section 10.4.2.	To align with safety being the primary objective.
Section 10.4.7.3: Final Analysis	Added a new section to define the final analysis database lock.	To provide clarification.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Appendix 2: Study Governance Considerations	• Added 2 sections: – BMS Commitment to Diversity in Clinical Trials – Data Protection, Data Privacy, and Data Security • Removed references to legally acceptable representative. • Revised text to remove the [redacted] in the destruction/return of [redacted] local regulations will be followed.	To align with BMS commitment to diversity in clinical trials and to comply with European Union Clinical Trials Regulation requirement. To align with changes in the protocol (legally acceptable representative was removed). To provide clarification on process of destruction or return of study intervention.
[redacted]		
Appendix 11: Product Quality Issues	Added a new appendix to include guidance on product quality issue reporting.	To provide information on potential product quality issues and how to report them.

TABLE OF CONTENTS

1 PROTOCOL SUMMARY

Protocol Title: A Phase 3, Open Label, Randomized, Non-Inferiority Pharmacokinetic Study of Nivolumab Subcutaneous (Nivo SC) Versus Intravenous (Nivo IV) Administration in Participants with Stage IIIA/B/C/D or Stage IV Adjuvant Melanoma Following Complete Resection

Brief Title: A Pharmacokinetic Study of Nivolumab Subcutaneous vs Intravenous Administration in Participants with Stage IIIA/B/C/D or Stage IV Melanoma Following Complete Resection

Rationale:

Study CA2096GE is a Phase 3, open-label, randomized study of nivolumab administered subcutaneously [redacted] versus intravenous (IV) administration of nivolumab (Nivo) in participants with resected Stage IIIA/B/C/D or Stage IV melanoma in an adjuvant setting.

Repeated IV infusion appointments require travel to a clinic or infusion center, time, and resources and have physical and emotional impacts on patients. For healthcare systems, the preparation and administration of IV infusions require time and resource utilization. Given that the growing cancer population will increase the burden on healthcare resources, there is a need for more efficient treatment options, such as alternative routes of administration and new delivery technologies.

The development of [redacted] aims to address the current and evolving burden of cancer and cancer treatment on patients, caregivers, health care providers (HCPs), and the healthcare system.

Overall Rationale for Protocol Amendment 01

Bristol-Myers Squibb has made a strategic decision to terminate the CA2096GE trial. This decision was not related to any safety concerns. Study recruitment has closed and treatment of ongoing, active participants will continue per Protocol Amendment 01. Changes implemented in this amendment aim to alleviate participant and site burden and include updates to sample collection, study procedures, and study design.

Objectives and Endpoints

Per Protocol Amendment 01, PK co-primary endpoints, secondary endpoints, and Part 2 of the study have been removed. Efficacy, patient-reported outcomes (PROs), and biomarker analyses will not be completed. Samples already collected for PK and immunogenicity assessments will be analyzed bioanalytically for nivolumab concentrations and anti-drug antibodies (ADAs) and reported as listings. Further collections for PK, ADAs, biomarkers, and PROs will be discontinued. Only safety assessments will be conducted.

Objectives	Endpoints
Primary	
• To assess the safety and tolerability of nivolumab SC [redacted] coformulated with rHuPH20 and nivolumab IV	• AEs/SAEs and treatment-related AEs/SAEs

Abbreviations: AE, adverse event; [redacted]; IV, intravenous; rHuPH20, recombinant human hyaluronidase PH20 enzyme; SAE, serious adverse event; SC, subcutaneous.

Overall Design:

Study CA2096GE is a multicenter, open-label, Phase 3 study that will assess the safety and tolerability of [redacted] vs Nivo IV in participants with completely resected Stage IIIA/B/C/D or Stage IV melanoma by American Joint Committee on Cancer (AJCC) 8th edition. This study is comprised of 2 arms: Arm A and Arm B.

Per Protocol Amendment 01, PK co-primary endpoints, secondary endpoints, and Part 2 of the study have been removed. Efficacy, PROs, and biomarker analyses will not be completed. Samples already collected for PK and immunogenicity assessments will be analyzed bioanalytically for nivolumab concentrations and ADAs and reported as listings. Further collections for PK, ADAs, biomarkers, and PROs will be discontinued. Only safety assessments will be conducted. Therefore, the study design has been adapted to reflect Protocol Amendment 01 changes, [redacted] Part 1 is no longer hypothesis-driven, but rather descriptive in nature (Arm A and Arm B), with the primary objective being safety and tolerability.

- Arm A (n = 6):
  - [redacted] 600 mg [redacted] of recombinant human hyaluronidase PH20 (rHuPH20) [redacted]
- Arm B (n = 8):
  - Nivo IV (BMS-936558) 240 mg Q2W for Cycles 1 through 4.
  - Nivo IV 480 mg every 4 weeks (Q4W) Cycle 5 onwards for up to a total of 52 weeks.
  - All dosing will be performed in-clinic.

[redacted]

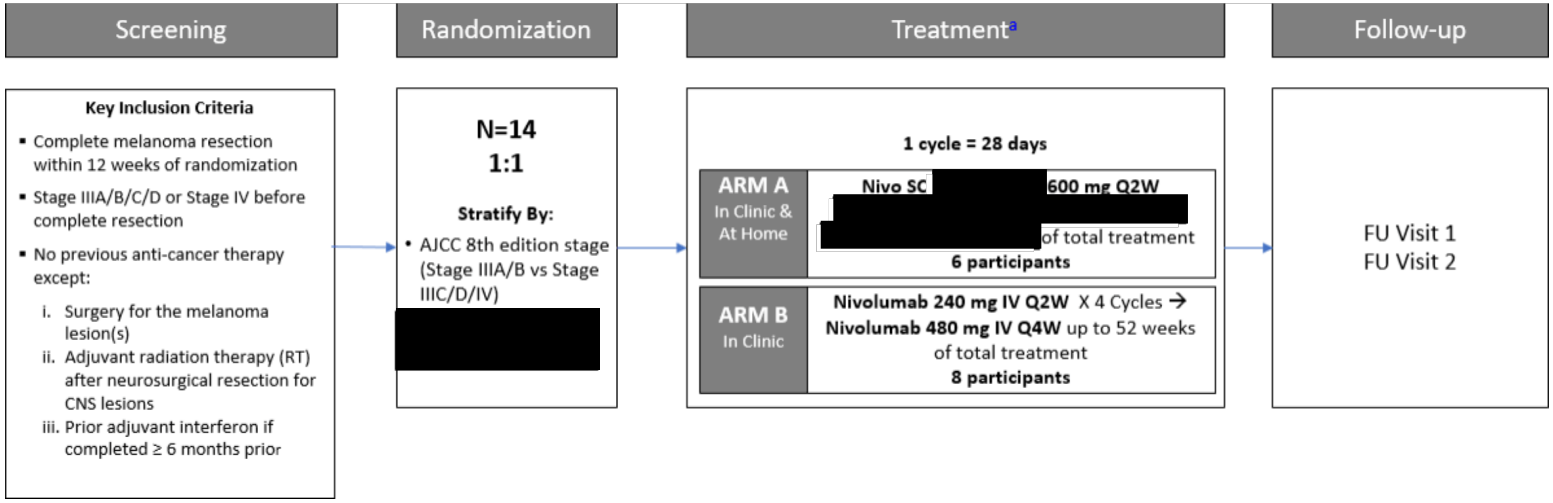
Participants will be stratified by stage (Stages IIIA/B vs IIIC/D/IV) per AJCC 8th edition [redacted]

All participants will be treated until recurrence of disease, unacceptable toxicity, participant withdrawal of consent, death, or a maximum of 52 weeks of treatment from first dose, whichever occurs first.

[redacted]

The study design schema is presented below.

Study Design Schema



Abbreviations: AJCC, American Joint Committee on Cancer; CNS, central nervous system; FU, follow-up; IV, intravenous; N, number of participants; Nivo, nivolumab; PK, pharmacokinetic, Q2W, every 2 weeks; Q4W, every 4 weeks; RT, radiation therapy; SC, subcutaneous; vs, versus.

[a] Treatment until recurrence of disease, unacceptable toxicity, participant withdrawal of consent, death, or a maximum of 52 weeks of treatment from first dose, whichever occurs first.

Number of Participants:

The trial has been terminated. [redacted] 14 participants randomized and treated in the study with 6 participants in Arm A and 8 participants in Arm B.

Study Population:

Not applicable per Protocol Amendment 01 (as of 24-Feb-2023, enrollment in this study has been closed).

Male and female participants ≥ 18 years of age or age of majority with completely resected Stage IIIA/B/C/D or Stage IV melanoma.

Key Inclusion:

- All participants must have been diagnosed with either Stage IIIA (> 1 mm tumor in lymph node)/B/C/D or Stage IV melanoma by AJCC 8th edition and have histologically confirmed melanoma (as documented in the pathology report) that is completely surgically resected (free of disease) with negative margins in order to be eligible. All melanomas, except uveal and mucosal melanoma, regardless of primary site of disease, will be allowed.
- Participants are eligible if central nervous system (CNS) metastases have been resected and participants are neurologically stable.
  - Prior resected CNS metastases must be without evidence of recurrence, as determined by magnetic resonance imaging (MRI) performed at least 4 weeks after resection is complete and within 28 days prior to randomization (Part 1) [redacted]
  - Participants must be off immunosuppressive doses of systemic steroids (>10 mg/day prednisone or equivalent) for at least 14 days prior to study drug administration and must have returned to neurologic baseline post-operatively.
  - For CNS lesion(s), a pathology report indicating that there has been complete resection of CNS lesion(s) will suffice as confirmation of negative margins.
- Complete resection must be performed within 12 weeks prior to randomization (Part 1) [redacted] Management of residual lymph nodes after positive sentinel lymph node biopsy (ie, completion lymph node dissection) will be as per local standards and recommendations for the individual participant.
- All participants must have disease-free status documented by a complete physical examination within 14 days prior to randomization (Part 1) [redacted] and imaging studies within 28 days prior to randomization/treatment assignment. Imaging studies must include computed tomography (CT) scan of the chest; CT or MRI scans of the abdomen, pelvis, and all known sites of resected disease; and brain MRI or CT (brain CT allowable if MRI is contraindicated).
- Participants must have an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 1.
- [redacted]

Key Exclusion:

- History of uveal or mucosal melanoma.
- Untreated/unresected CNS metastases or leptomeningeal metastases.
- Participants with an active, known or suspected autoimmune disease. Participants with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
- Participants with serious or uncontrolled medical disorders within 4 weeks prior to screening.
  - Additionally, in the case of prior severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, 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 investigational treatment.
- Concurrent malignancy (present during screening) requiring treatment or history of prior malignancy active within 2 years prior to randomization (Part 1) [redacted] (ie, participants with a history of prior malignancy are eligible if treatment was completed at least 2 years before randomization/treatment assignment and the patient has no evidence of disease). Participants with history of prior early stage basal/squamous cell skin cancer or non-invasive or in situ cancers that have undergone definitive treatment at any time are also eligible.
- Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) within 14 days or other immunosuppressive medications within 30 days of start of study treatment. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
- Any condition that according to investigator criteria makes a participant ineligible from participation in the study, including but not limited to medical conditions (including psychological, psychiatric), or social conditions; or conditions that can impact ability to comply with protocol requirements (eg, conditions that preclude the use of IV or subcutaneous [SC] route of study drug administration) or that can put the participant at risk. Participants with history of self-harm including suicidal attempts will be excluded from the study.
- Prior immunotherapy treatments for any prior malignancies are not permitted (such as, but not limited to anti-programmed death-1, anti-programmed death-ligand 1, anti-programmed death-ligand 2, or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways).
- Participants treated with anti-cancer therapy directed against the resected melanoma (for example, but not limited to, systemic, local, radiation, and radiopharmaceuticals) except:
- Surgery for the melanoma lesion(s)
  - Adjuvant radiation therapy after neurosurgical resection for CNS lesions
  - Prior adjuvant interferon completed ≥ 6 months prior to randomization (Part 1) [redacted]
- Treatment with any live attenuated vaccine within 30 days of first study treatment (Vaccines that are not live attenuated are allowed, including COVID-19 vaccines).
- History of allergy or hypersensitivity to study drug components [redacted]

Intervention Groups and Duration:

As described in Overall Design.

Study intervention:

Study Intervention for CA2096GE		
Medication	**Potency**	**IMP/Non-IMP**
Subcutaneous nivolumab administered [redacted] coformulated with rHuPH20	[redacted]	IMP
Nivolumab IV	10 mg/mL	IMP

Abbreviations: IMP, investigational medicinal product; IV, intravenous; Non-IMP, non-investigational medicinal product; rHuPH20, recombinant human hyaluronidase PH20.

Statistical Methods

- This is an open-label, parallel group study in which participants are randomized 1:1 to either of the 2 treatment groups: subcutaneous nivolumab [redacted] or nivolumab administered intravenously. Randomization will be stratified by AJCC 8th edition staging and weight.
- The aim of the study is to assess the safety and tolerability of [redacted] and Nivo IV. This has changed from the original protocol's study objective of PK. Sample size calculations are not based on statistical considerations. There were 14 participants randomized and treated at the time of Protocol Amendment 01.

Data Monitoring Committee: Yes

A safety DMC will be implemented in this study to provide safety oversight throughout the course of Part 1 of the study. The DMC charter will describe the procedures related to the committee operations in greater detail. On 26-Oct-2022, enrollment was paused and a total of 14 participants had been randomized. On 24-Feb-2023, the study was terminated with no additional participants having been randomized. As this is an open-label study, the Sponsor will continue the safety monitoring of remaining participants in the study. No subsequent DMC meeting will occur.

Other Committee: Yes

A Study Steering Committee (SSC) will be established to provide advisory oversight of the quality of the trial, with the objective of ensuring scientific integrity and the successful conduct of the CA2096GE Study. On 26-Oct-2022, enrollment was paused and a total of 14 participants had been randomized. On 24-Feb-2023, the study was terminated with no additional participants having been randomized. The Sponsor will continue to ensure the scientific integrity and successful conduct of the study. No SSC meeting will occur.

Brief Summary:

The purpose of this study is to assess the safety and tolerability of [redacted] and Nivo IV. Study details include the following:

Study Duration: approximately 16 months

Study Intervention Duration: 52 weeks

Study Visit Frequency:

Arm A [redacted] 600 mg Q2W)

[redacted]

Arm B (Nivo IV 240 mg Q2W/480 mg Q4W)

In-clinic visits will be scheduled Q2W during Cycle 1, Day 1 through Cycle 4, Day 15, followed by Q4W for the remainder of study treatment.

2 SCHEDULE OF ACTIVITIES

An overview of the schedule of major assessments in this study are provided in Table 2-1 (Screening), Table 2-2 (On-Treatment Arm A), Table 2-3 (On-Treatment Arm B), Table 2-4 [redacted] and Table 2-5 (Follow-up Assessments).

In the event that multiple procedures are required at a single time point, vital signs may be obtained up to 10 minutes earlier or later, and clinical laboratory samples may be obtained up to 5 minutes earlier than the nominal time point.

Table 2-1: Screening Procedural Outline (CA2096GE) Part 1 [redacted]

Not applicable per Protocol Amendment 01 (enrollment closed).

Procedure	Screening Visit (Day -28 to Day -1)	Notes:[a] All windows are based on calendar days.
Eligibility Assessments		
Informed Consent	X	Must be obtained prior to performing any screening procedures. Study allows for re-enrollment of a participant that has discontinued the study as a pre-treatment failure. If re-enrolled, the participant must be re-consented and assigned a new participant number from IRT.
Contact IRT	X	Register in IRT system to obtain participant number on the day of consent.
Inclusion/Exclusion Criteria	X	Must be confirmed prior to randomization (Part 1) [redacted] See Sections 6.1 and 6.2.
Medical History	X	All medical history relevant to the disease (including COVID-19) under study.
Tumor Sample Submission	X	Formalin fixed, paraffin-embedded (FFPE) tumor tissue block (preferred) or a minimum of 15 unstained slides* of tumor tissue obtained from the recent resection (preferred) or an archival biopsy conducted within 6 months prior to enrollment, and preferably with no intervening systemic anti-cancer treatment between time of acquisition and enrollment, must be submitted to the central lab. Tissue availability needs to be determined during the screening period. It is recommended that tumor tissue is submitted during the screening period, however, it must be submitted no later than 14 days post-randomization/treatment assignment. Fine-needle aspirates or other cytology samples are not acceptable. *If despite best efforts, a minimum of 15 unstained slides are not obtainable, submission of 5 unstained slides is acceptable. Please refer to Section 9.8 and Lab Manual for additional information.
Review of Pathology Report	X	Confirm negative margins prior to randomization (Part 1) [redacted] and file as a source document.
[redacted]		

Table 2-1: Screening Procedural Outline (CA2096GE) Part 1 [redacted]

Not applicable per Protocol Amendment 01 (enrollment closed).

Procedure	Screening Visit (Day -28 to Day -1)	Notes:[a] All windows are based on calendar days.
Body Imaging	X	Contrast-enhanced CT of the chest (if CT contrast is contraindicated, then non-contrast CT should be acquired). CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease, within 28 days prior to randomization (Part 1) [redacted] See Section 9.1.1 for further details.
Brain Imaging	X	MRI of the brain (without and with contrast) is required for ALL participants during screening to rule out brain metastases, within 28 days prior to randomization (Part 1) [redacted] CT of the brain (without and with contrast) can be performed if MRI is contraindicated. See Section 9.1.1 for further details.
Safety Assessments		
Physical Examination, Measurements, Vital Signs, Performance Status, and Assessment of Signs and Symptoms	X	Height, weight, ECOG Performance Status (Appendix 8), BP, heart rate, temperature, and oxygen saturation by pulse oximetry at screening only. Assess all signs and symptoms. Must be collected within 14 days prior to randomization (Part 1) [redacted]
Concomitant Medication Collection	X	Within 14 days prior to randomization (Part 1) [redacted] Document vaccine use within 30 days prior to first dose of study treatment. See Sections 6.2 and 7.7.
Serious Adverse Events (SAE) Assessment	X	All SAEs must be collected from the time of signing the informed consent, including those thought to be associated with protocol-specified procedures. SAEs are to be assessed continuously using NCI CTCAE v5. For participants who are enrolled but not randomized, SAEs must be collected for 30 days from the date of signing the informed consent. For participants who are randomized but not treated, SAE collection should continue for 30 days from the date of randomization (Part 1) [redacted]. All SAEs/AEs related to SARS-CoV-2 will follow the SAE reporting requirements as described above. See Section 9.2.1.

Table 2-1: Screening Procedural Outline (CA2096GE) Part 1 [redacted]

Not applicable per Protocol Amendment 01 (enrollment closed).

Procedure	Screening Visit (Day -28 to Day -1)	Notes:[a] All windows are based on calendar days.
ECG	X	At rest. Within 14 days prior to randomization (Part 1) [redacted]
Laboratory Tests		
Clinical Laboratory Assessments	X	On-site/local laboratory tests must be performed within 14 days prior to randomization (Part 1) [redacted] Viral testing to be completed within 28 days prior to randomization. For HIV: testing at sites where locally mandated; see Appendix 10. Refer to Section 9.4.4 for list of laboratory tests to conduct.
Pregnancy Test (Women of Childbearing Potential [WOCBP] Only)	X	Serum or urine pregnancy test (minimum sensitivity equivalent units 25 IU/L or equivalent units of HCG) to be done at screening visit and repeated within 24 hours prior to first dose of study treatment. See Section 6.1.
FSH	X	Women only - for confirmation of postmenopausal status, defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes for females under the age of 55 years. Women must have a serum FSH level > 40 mIU/mL to confirm menopause.
Study Treatment		
Randomize (Part 1 only)	X	IRT contact for randomization into 1 of the 2 treatment arms should occur when eligibility criteria are met. Study treatment must begin within 3 calendar days of randomization in IRT.
[redacted]		

Abbreviations: AE, adverse event; [redacted]; BP, blood pressure; COVID-19, coronavirus disease 2019; CRF, case report form; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; FFPE, formalin-fixed paraffin embedded; FSH, follicle stimulating hormone; HCG, human chorionic gonadotropin; HIV, human immunodeficiency virus; IRT, Interactive Response Technology; IU, international units; L, liter; MRI, magnetic resonance imaging; NCI, National Cancer Institute; Nivo, nivolumab; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SC, subcutaneous; v, version; WOCBP, women of childbearing potential.

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

Table 2-2: On Study Treatment Procedural Outline (Arm A) [redacted] (CA2096GE)

Procedure	Arm A [redacted] 600 mg Q2W with 8,000 U rHuPH20[a] Cycle Length = 28 Days						Notes:[b]
	In-clinic Period[c]			[redacted]			
	Cycles 1 - 4		Cycle 5	Cycle 5	Cycles 6 - 13		
	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15	Dosing windows are ± 1 day
Study Treatment							
In-clinic Dosing Visit	X	X	X				For dosing, clinical labs, and other safety assessments.
In-clinic Non-dosing Visit	C1D2, C1D4, C1D8, and C1D22				X		C6D1-C13D1: clinical labs, pregnancy test (if applicable) and other safety assessments.
[redacted]							
Study Treatment Administration	X	X	X	X	X	X	[redacted]
[redacted]							

Table 2-2: On Study Treatment Procedural Outline (Arm A [redacted]) (CA2096GE)

Procedure	Arm A [redacted] 600 mg Q2W with 8,000 U rHuPH20[a] Cycle Length = 28 Days						Notes:[b]
	In-clinic Period[c]			[redacted]			
	Cycles 1 - 4		Cycle 5	Cycle 5	Cycles 6 - 13		
	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15	Dosing windows are ± 1 day
Study Calls							
24 Hours Post-injection Phone Assessment	See Table 9.4.5-1 for required time points.						Refer to Section 9.4.5.2 for additional details.
Safety Assessment							
Physical Examination, Measurements, Vital Signs, and Performance Status	X	X	X		X		Physical examination, including targeted physical examination for detection of disease recurrence, weight, BP, heart rate, temperature, pulse oximetry, and ECOG performance status (refer to Appendix 8). After Cycle 5, Day 1, this assessment will be performed once every 4 weeks in the clinic (non-dosing visits).
Adverse Event (AE), Serious Adverse Event (SAE) Assessment	Continuously						Record at each visit. Collect continuously throughout the treatment period. All AEs (SAEs or non-serious AEs), including injection-related AEs and those associated with SARS-CoV-2 infection, must be collected continuously during the treatment period.
[redacted]	[redacted]						Record at each visit. Collect continuously throughout the treatment period. [redacted] those associated with SARS-CoV-2 infection, must be collected continuously during the treatment period.
Report of Product Complaints	Continuously						By site and participant/participant caregiver. Refer to Appendix 5.

Table 2-2: On Study Treatment Procedural Outline (Arm A [redacted]) (CA2096GE)

Procedure	Arm A [redacted] 600 mg Q2W with 8,000 U rHuPH20[a] Cycle Length = 28 Days						Notes:[b]
	In-clinic Period[c]			[redacted]			
	Cycles 1 - 4		Cycle 5	Cycle 5	Cycles 6 - 13		
	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15	Dosing windows are ± 1 day
Concomitant Medications Use	Continuously						Record at each visit.
Laboratory Tests							
Pregnancy Test (WOCBP)	X		X		X		Serum or urine within 24 hours prior to first dose and then every 4 weeks (± 1 week) regardless of dosing schedule.[d]
Clinical Laboratory Assessments	X	X	X		X		During Cycle 1, Day 1 to Cycle 5, Day 1, perform on site/local laboratory testing within 72 hours prior to each dose. After Cycle 5, Day 1, perform testing every 4 weeks (within 72 hours prior to dosing) during in-clinic visits. For the first treatment visit, labs need not be repeated if they were performed within 72 hours and the results are available and have been reviewed for eligibility. Refer to Section 9.4.4 for the list of laboratory tests to be conducted.
Efficacy Surveillance							
Body Imaging	X (see Notes)						Contrast-enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease every 12 weeks (± 7 days) is recommended; however, imaging per local standard of care is allowed, starting from date of first dose until investigator-assessed local, regional, or distant recurrence or the 100-day safety follow-up (whichever comes first) for all participants. See Section 9.1.1 for details. If a participant starts systemic therapy for melanoma recurrence, or for a new non-melanoma tumor after study drug discontinuation, follow-up scans for this trial should be discontinued.

Table 2-2: On Study Treatment Procedural Outline (Arm A [redacted]) (CA2096GE)

Procedure	Arm A [redacted] 600 mg Q2W with 8,000 U rHuPH20[a] Cycle Length = 28 Days						Notes:[b]
	In-clinic Period[c]			[redacted]			
	Cycles 1 - 4		Cycle 5	Cycle 5	Cycles 6 - 13		
	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15	Dosing windows are ± 1 day
Brain Imaging	X (see Notes)						For participants with a history of brain metastasis or symptoms, it is recommended to perform a surveillance MRI (without and with contrast) approximately every 12 weeks ± 7 days; however, brain imaging per local standard of care is allowed, starting from date of first dose until investigator-assessed local, regional, or distant recurrence or the 100-day safety follow-up (whichever comes first), for all participants or sooner if clinically indicated. See Section 9.1.1 for further details.
Health Outcomes Assessments[e]							
[redacted]							

Abbreviations: AE, adverse event; [redacted]; BP, blood pressure; C, cycle; CRF, case report form; CT, computed tomography; D, day; [redacted] ECOG, Eastern Cooperative Oncology Group; MRI, magnetic resonance imaging; Nivo, nivolumab; Q2W, every 2 weeks; rHuPH20, recombinant human hyaluronidase PH20 enzyme; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SC, subcutaneous; WOCBP, women of childbearing potential.

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

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

[c] Study treatment must be administered in-clinic for a minimum of Cycle 1, Day 1 through Cycle 5, Day 1, inclusive.

[d] If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be discontinued from study intervention if the serum pregnancy result is positive.

[redacted]

Table 2-3: On Study Treatment Procedural Outline (Arm B) (Nivo IV) (CA2096GE)

Procedure	Arm B Nivo IV 240 mg Q2W for Cycles 1 - 4 and 480 mg Q4W for all subsequent cycles.[a] Cycle Length = 28 Days			Notes:[b]
	Cycles 1 - 4		All Subsequent Cycles	For Q2W dosing cycles, participants may be dosed no less than 12 days from the previous dose. Dosing windows for Q2W = ± 3 days; for Q4W = ± 3 days.
	Day 1	Day 15	Day 1 Only	
Study Treatment				
In-clinic Dosing Visit	X	X	X	
In-clinic Non-dosing Visit	C1D8 and C1D22			
Dispense Study Drug	X	X	X	Participant must receive the first dose of study medication within 3 calendar days from randomization.
Study Treatment Administration	X	X	X	Refer to Section 7.1.1 for details.
Safety Assessment				
Physical Examination, Measurements, Vital signs, and Performance Status	X	X (see Notes)	X	Physical examination, including targeted physical examination for detection of disease recurrence, weight, BP, heart rate, temperature, pulse oximetry, and ECOG Performance Status (Appendix 8).
Assessment of IV Injection Site	X (see Notes)	X (see Notes)		Only applicable for Cycle 1, Days 1 and 15. Refer to Section 7.1.1.
Adverse Event (AE) Assessment and Serious Adverse Events (SAE)	Continuously			Record at each visit. Collect continuously throughout the treatment period. All AEs (SAEs or non-serious AEs), including infusion-related AEs and those associated with SARS-CoV-2 infection, must be collected continuously during the treatment period.
Concomitant Medications Use	Continuously			Record at each visit.

Table 2-3: On Study Treatment Procedural Outline (Arm B) (Nivo IV) (CA2096GE)

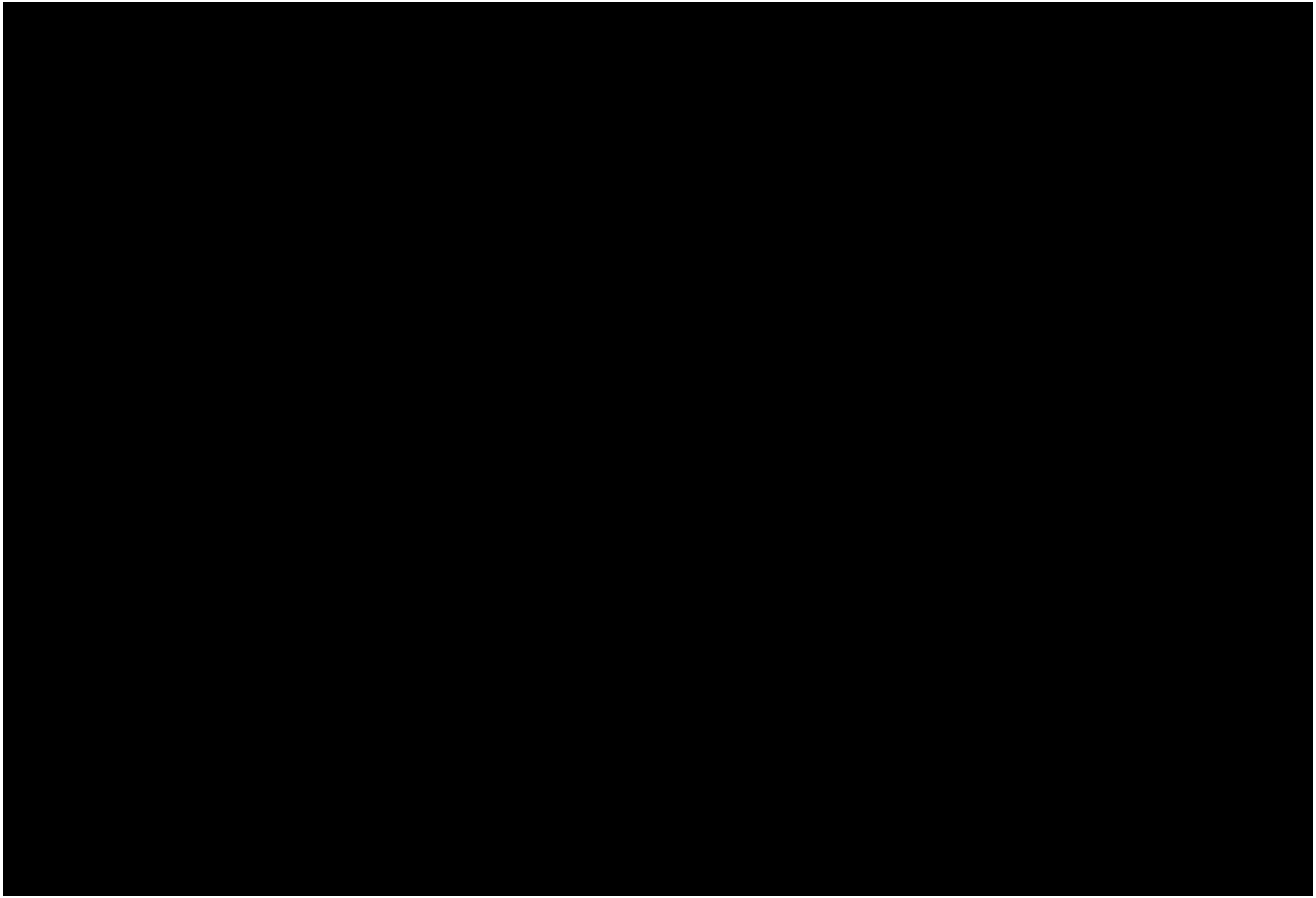
Procedure	Arm B Nivo IV 240 mg Q2W for Cycles 1 - 4 and 480 mg Q4W for all subsequent cycles.[a] Cycle Length = 28 Days			Notes:[b]
	Cycles 1 - 4		All Subsequent Cycles	For Q2W dosing cycles, participants may be dosed no less than 12 days from the previous dose. Dosing windows for Q2W = ± 3 days; for Q4W = ± 3 days.
	Day 1	Day 15	Day 1 Only	
Laboratory Tests				
Pregnancy Test (WOCBP)	X		X	Serum or urine within 24 hours prior to first dose and then every 4 weeks (± 1 week) regardless of dosing schedule.[c]
Clinical Laboratory Assessments	X	X	X	Perform on site/local laboratory testing within 72 hours prior to each dose. For the first treatment visit, labs need not be repeated if they were performed within 72 hours and the results are available and have been reviewed for eligibility. Refer to Section 9.4.4 for the list of laboratory tests to be conducted.
Efficacy Surveillance				
Body Imaging	X (see notes)			Contrast-enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease every 12 weeks (± 7 days) is recommended; however, imaging per local standard of care is allowed, starting from date of first dose until investigator assessed local, regional, or distant recurrence or the 100-day safety follow-up (whichever comes first) for all participants. See Section 9.1.1 for further details. If a participant starts systemic therapy for melanoma recurrence, or for a new non-melanoma tumor after study drug discontinuation, follow-up scans for this trial should be discontinued.
Brain Imaging	X (see notes)			For participants with a history of brain metastasis or symptoms, it is recommended to perform a surveillance MRI (without and with contrast) approximately every 12 weeks ± 7 days; however, brain imaging per local standard of care is allowed, starting from date of first dose until investigator-assessed local, regional, or distant recurrence or the 100-day safety follow-up (whichever comes first), for all participants or sooner if clinically indicated. See Section 9.1.1 for further details.

Abbreviations: AE, adverse event; BP, blood pressure; C, cycle; CRF, case report form; CT, computed tomography; D, day; ECOG, Eastern Cooperative Oncology Group; IV, intravenous; MRI, magnetic resonance imaging; Nivo, nivolumab; Q2W, every 2 weeks; Q4W, every 4 weeks; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WOCBP, women of childbearing potential.

[a] If a dose is delayed, the procedures scheduled for that same time point must also be delayed to coincide with when that time point's dosing actually occurs, with the exception of tumor assessments, which must occur as scheduled. The start of 480 mg Q4W dosing must occur on C5D1 (14 days, ± 3 days) following C4D15.

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

[c] If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be discontinued from study intervention if the serum pregnancy result is positive.



[redacted]

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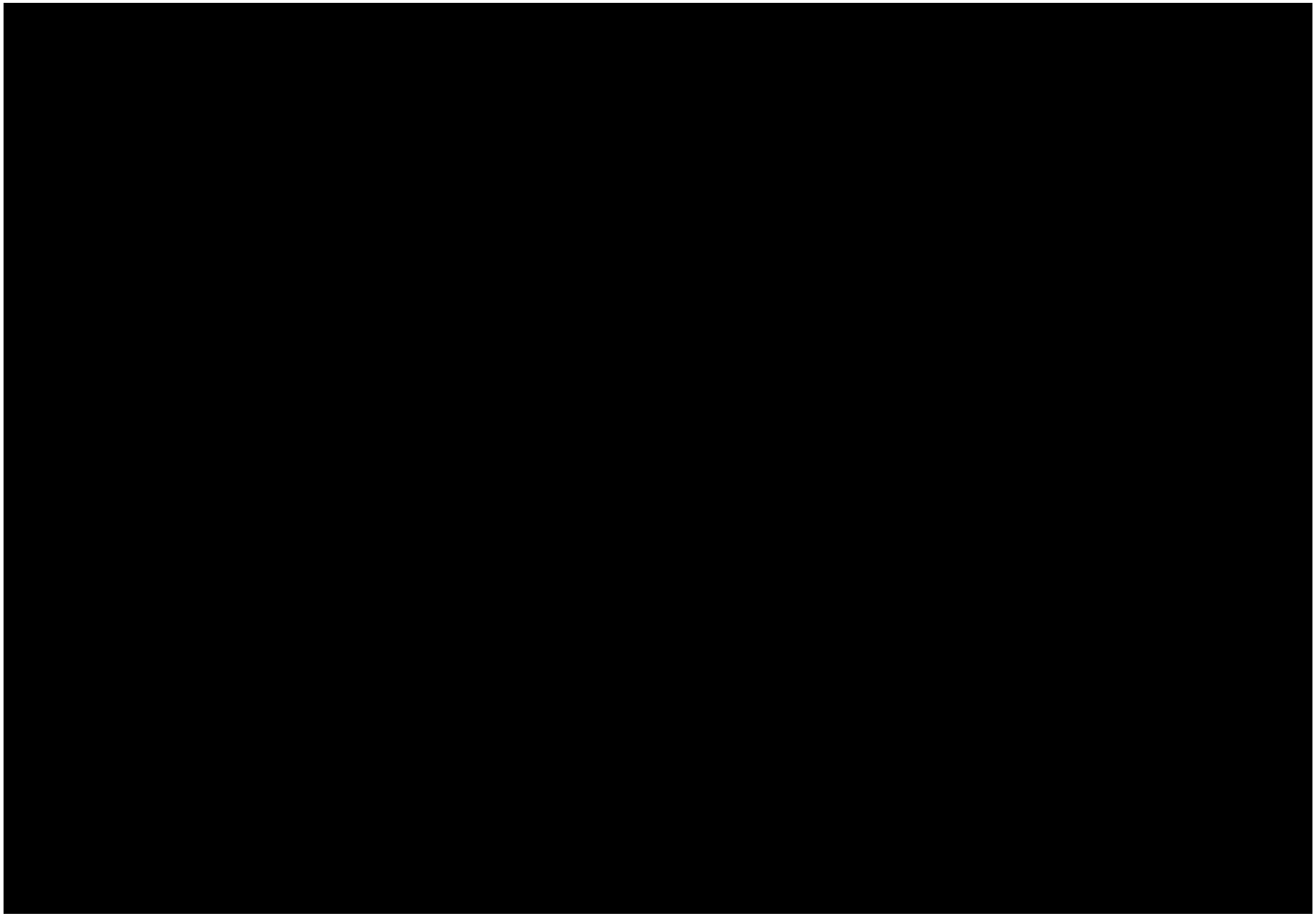


[redacted]

[redacted]

Table 2-5: Follow-up Assessments (CA2096GE)

Procedure	Follow-up Visits 1 & 2[a] (In-clinic)	Notes:[b]
Safety Assessment		
Physical Examination, Measurements, Vital Signs, and Performance Status	X	Physical examination, including targeted physical examination for detection of disease recurrence, weight, BP, heart rate, temperature, pulse oximetry, and ECOG performance status (refer to Appendix 8).
Adverse Event (AE) and Serious Adverse Events (SAE) Assessment	X	Record at each visit. Collect continuously throughout the treatment period and for a minimum of 100 days following discontinuation of dosing. *Beyond 100 days from the last dose of study therapy, participants will be followed for drug-related AEs/SAEs/[redacted] until resolution, returns to baseline, or is deemed irreversible, or until the participant is lost to follow-up or withdraws study consent. All SAEs and non-serious AEs should be collected continuously during the treatment period and for a minimum of 100 days following discontinuation of study treatment. Participants will be followed for all SAEs and all AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection until resolution, the condition stabilizes, the event is otherwise explained, the event is deemed irreversible, the participant is lost to follow-up (as defined in Section 8.3), or for suspected cases, until SARS-CoV-2 infection is ruled-out.
Concomitant Medications Review	X	Record at each visit.
Subsequent Cancer Therapy	X	Include documentation of subsequent cancer therapy (ie, systemic therapy, tumor-directed surgery, or radiation therapy).
Pregnancy Test (WOCBP)	X	Serum or urine (minimum sensitivity equivalent units 25 IU/L or equivalent units of HCG).
Clinical Laboratory Assessments	X	To be performed at Follow-up Visit 1, repeat at Follow-up Visit 2 if study drug-related toxicity persists. Refer to Section 9.4.4 Clinical Safety Laboratory Assessments for the list of laboratory tests.
Survival Status	X	Include documentation of subsequent cancer therapy (ie, systemic therapy, tumor-directed surgery, or radiation therapy).

Table 2-5: Follow-up Assessments (CA2096GE)

Procedure	Follow-up Visits 1 & 2[a] (In-clinic)	Notes:[b]
Body Imaging	See Notes.	Contrast-enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease every 12 weeks (± 7 days) is recommended; however, imaging per local standard of care is allowed, starting from date of first dose until investigator-assessed local, regional, or distant recurrence or the 100-day safety follow-up (whichever comes first) for all participants. See Section 9.1.1 for further details. If a participant starts systemic therapy for melanoma recurrence, or for a new non-melanoma tumor after study drug discontinuation, follow-up scans for this trial should be discontinued.
Brain Imaging	See Notes.	For participants with a history of brain metastasis or symptoms, it is recommended to perform a surveillance MRI (without and with contrast) approximately every 12 weeks ± 7 days; however, brain imaging per local standard of care is allowed, starting from date of first dose until investigator-assessed local, regional, or distant recurrence or the 100-day safety follow-up (whichever comes first), for all participants or sooner if clinically indicated. See Section 9.1.1 for further details.

Abbreviations: AE, adverse event; BP, blood pressure; CRF, case report form; CT, computed tomography; [redacted] ECOG, Eastern Cooperative Oncology Group; HCG, human chorionic gonadotropin; MRI, magnetic resonance imaging; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WOCBP, women of childbearing potential.

[a] Participants must be followed for at least 100 days after last dose of study treatment. Follow-up Visit 1 must occur 30 days from the last dose (± 7 days) or can be performed on the date of discontinuation if that date is greater than 30 days after last dose. Follow-up Visit 2 occurs approximately 100 days (± 7 days) from last dose of study medication.

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

[c] [redacted]

3 INTRODUCTION

The burden of cancer on the healthcare system is increasing at a rapid pace, with potential to cause significant impact to both patients and the healthcare system. In 2018, an estimated 18.1 million new cases of cancer were diagnosed globally; however, by 2040, that number will increase by more than 11 million, to approximately 29.5 million cancer cases.[1]

Globally, individuals and families suffering from cancer endure significant physical, financial, and emotional strain.[2,3,4,5,6,7,8,9,10] One of these burdens includes the treatment route of administration, which has largely been intravenous (IV) therapies. Burdens associated with IV therapies affect patients, healthcare providers (HCPs), and the healthcare system in a variety of ways.

Repeated IV infusion appointments require travel to a clinic or infusion center, time, and resources and have physical and emotional impacts on patients. For healthcare systems, the preparation and administration of IV infusions require time and resource utilization. Given that the growing cancer population will increase the burden on healthcare resources, there is a need for more efficient treatment options, such as alternative routes of administration and new delivery technologies.

The development of nivolumab administered subcutaneously [redacted] aims to address the current and evolving burden of cancer and cancer treatment on patients, caregivers, HCPs, and the healthcare system.[11]

- For patients, potential advantages include the following:
  - Patients prefer subcutaneous (SC) over IV administration as this option provides them with more comfort and convenience
  - Time savings associated with shorter injection time, decreased wait times at infusion centers, and alleviating the travel time to clinics resulting in less disruption to patients' daily lives
  - Obviating need for intravenous access (potential reduction in associated complications such as infections)
  - Potential to improve quality of life by reducing psychological stress and anxiety associated with IV therapy or treatment at an inpatient or outpatient infusion center
- For HCPs, Nivo SC may reduce the patient chair time traditionally needed for IV therapies.
- From the healthcare system perspective, Nivo SC may increase efficiencies for clinics, with reduced healthcare resource utilization for administration (no IV setup). Nivo SC has reduced cost of care related to physician and pharmacy preparation, and administration expenses. This may also lead to improved access to treatment in capacity-constrained areas or during times of reduced healthcare resources, as currently seen with the global coronavirus disease 2019 (COVID-19) pandemic.
- In addition to the above-mentioned advantages for Nivo SC, for patients, nivolumab SC [redacted] could reduce the burden of treatment time, improve the drug administration experience, and offer flexibility and convenience.

OPDIVO® (nivolumab, BMS-936558), as monotherapy or in combination with cabozantinib or ipilimumab and/or chemotherapy, is currently indicated for the treatment of multiple tumor types and lines of therapy including adjuvant treatment of melanoma.[13,14] OPDIVO® is currently only available for administration via IV infusion.

Bristol-Myers Squibb (BMS) is committed to improving drug delivery of immuno-oncology agents, including SC administration. Under Investigational New Drug 138,302, BMS is developing a SC formulation of high concentration nivolumab (BMS-986298) coformulated with a permeation enhancer (recombinant human hyaluronidase PH20 enzyme [rHuPH20] Halozyme Therapeutics Inc.) to offer an alternative administration route for nivolumab delivery. SC nivolumab can be administered via manual injection (vial and syringe) by a trained HCP. rHuPH20 is a transiently active, locally acting permeation-enhancing enzyme, which enhances the permeation of large volumes of SC-administered fluid, allowing for reduced administration times and has been approved by the United States (US) Food and Drug Administration for use with other monoclonal antibodies, including HyQvia, Rituxan HYCELA, Herceptin HYLECTA, DARZALEX Faspro, and PHESGO™.

The coformulated drug product (DP) nivolumab + rHuPH20 administered subcutaneously by a trained HCP in clinic is being formally evaluated for pharmacokinetics (PK) and efficacy non-inferiority compared to Nivo IV as part of another ongoing protocol, CA20967T, in participants with advanced/metastatic renal cell carcinoma.

As ongoing research with nivolumab continues with new combination regimens across multiple tumor types and different lines of therapies, the approval of nivolumab SC, as vial & syringe manual injection for use in ambulatory clinic [redacted] (would provide therapeutic alternatives to intravenous delivery and meet the needs of a diverse patient population across different lines of therapy. Once approved, the vial and syringe option for SC administration will provide greater convenience and flexibility for patients.

3.1 Study Rationale

Overall Rationale for Protocol Amendment 01

BMS has made a strategic decision to terminate the CA2096GE trial. This decision was not related to any safety concerns. Study recruitment has closed and treatment of ongoing, active participants will continue per Protocol Amendment 01. Changes implemented in this amendment aim to alleviate participant and site burden and include updates to sample collection, study procedures, and study design.

3.1.1 Research Hypotheses

Not applicable per Protocol Amendment 01. Due to study termination, the fact that enrollment was stopped, and the small sample size, the study is not powered to perform hypothesis testing.

Only Part 1 of the study will be subjected to statistical hypothesis testing. [redacted]

Part 1: SC [redacted] administration of nivolumab (BMS-986298) 600 mg coformulated with rHuPH20 [redacted] will provide non-inferior PK (measured by time-averaged concentration over the first 28 days [Cavgd28] and minimum nivolumab serum concentration at steady-state [Cminss]) to IV administration of nivolumab (BMS-936558) 240 mg IV Q2W in the adjuvant melanoma population.

3.2 Background

Melanoma accounts for less than 5% of all skin cancers; however, it causes the greatest number of skin cancer-related deaths worldwide.[15] There were 325,000 new cases of melanoma of the skin diagnosed in 2020, which represented 1.7% of global cancer diagnoses.[16] In the US in 2022, it is estimated there will be 99,780 new cases of melanoma and 7,650 deaths due to melanoma.[17] Melanoma is well-known for its ability to metastasize to virtually any organ or tissue. The most common initial sites of distance metastases are the non-visceral (skin, subcutaneous tissue, and lymph nodes), which are recurrence sites for 42% to 59% of participants in various studies. Visceral locations are the lung, brain, liver, gastrointestinal tract, and bone; the visceral sites are the initial sites of relapse in approximately 25% of all patients diagnosed with melanoma who experience recurrence. Early melanoma detection followed by surgical excision is usually curative. In contrast, advanced melanoma frequently usually has poor prognosis.

The disease course for melanoma has fundamentally changed with the introduction of immunotherapies targeting the cytotoxic T lymphocyte associated antigen 4 (CTLA-4) and programmed death-1 (PD-1) checkpoints as well as BRAF and MEK inhibitors. Such agents have dramatically improved outcomes for patients with metastatic melanoma.

In spite of these advances, opportunities exist to continue enhancing patient treatment outcomes and quality of life.

3.2.1 Adjuvant Treatment of Stage III/IV Melanoma

CA209238, a Phase 3, randomized double-blind study evaluating Nivo IV 3 mg/kg (n = 453) versus ipilimumab IV 10 mg/kg (n = 453) in participants with Stage IIIB/C or Stage IV melanoma who were at high risk of recurrence following complete surgical resection. Participants receiving nivolumab had superior 12-month recurrence-free survival (RFS) rate of 70.5% (95% CI, 66.1 to 74.5), as compared to 60.8% in participants receiving ipilimumab (95% CI, 56.0 to 65.2).[18]

In CA209238, participants were included based on American Joint Committee on Cancer (AJCC) 7th edition. AJCC 8th edition (see Appendix 9) was implemented on 01-Jan-2018. The participant data from CA209238 were reviewed using the new staging classification and it was determined that some Stage IIIB participants who were T1bN1a and T1bN2a in the 7th edition would now be mapped as Stage IIIA in the 8th edition, and some Stage IIIA participants would be classified as Stage IIIB (T3a N1–2a), suggesting IIIA participants can be considered reasonable candidates for trial. Furthermore, with a 4-year minimal follow-up, nivolumab monotherapy continued to show durable, long-term RFS benefit, and a better safety profile compared to ipilimumab.

Most recently, data from Phase 3, randomized, double-blind study CA209915 (which included control arm of Nivo IV administered 480 mg every 4 weeks [Q4W]) support the activity of flat

dose (480 mg Q4W) nivolumab with an RFS rate at 3 years of 70% (95% CI, 45 - 85) in patients with completely resected Stage IIIB/C/D or Stage IV melanoma.[19] Treatment benefit observed with nivolumab 480 mg Q4W was consistent with the originally assessed Q2W weight-based dose in CA209238.

Additionally, nivolumab adjuvant therapy was efficacious regardless of programmed death ligand-1 (PD-L1) expression status across adjuvant melanoma trials. The results from these studies further support the choice of adjuvant melanoma in CA2096GE. Moreover, among all the solid tumors, malignant melanoma occurrence is one of the highest in the younger patient populations and notably is the second most common cancer in young women < 30 years of age in the United States of America (USA).[17] The younger/middle-aged patient population often have a much better prognosis and performance status in the adjuvant setting [redacted]

These data supported the global approval of nivolumab IV for adjuvant treatment of melanoma.

3.2.2 Nivolumab Mechanism of Action

Nivolumab (also referred to as BMS-936558, MDX1106, or ONO-4538) is a human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]-S228P) that targets the programmed death-1 (PD-1) cluster of differentiation 279 (CD279) cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes. Binding of PD-1 to its ligands, programmed death ligands 1 (PD-L1) and 2 (PD-L2), results in the downregulation of lymphocyte activation. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens.

Nivolumab is expressed in Chinese hamster ovary (CHO) cells and is produced using standard mammalian cell cultivation and chromatographic purification technologies. The clinical study product is a sterile solution for parenteral administration.

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

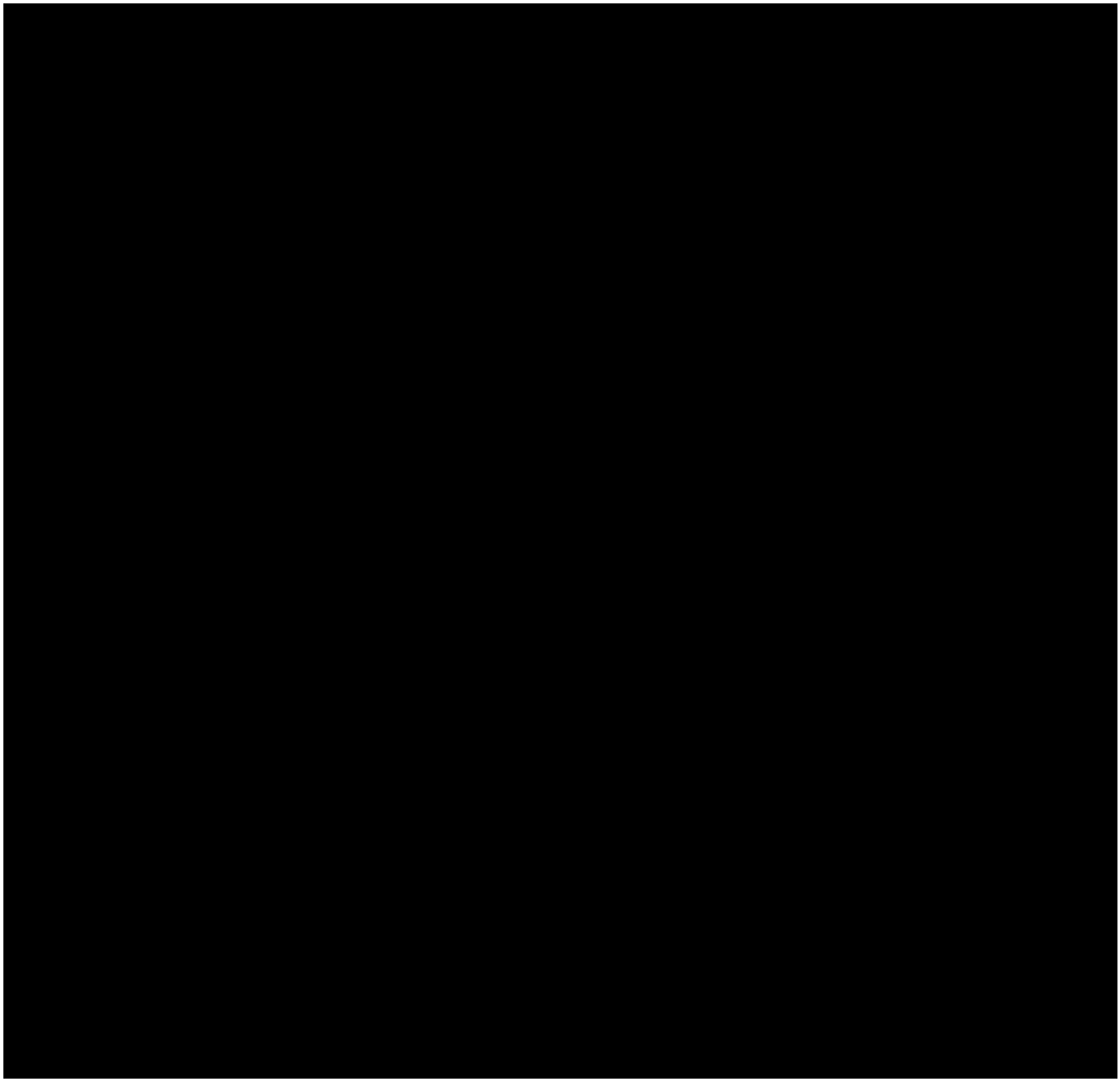
3.2.3 Nivolumab Clinical Activity

Beyond nivolumab activity in the adjuvant treatment of Stage III/IV melanoma, nivolumab has demonstrated durable responses exceeding 6 months as monotherapy in other several tumor types, including NSCLC, melanoma, RCC, cHL, SCLC, gastric cancer, SCCHN, urothelial cancer, HCC, and CRC. In confirmatory trials, nivolumab as monotherapy demonstrated a statistically significant improvement in OS as compared with the current standard of care in patients with advanced or metastatic NSCLC, unresectable or metastatic melanoma, advanced RCC, or recurrent or metastatic SCCHN. Details of the clinical activity in these various malignancies are provided in the USPI and SmPC.

3.2.4 Recombinant Human Hyaluronidase PH20 Enzyme (rHuPH20)

rHuPH20 is a glycosylated 447-amino acid single-chain recombinant human polypeptide that depolymerizes hyaluronan in the SC space locally at the site of injection. Hyaluronan is a repeating polymer of N-acetyl-glucosamine and glucuronic acid that contributes to the soluble gel-like component of the extracellular matrix of the skin.

Depolymerization of hyaluronan by rHuPH20 results in a transient reduction in the viscosity of the gel-like phase of the extracellular matrix and increased hydraulic conductance that facilitates the dispersion and absorption of injected drugs (see rHuPH20 Investigator's Brochure [IB]).[20] Use of rHuPH20 enables the delivery of large volumes of liquid into the SC space (approximately 2 to 20 mL), decreasing dose administration times.



[redacted]

3.3 Benefit/Risk Assessment

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

Overall, the safety profile of nivolumab monotherapy is manageable and generally consistent across completed and ongoing clinical trials with no maximum tolerated dose reached at any dose tested up to 10 mg/kg. Most AEs were low-grade (Grade 1 to 2) with relatively few related high-grade (Grade 3 to 4) AEs. There was no pattern in the incidence, severity, or causality of AEs with respect to nivolumab dose level.

A pattern of immune-related adverse events has been defined, for which management algorithms have been developed; these are provided in Appendix 7. Most high-grade events were manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in these algorithms.

Additional details on the safety profile of nivolumab, including results from other clinical studies, are also available in the nivolumab IB (Nivo SC and Nivo IV).

In safety data from CA2098KX, SC nivolumab showed a safety profile that was similar to the safety profile observed in the nivolumab monotherapy program.

SC administration of rHuPH20 alone or in combination with biological products was generally well-tolerated in all clinical study populations. Most AEs were mild, transient injection site reactions including erythema, pain, bruising, pruritus, burning, tenderness, edema, induration, irritation, paresthesia, numbness, and rash. Moderate injection site reactions, which were reported less frequently, include burning, erythema, pain, and numbness. Mild-to-moderate headache was also commonly reported.

AEs have otherwise generally reflected the adverse reaction profiles of the coadministered drug or have been associated with the rapid introduction of a relatively large volume of fluid into the SC space. The individual doses ranged from 15 U to 96,000 U of rHuPH20. It should be noted that at the highest single dose of 96,000 U, AEs were predominantly mild injection site reactions; there were no deaths, SAEs, or discontinuations due to AEs.[20]

No local or systemic adverse events have been associated with positive binding or neutralizing rHuPH20 antibody titers in clinical trials with rHuPH20.[30]

[redacted]

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-986298 and BMS-936558 is unknown.

3.3.1 Risk Assessment

Table 3.3.1-1: Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s)		
Immune-mediated AEs (eg, colitis diarrhea/colitis, pneumonitis, hepatitis, nephritis, endocrinopathy, rash, neurologic, AEs)	BMS-936558 IB BMS-986298 IB	Recommended IMAE management algorithms are included in Appendix 7 or as per institutional protocol/investigator discretion
Potential Infusion-related Reaction	BMS-936558 IB	Please refer to Section 7.4.5 of protocol
Potential Injection Site Reaction [redacted]	BMS-986298 IB	Please refer to Section 7.4.5 of protocol
Cardiovascular AEs (ie, myocarditis, troponin elevation)	BMS-936558 IB BMS-986298 IB	Management of myocarditis per AE Management Algorithm in Appendix 7 or as per institutional protocol/ investigator discretion
Study Procedures		
Tumor Biopsy (eg, pain, infection)	Not applicable	Per institutional protocol/investigator discretion
Phlebotomy (eg, pain, ecchymosis, bleeding, syncope)	Not applicable	Per institutional protocol/investigator discretion

Table 3.3.1-1: Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
SC Injection [redacted]	Refer to Section 3.3	[redacted]
MRI	Not applicable	Per institutional protocol/investigator discretion
CT	Not applicable	Per institutional protocol/investigator discretion
Allergy to Contrast Agent (eg, reaction to anaphylaxis)	Not applicable	Prophylaxis and/or treatment per institutional protocol/investigator discretion
Other (if applicable)		
[redacted]		
Non-clinical Safety (animal studies)	BMS-986298 IB	Not applicable

Abbreviations: AE, adverse event; [redacted] CT, computed tomography; HCP, healthcare provider; IB, Investigator Brochure; IFU, Instructions For Use; IMAE, immune-mediated adverse event; MRI, magnetic resonance imaging; Nivo, nivolumab; SC, subcutaneous.

3.3.2 Benefit Assessment

This study will also investigate recurrence-free survival in Stage III/IV completely resected melanoma participants. Currently, nivolumab monotherapy is an approved option for adjuvant treatment of melanoma in many countries.

Despite the availability of Nivo IV, there is a need to improve patient quality of life in cancer care. In addition to the benefits of nivolumab to potentially improve RFS and overall survival (OS), participants would benefit from the use of the SC route of administration and the convenience of [redacted] self-administration of nivolumab coformulated with rHuPH20.

3.3.3 Nivolumab Overall Benefit/Risk Conclusion

The Sponsor will evaluate the benefit/risk profile of the study on an ongoing basis. This evaluation will be based on all available data with particular attention to [redacted] safety trends in this or any other clinical study of BMS-986298 or BMS-936558 whose severity and/or frequency suggest that participants would be exposed to an unreasonable and significant risk of illness or injury.

4 OBJECTIVES AND ENDPOINTS

Per Protocol Amendment 01, PK co-primary endpoints, secondary endpoints, [redacted] of the study have been removed. Efficacy, patient-reported outcomes (PROs), and biomarker analyses will not be completed. Samples already collected for PK and immunogenicity assessments will be analyzed bioanalytically for nivolumab concentrations and anti-drug antibodies (ADAs) and reported as listings. Further collections for PK, ADAs, biomarkers, and PROs will be discontinued. Only safety assessments will be conducted.

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the safety and tolerability of nivolumab SC [redacted] coformulated with rHuPH20 and nivolumab IV	• AEs/SAEs and treatment-related AEs/SAEs
Exploratory	
[redacted]	
• To assess nivolumab concentrations following 600 mg SC [redacted] coformulated with rHuPH20 (Arm A) and 240 mg IV Q2W (Arm B)	• Nivolumab concentrations
• To assess immunogenicity of nivolumab SC [redacted] coformulated with rHuPH20 (Arm A) and nivolumab IV (Arm B)	• Anti-nivolumab antibodies, NAb, and titers • Anti-rHuPH20 antibodies, NAb, and titers
• To assess the efficacy of nivolumab following 600 mg SC [redacted] coformulated with rHuPH20 (Arm A) and 240 mg IV Q2W (Arm B)	• RFS (per investigator) and OS rate at 12 months

Abbreviations: AE, adverse event; [redacted]; BMS, Bristol-Myers Squibb Company; eCRF, electronic case report form; IMAE, immune-mediated adverse event; IV, intravenous; NAb, neutralizing antibody; OS, overall survival; Q2W, every 2 weeks; RFS, recurrence-free survival; rHuPH20, recombinant human hyaluronidase PH20 enzyme; SAE, serious adverse event; SC, subcutaneous.

The primary trial objective is to assess the safety and tolerability of [redacted] and Nivo IV.

5 STUDY DESIGN

5.1 Overall Design

Study CA2096GE is a multicenter, open-label, Phase 3 study. **Per Protocol Amendment 01, PK co-primary endpoints, secondary endpoints, [redacted] of the study have been removed. Efficacy, PROs, and biomarker analyses will not be completed. Samples already collected for PK and immunogenicity assessments will be analyzed bioanalytically for nivolumab concentrations and ADAs and reported as listings. Further collections for PK, ADAs, biomarkers, and PROs will be discontinued. Only safety assessments will be conducted.** Therefore, the study design has been adapted to reflect the Protocol Amendment 01 changes, [redacted]. Part 1 is no longer hypothesis-driven, but rather descriptive in nature (Arm A and Arm B), with the primary objective being safety and tolerability and exploratory objective as described in Table 4-1.

- Arm A (n = 6):
  - [redacted]
- Arm B (n = 8):
  - Nivo IV (BMS-936558) 240 mg Q2W for Cycles 1 through 4.
  - Nivo IV 480 mg Q4W Cycle 5 onwards for up to total of 52 weeks.
  - All dosing will be performed in-clinic.

[redacted]

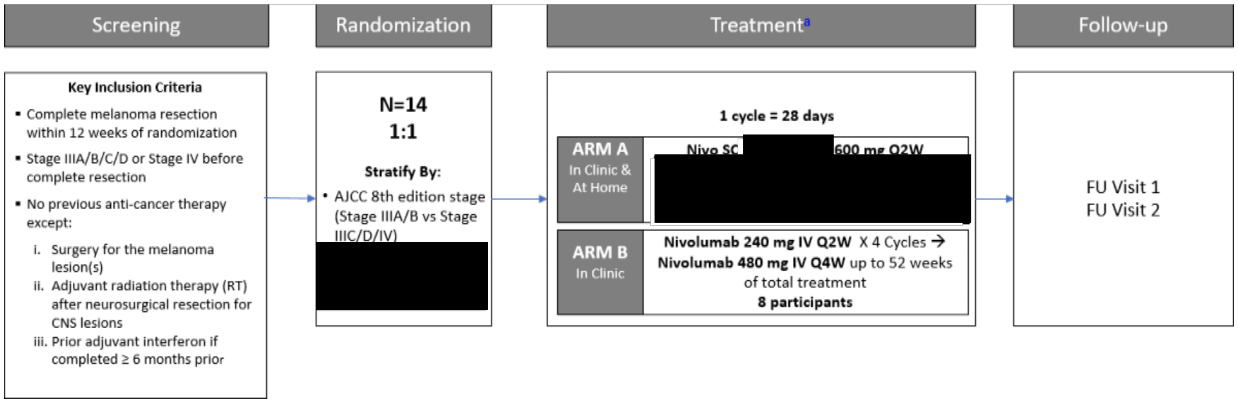
Participants will be stratified by stage (Stage IIIA/B vs Stage IIIC/D/IV) per AJCC 8th edition [redacted]

All participants will be treated until recurrence of disease, unacceptable toxicity, participant withdrawal of consent, death, or a maximum of 52 weeks of treatment from first dose, whichever occurs first.

[redacted]

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

Figure 5.1-1: Study Design Schema



Abbreviations: AJCC, American Joint Committee on Cancer; CNS, central nervous system; FU, follow-up; IV, intravenous; N, number of participants; Nivo, nivolumab; PK, pharmacokinetic, Q2W, every 2 weeks; Q4W, every 4 weeks; RT, radiation therapy; SC, subcutaneous; vs, versus.

[a] Treatment until recurrence of disease, unacceptable toxicity, participant withdrawal of consent, death, or a maximum of 52 weeks of treatment from first dose, whichever occurs first.

5.1.1 Screening Period [redacted]

Not applicable per Protocol Amendment 01 (enrollment closed).

Screening will occur between Day -28 and Day -1. Participants will provide written informed consent to participate in the study before completing any protocol-specified procedures or evaluations not considered to be part of the participants' standard care. After signing the informed consent form (ICF), participants will be evaluated based on the assessments outlined in the Schedule of Activities (Section 2, Table 2-1) and inclusion and exclusion criteria (Sections 6.1 and 6.2, respectively) within 28 days (unless otherwise specified) prior to randomization (Part 1) [redacted] Participants will be enrolled using Interactive Response Technology (IRT) on the day of consent. Each participant will be registered in to the IRT system to obtain a participant number. Participants who complete the Screening Period and meet the criteria for inclusion/exclusion will begin the Treatment Period.

A formalin fixed, paraffin-embedded (FFPE) tumor tissue block (preferred) or a minimum of 15 unstained slides of tumor tissue obtained from the recent resection (preferred) or an archival biopsy conducted within 6 months prior to enrollment, and preferably with no intervening systemic anti-cancer treatment between time of acquisition and enrollment, must be submitted to the central lab. If despite best efforts, a minimum of 15 unstained slides are not obtainable, submission of 5 unstained slides is acceptable. Tissue availability needs to be determined during the screening period. It is recommended that tumor tissue be submitted during the screening period; however, it must be submitted no later than 14 days post-randomization/treatment assignment. Fine-needle aspirates or other cytology samples are not acceptable. (see Section 9.8.1 and Lab Manual for additional information).

5.1.2 Treatment Period

The Treatment Period begins at the time of randomization and will end at the beginning of the Follow-up Period (Follow-up Visit 1). Each cycle consists of 28 days. Treatment cycles will be counted from Cycle 1, Day 1 continuously regardless of dose interruptions or missed doses. Participants will undergo safety and efficacy assessments as defined in the Schedule of Activities (Section 2). Every effort should be made to schedule visits within the protocol-specified windows. Please refer to Sections 7.1.1 and 7.1.2 for treatment administration details.

Results of efficacy surveillance must be reviewed by investigator and documented before dose administration of the next cycle.

Participant safety will be preserved through:

- Protocol-defined visits to the clinic
- Phone communication with the participant (see Section 9.4.5)
- Regular monitoring of labs and symptoms
- Other safety reporting to the HCP by the participant or the participant's caregiver
- All participants will be treated until recurrence of disease, unacceptable toxicity, participant withdrawal of consent, death, or a maximum of 52 weeks of treatment from first dose, whichever occurs first.

Biomarker assessments are no longer applicable per Protocol Amendment 01.

5.1.2.1 Randomized Study Cohort

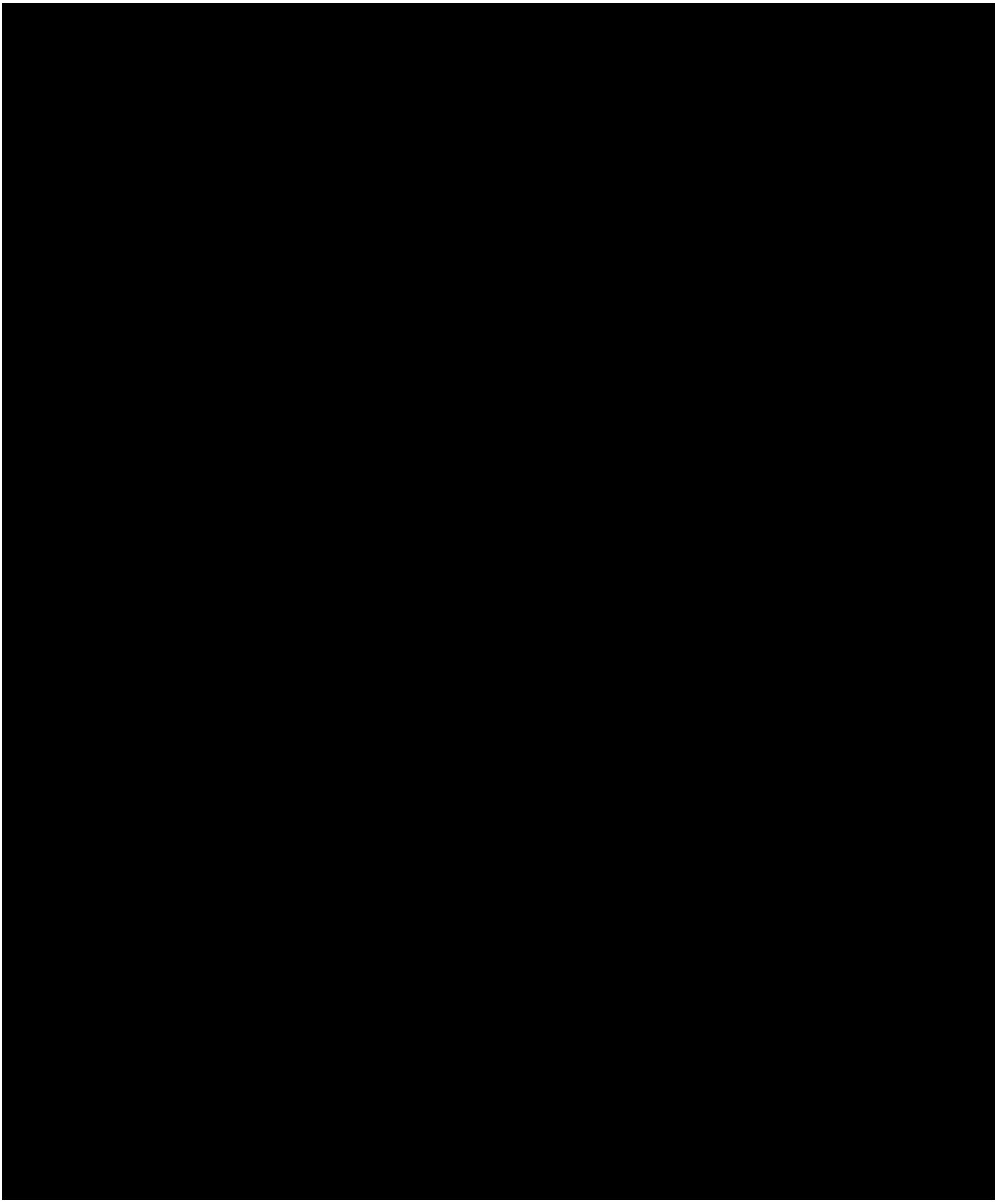
Arm A: Participants randomized to Arm A will receive [redacted] with rHuPH20 [redacted]

[redacted]

[redacted]

Arm B: Participants randomized to Arm B will receive Nivo IV 240 mg Q2W during the first 4 cycles. Following Cycle 4, participants will receive Nivo IV 480 mg Q4W. All doses/visits will be in-clinic.

[redacted]



5.1.3 Follow-Up Period

Safety Follow-up will begin after the Treatment Period, when the participant has completed up to 52 weeks of treatment or discontinues study treatment for any reason (see Section 8.1). The Safety Follow-up Period consists of 2 Follow-up Visits: Visit 1 (to occur 30 days [± 7 days] from date of last treatment dose) and Visit 2 (to occur 100 days [± 7 days] from date of last treatment dose). All adverse events (AEs)/serious adverse events (SAEs) (including AEs/SAEs related to severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) should be collected continuously using National Cancer Institute (NCI) Common Technical Criteria for Adverse Events (CTCAE) version 5 (v5) during the Safety Follow-up.

Beyond the 100 days from the last dose of study therapy, participants will be followed for all drug-related AEs/SAEs until AE resolves, returns to baseline, is deemed irreversible, until the participant is lost to follow-up, or withdraws study consent.

Beyond the 100 days from the last dose of study treatment, all AEs/SAEs associated with confirmed or suspected SARS-CoV-2 infection will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, the event is deemed irreversible, or until the participant is lost to follow-up (as defined in Section 8.3). For suspected cases, participants should be followed until SARS-CoV-2 infection is ruled-out as per institutional policy on SARS-CoV-2.

Participants who are randomized but who are never treated or who discontinue study treatment for any reason other than tumor recurrence should continue to have surveillance assessments until recurrence of disease or study discontinuation as per the Schedule of Activities, Section 2. Surveillance assessments should not be delayed until the planned follow-up visits.

5.1.4 Data Monitoring Committee and Other Committees

Data Monitoring Committee: A safety DMC will be implemented in this study to provide safety oversight throughout the course of Part 1 of the study. The DMC charter will describe the procedures related to the committee operations in greater detail. On 26-Oct-2022, enrollment was paused and a total of 14 participants had been randomized. On 24-Feb-2023, the study was terminated with no additional participants having been randomized. As this is an open-label study, the Sponsor will continue the safety monitoring of remaining participants in the study. No subsequent DMC meeting will occur.

Study Steering Committee: A Study Steering Committee (SSC) will be established to provide advisory oversight of the quality of the trial, with the objective of ensuring scientific integrity and the successful conduct of the CA2096GE Study. On 26-Oct-2022, enrollment was paused and a total of 14 participants had been randomized. On 24-Feb-2023, the study was terminated with no additional participants having been randomized. The Sponsor will continue to ensure the scientific integrity and successful conduct of the study. No SSC meeting will occur.

5.2 Number of Participants

The trial has been terminated. [redacted] 14 participants randomized and treated in the study with 6 participants in Arm A and 8 participants in Arm B.

5.3 End of Study Definition

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

End of trial is defined as the last participant last visit or completion of Follow-up Visit 2.

Study completion is defined as the final date on which data for the primary endpoint were or are expected to be collected, if this is not the same.

A participant is considered to have completed the study if he/she has completed the end of trial (Follow-up Visit 2).

5.4 Scientific Rationale for Study Design

5.4.1 Rationale for One Year Duration of Treatment

There is no consensus about the optimal treatment duration for patients in the adjuvant setting. For trials of interferon, various treatment frequencies and durations have been investigated (ranging between 6 months and 5 years).[18,19] There is a significant geographic variability in the duration of interferon therapy, usually ranging between 1 and 1.5 years throughout the world. In order to minimize toxicity leading to discontinuation of study drug while maintaining expected efficacy of the study drug, the decision was reached to limit the duration of study therapy of nivolumab on CA2096GE to 1-year maximum duration. This is supported by data from CA209238, which was approved for nivolumab as adjuvant treatment of melanoma.

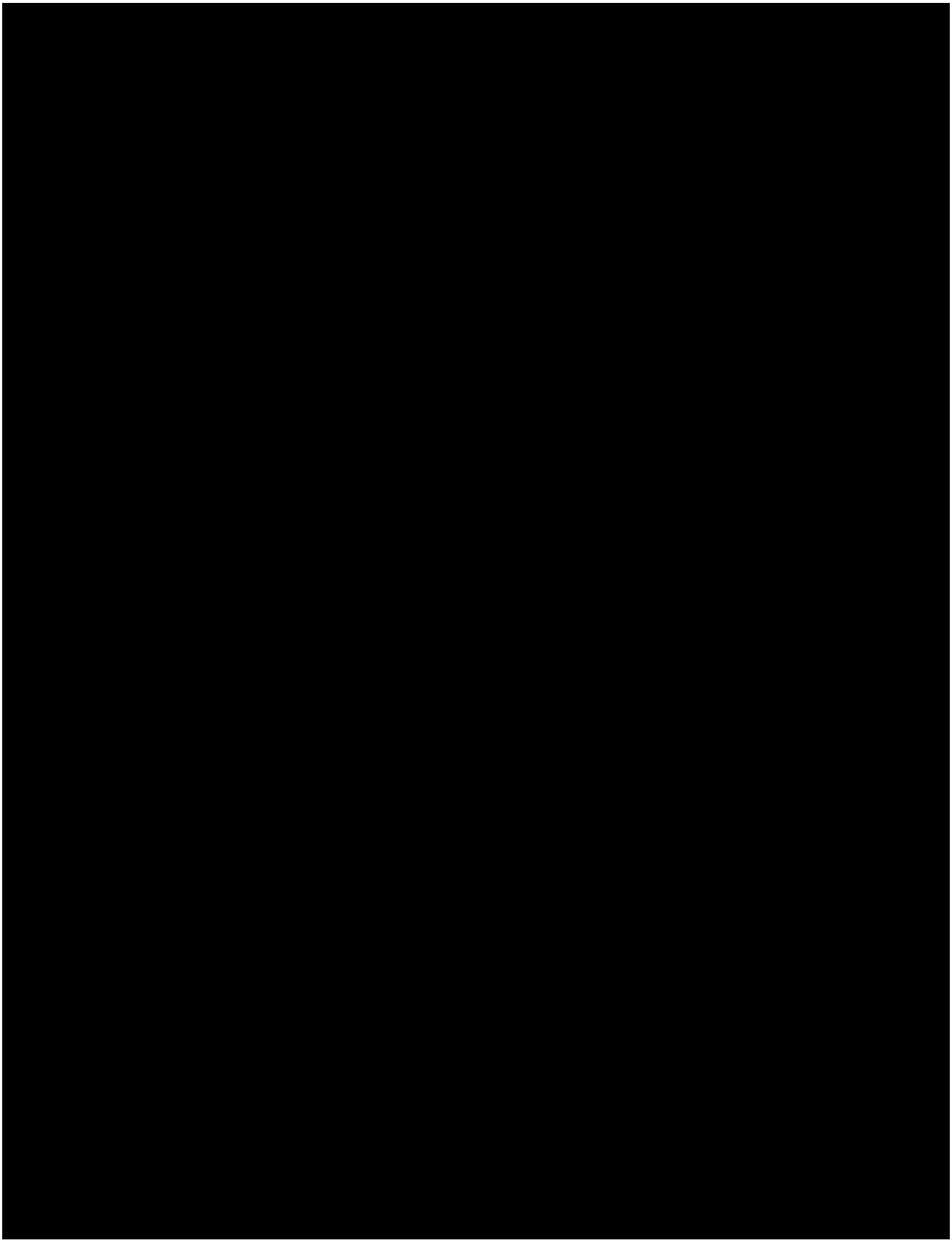
5.4.2 Rationale for Part 1 Endpoints and Non-Inferiority Margin

Not applicable per Protocol Amendment 01. The following information refers to the original study design.

PK co-primary endpoints for Part 1 of this study are Cavgd28 and Cminss. The co-primary endpoints would help to establish PK non-inferiority between the 2 different routes of administration (SC [redacted] and IV). The use of co-primary PK endpoints will provide data on exposure to nivolumab at different time points during treatment. Cavgd28 is the time-averaged concentration over the first 28 days of dosing and represents an early measure of exposure. The Cminss endpoint is a steady-state measure of exposure that can be used to assess accumulation with repeat dosing and as surrogate for long-term administration with [redacted]. Blood sampling time points have been selected to adequately characterize the co-primary PK endpoints (Cavgd28 and Cminss) while minimizing the burden to patients and HCPs.

Non-inferiority of [redacted] to Nivo IV will be concluded if the lower limit of the 2-sided 90% CIs for the ratio of geometric means for nivolumab (SC vs IV) Cavgd28 and Cminss is not lower than 0.8; as this criterion is consistent with regulatory advice.

Non-inferior PK exposures at early and late time points, particularly when the dose administration is given by the participant (instead of HCP), ensure effective drug levels are maintained over time and provide pharmacologic surrogate of disease control similar to approved Nivo IV.



[redacted]

5.4.6 Rationale for Inclusion of Clinical Outcome Assessments/PROs (Part 1)

Not applicable per Protocol Amendment 01. The following information refers to the original study design.

The evaluation of clinical outcomes assessments (COAs) such as patient-reported outcomes (PROs) is an increasingly important aspect of clinical efficacy and safety in oncology trials. Such data provide an understanding of the impact of treatment from the participant's perspective and offer insights into patient experience that may not be captured through physician reporting. Additionally, generic health-related quality of life (HRQoL) measures provide data needed for calculating utility values to inform health economic models.

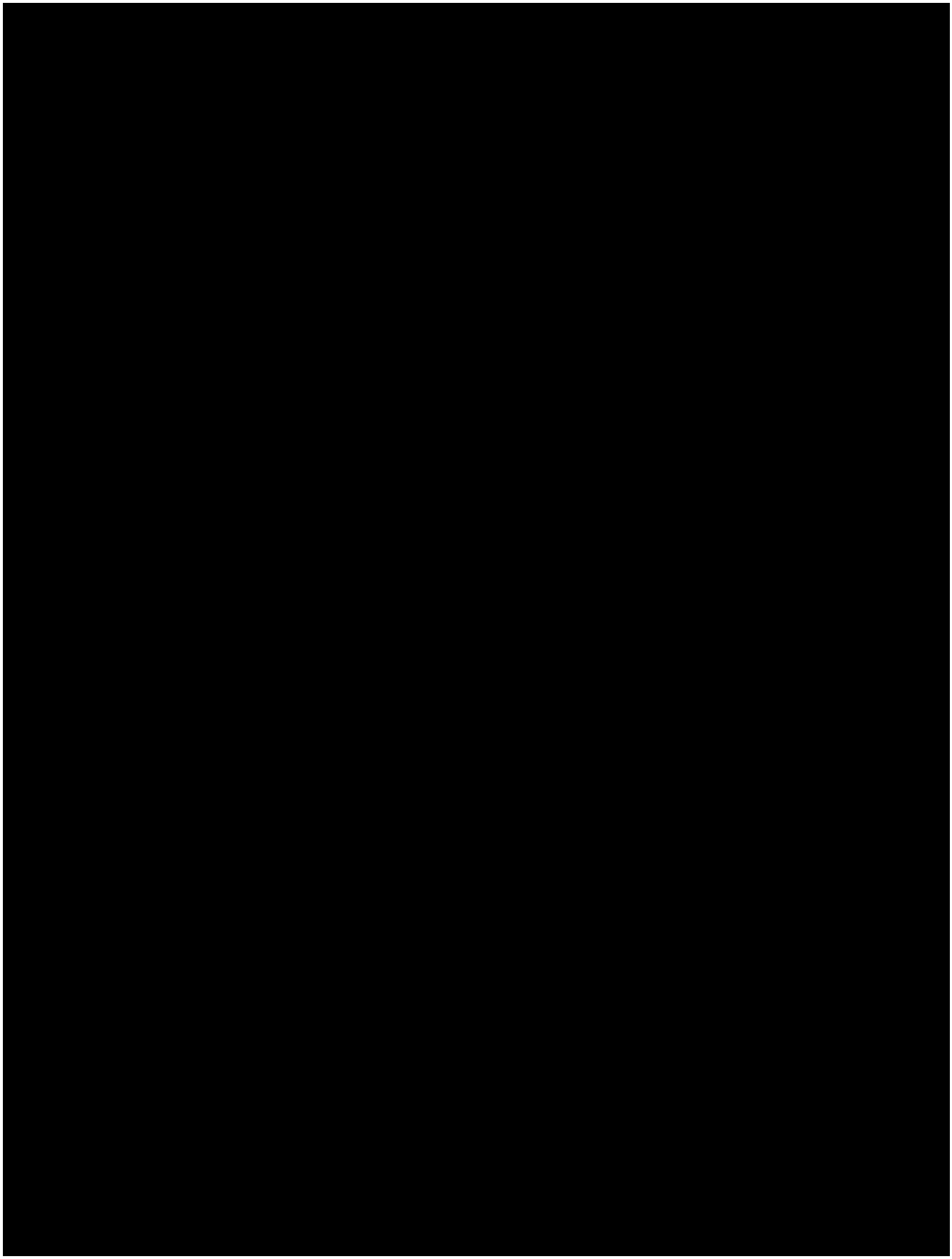
To explore overall participant self-confidence with SC injection the Self-Confidence domain of the Self-Injection Assessment Questionnaire (SIAQ) will be used in the Part 1 Arm A (SC arm) only. Participant satisfaction with route of administration (IV versus SC) will be assessed using a modified version of the Cancer Treatment Satisfaction Questionnaire (CTSQ), namely the Satisfaction with Cancer Therapy domain. The Functional Assessment of Cancer Therapy - General 7 item version (FACT-G7) will be used to evaluate HRQoL. The FACT-G7 has been shown to be a valid, reliable, and rapid measure for monitoring symptoms and concerns in oncology practice and research. A modified version of the Treatment Administration Satisfaction Questionnaire (TASQ) will be used to assess Satisfaction, Physical Impact, Psychological Impact, Impact on Activities of Daily Living, and Convenience between IV and SC Routes of Administration. The EuroQol-5 Dimension-5 Level (EQ-5D-5L) will be used for economic evaluations and overall health status.

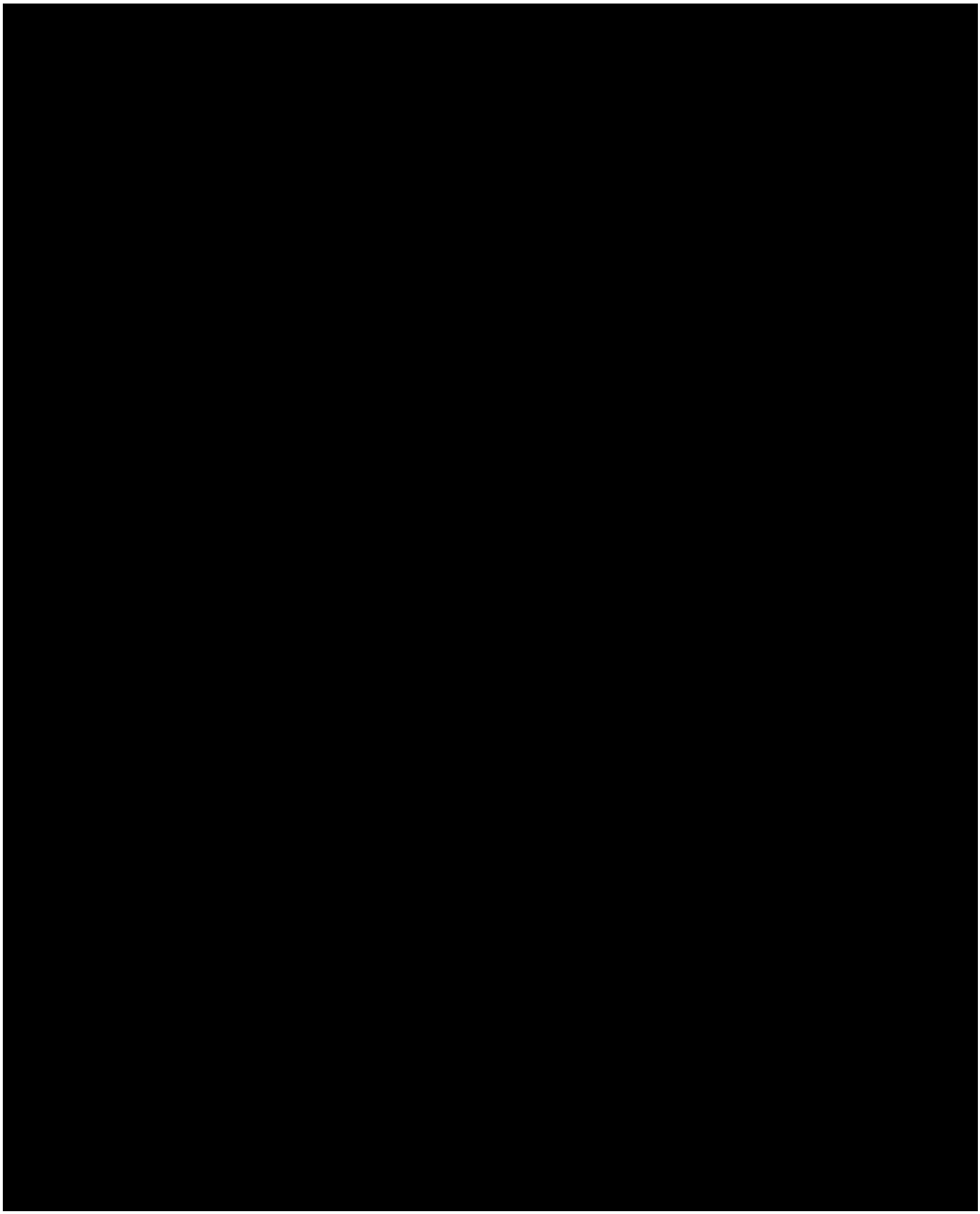
5.4.7 Rationale for Open Label

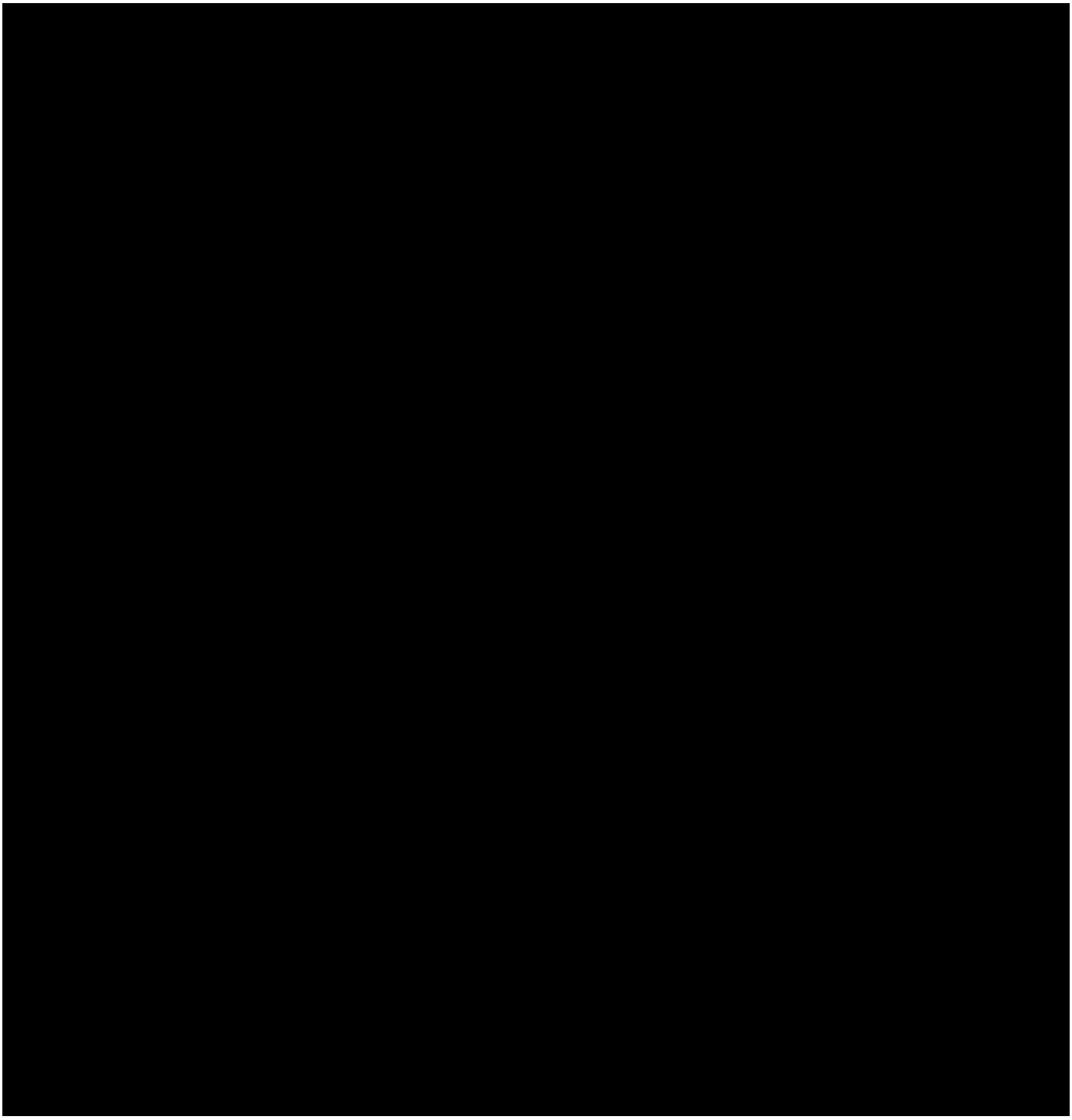
The expected incidence of AEs with nivolumab have been extensively studied and defined in prior clinical trials and are not expected to differ based on route of administration or delivery systems, (when not considering injection site reactions or procedure related AEs) as further demonstrated by the preliminary safety data from the nivolumab SC injection study, CA2098KX; therefore, an open-label approach is justified. In addition, the technical challenges associated with blinding favor the open-label design. The BMS study team will not conduct aggregate analyses by treatment group prior to pre-specified database locks (Sponsor blind approach).

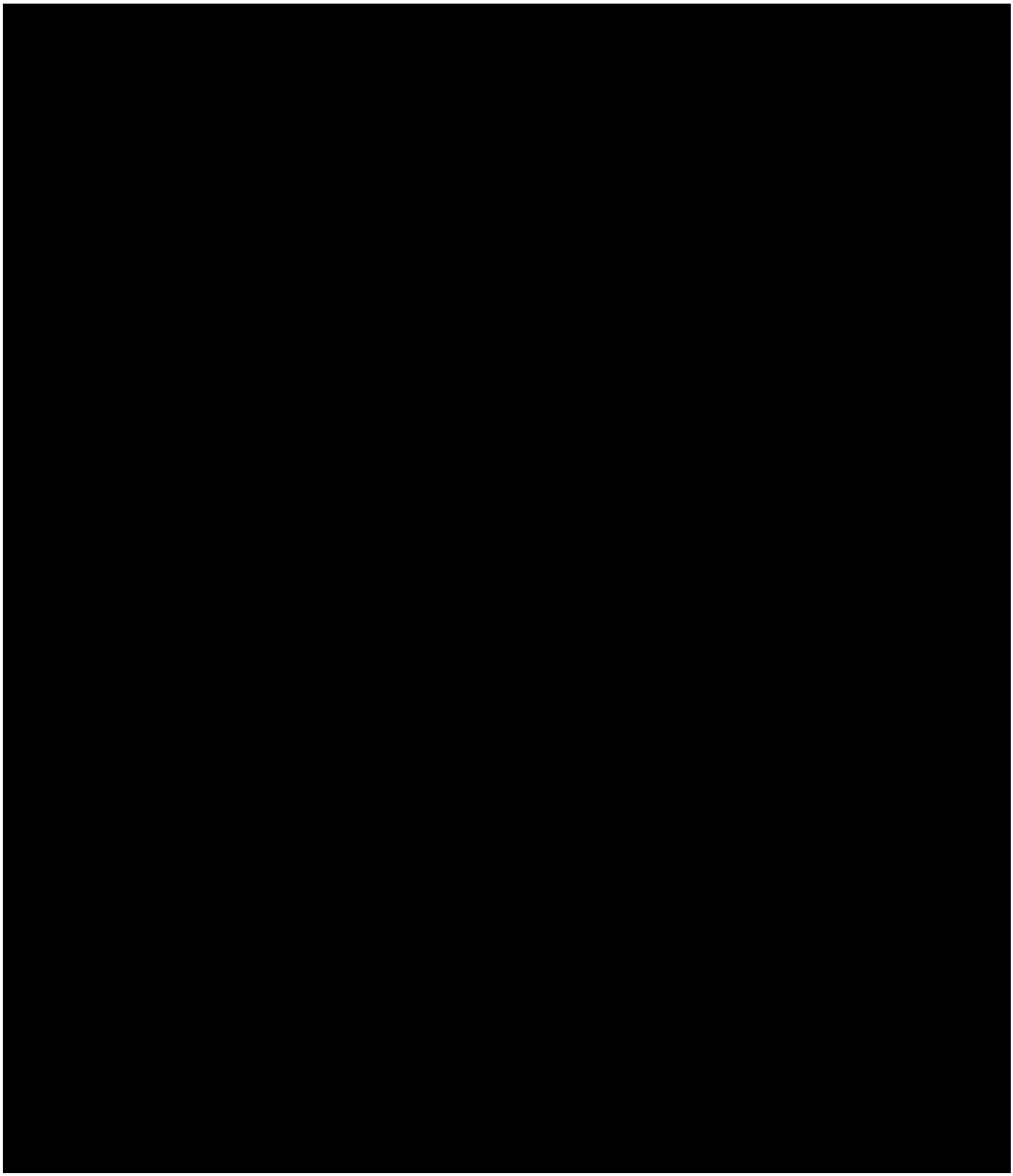
5.5 Justification for Dose

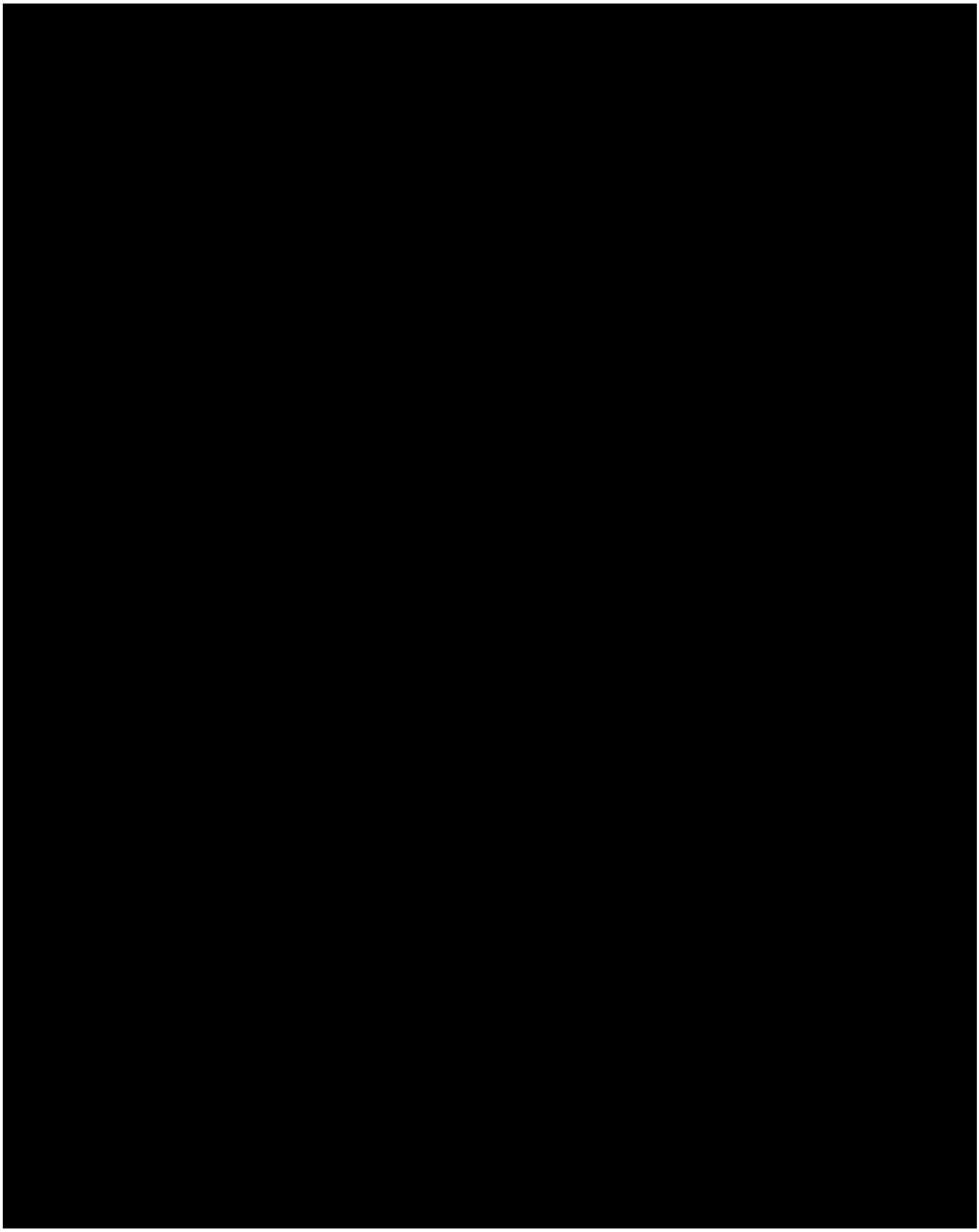
[redacted]











[redacted]

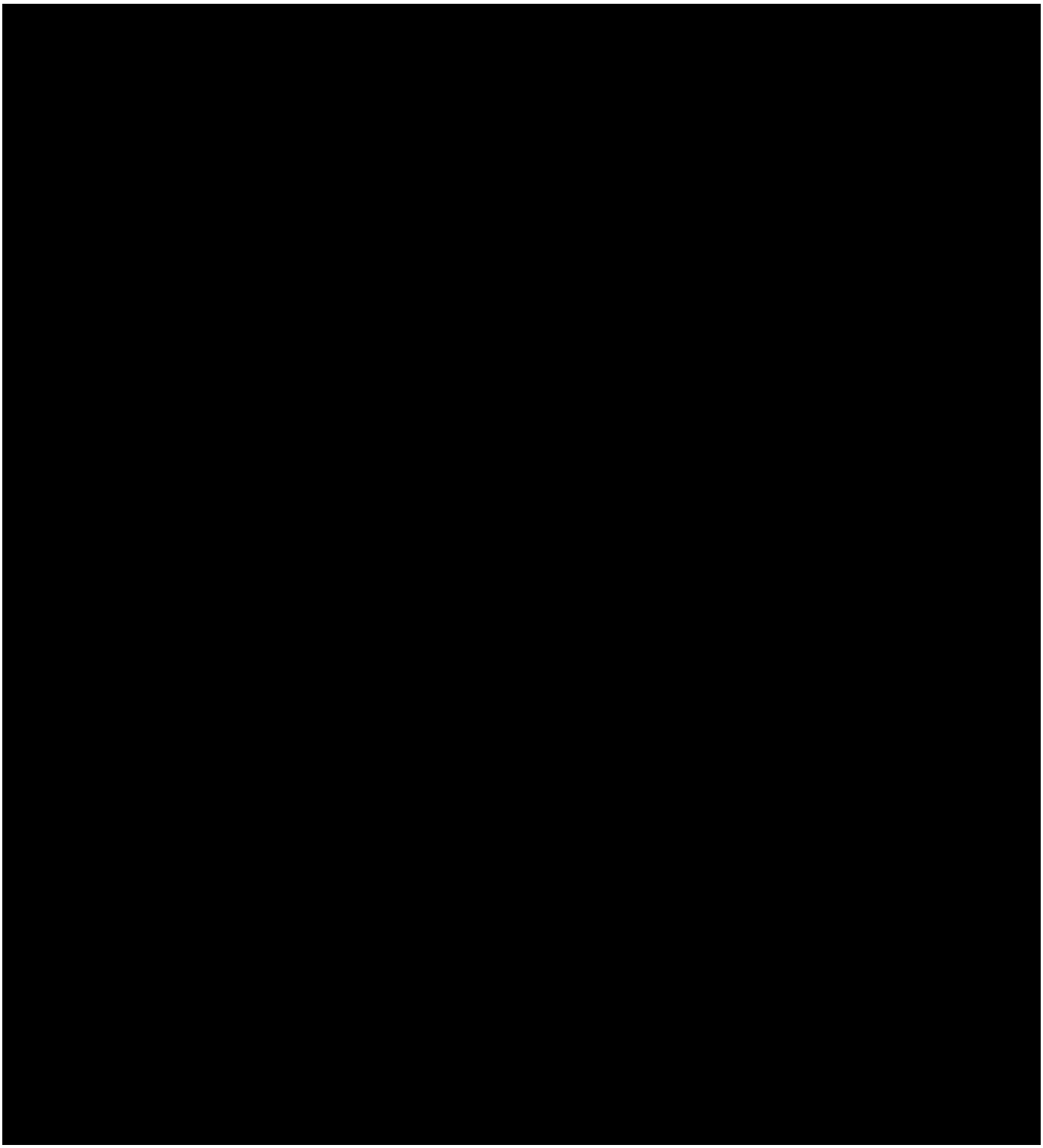
5.5.2 Rationale for Dosing Regimen - Intravenous (Arm B)

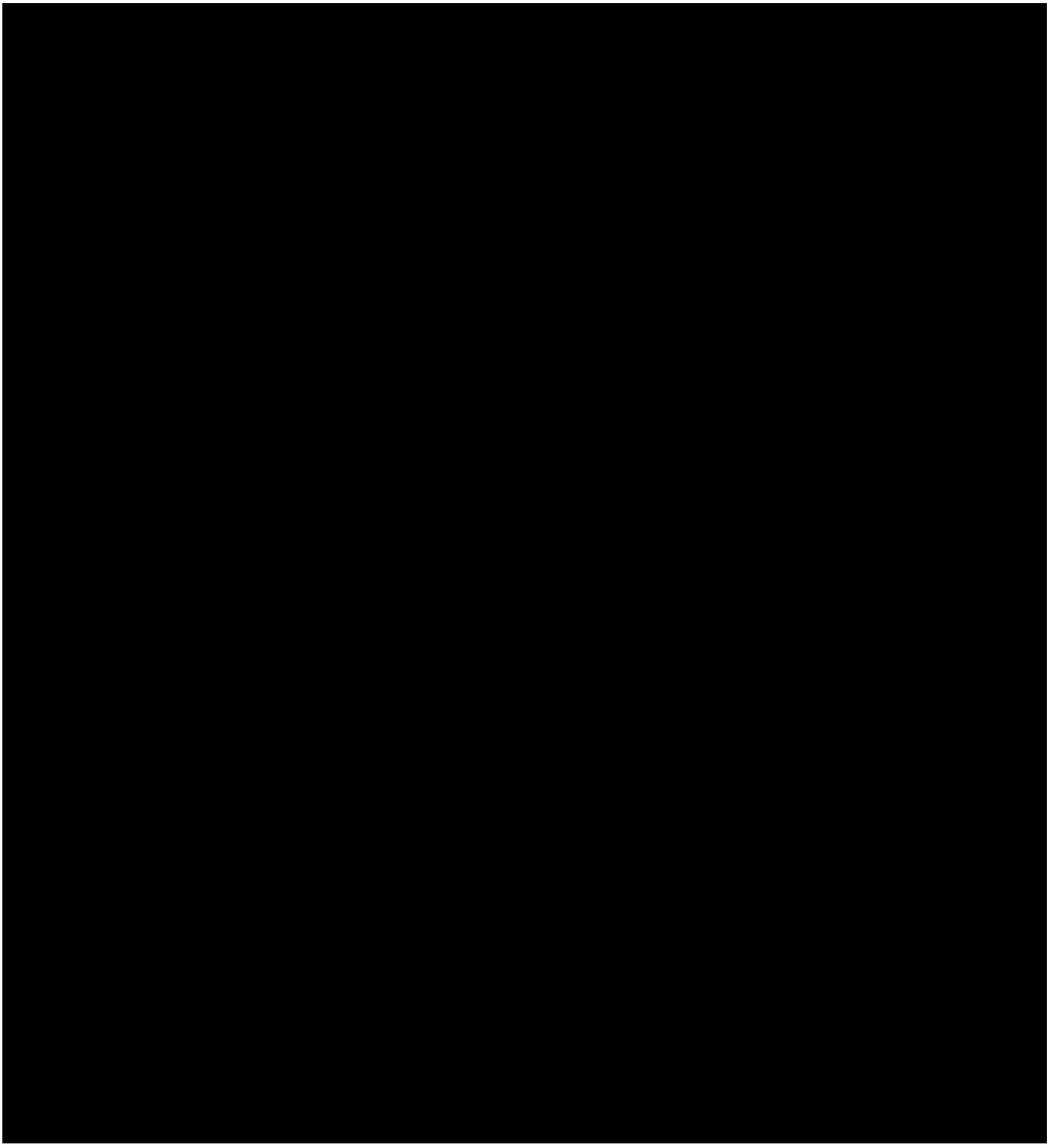
Nivolumab monotherapy was originally approved as a body weight-based dose of 3 mg/kg IV Q2W and was recently updated to flat-dosing regimens of 240 mg Q2W or 480 mg Q4W in multiple indications. For this study, the selected dose of 240 mg via IV Q2W is per dose/schedule approved for this patient population. In addition, there is extensive PK, safety, and efficacy data available at this dose across multiple tumors and dosing regimens. Global development with flat doses of nivolumab are ongoing in a broad range of clinical trials in a variety of additional tumor types. Based on the aforementioned nivolumab 240 mg IV Q2W is considered an appropriate and globally accepted comparator to [redacted]

In relation to transition to 480 mg IV Q4W, most recently, data from the comparator arm in study CA209915 support that the activity of flat dose (480 mg IV Q4W) nivolumab performs similarly to the originally assessed 3 mg/kg IV Q2W dosing schedule in study CA209238.

Additional details on nivolumab posologies and risk-benefit can be found in the BMS-936558 investigator brochure.

[redacted]





5.5.4 Rationale for Switch from Q2W to Q4W (Arm B [IV])

In order to mitigate participant burden, a switch from Q2W to Q4W will occur after Cycle 5 for participants in Arm B receiving IV nivolumab. Cycle 5 has been selected as the time for the switch as it was the time at which the primary endpoints in the original study design were being collected.

5.5.5 Rationale for Continued Adjuvant Therapy for Participants Who Are Diagnosed with Melanoma in Situ During Study Treatment

Malignant melanoma in situ (MMIS) Stage 0 includes Tis, N0, M0, demonstrates a radial growth phase in which the proliferation of malignant melanocytes is confined to the epidermis. Patients with a new Stage 0 melanoma are at minimal risk from that new tumor. The risk of death develops from advanced Stage IIIB/C/D or Stage IV melanoma for which they are receiving treatment during the clinical trial. Opdivo (nivolumab) is approved for the adjuvant treatment of adult patients with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection. Consequently, in the absence of intolerable toxicity, patients with diagnosed MMIS should continue adjuvant therapy using the same dose and schedule for their original melanoma for a maximum of 1-year total duration starting from first dose (maximum of 13 doses). Melanoma in situ will not be considered a new primary malignancy.

5.5.6 Safety/IMG with SC Nivolumab + rHuPH20

In the Phase 1/2 CA2098KX study, the safety profile of Q2W and Q4W nivolumab SC monotherapy in participants with advanced/metastatic cancer was evaluated. The preliminary review of the study safety data showed that nivolumab SC vial and syringe across all studied doses was safe, tolerable, and manageable with an AE profile consistent with nivolumab when administered via IV.

- Sixty-seven participants in Part A (Group 1) and Part B (Group 2, 3, 4) received 1 SC nivolumab dose (720 mg or 960 mg) with or without rHuPH20 followed by IV nivolumab. Upon selection of the dose, 28 of these participants who were still on study at the time of the amendment, transitioned to SC nivolumab 1,200 mg + rHuPH20 Q4W (Part C)
- Thirty-six participants in Part D received SC nivolumab dose of 1,200 mg + rHuPH20 Q4W from the beginning of therapy
- Thirty-six participants in Part E received SC nivolumab dose of 600 mg + rHuPH20 Q2W from the beginning of therapy

Part A/B: Participants received single-dose SC nivolumab, either 720 mg (with or without rHuPH20) or 960 mg (with or without rHuPH20): The safety data from single-dose SC nivolumab followed by IV (Cycle 2+) included treatment-related AEs and SAEs previously reported within the Nivo IV IB with the exception of SC local reactions.[34] With respect to local AEs reported with SC injection, the local site reactions were low incidence, of low grade, and manageable.

Part C (transitioning to 1,200 mg + rHuPH20 from prior single-dose SC and IV): Interpretation of treatment-related AEs in Part C was difficult and clear attribution of systemic treatment-related AEs to SC nivolumab (vs IV) was not possible given switching between formulations and the long half-life of nivolumab.

Of the 28 participants that transitioned from Part A/B to Part C, any Grade AEs after transitioning to SC nivolumab were reported in 26 (93%) participants. Treatment-related AEs were reported in 16 (57%) participants after transitioning to Part C, all of which were Grade 1 to 2. In the majority of participants, low-grade treatment-related AEs were reported in the general disorders and

administration site conditions and skin and subcutaneous disorders SOCs. Within the general disorders and administration site conditions SOC, there were 3 (33.3%), 2 (33.3%), 3 (60.0%), and 1 (12.5%) participants that were reported with low-grade treatment-related AEs in Groups 1, 2, 3, and 4, respectively. Within the skin and subcutaneous disorders SOC, there were 2 (22.2%), 1 (16.7%), 0 (0.0%), and 1 (12.5%) participants that were reported with low-grade treatment-related AEs in Groups 1, 2, 3, and 4, respectively. No participants were reported to develop new or worsening Grade 3 or higher treatment-related AEs, and there were no reported treatment-related AEs leading to discontinuation or death.

Part D (1,200 mg + rHuPH20): Any grade AEs were reported in all 36 participants, of these there were 17 (47.2%) reports of Grade 3 to 4 AEs and 4 (11.1%) reports of Grade 5 AEs. Any grade treatment-related AEs were reported in 28 (77.8%) participants; of these there were 6 (16.7%) reports of Grade 3 to 4 treatment-related AEs. Treatment-related SAEs were reported in 3 (8.3%) participants, all were Grade 3 to 4. In the majority of participants, treatment-related AEs were reported in the general disorders and administration site conditions, skin and subcutaneous disorders, and endocrine disorders SOCs. Within the general disorders and administration site conditions SOC, there were 16 (44.4%) participants that were reported with low-grade treatment-related AEs. Within the skin and subcutaneous disorders SOC, there were 12 (33.3%) participants that were reported with low-grade treatment-related AEs, of these there were 3 (8.3%) reports of Grade 3 to 4 treatment-related AEs. Within the endocrine disorders SOC, there were 10 (27.8%) participants that were reported with low-grade treatment-related AEs. Of the reported treatment-related AEs, 4 participants (11.1%) were reported with AEs leading to treatment discontinuation. There was no reported treatment-related AE leading to death. No dose-related safety concerns were noted. Results to date suggest that SC nivolumab with rHuPH20 is safe and well-tolerated, which supports further clinical investigation.

Part E (600 mg + rHuPH20): In 36 participants, any grade AEs were reported in 27 (75.0%) participants; of these there were 10 (27.8%) reports of Grade 3 to 4 AEs, and 1 (2.8%) report of a Grade 5 AE. Any grade treatment-related AEs were reported in 20 (55.6%) participants; of these there were 3 (8.3%) reports of Grade 3 to 4 treatment-related AEs. There was 1 (2.8%) report of a treatment-related SAE of Grade 3 to 4. In the majority of participants, treatment-related AEs were reported in the skin and subcutaneous disorders and general disorders and administration site conditions SOCs. Within the skin and subcutaneous disorders SOC, there were 10 (27.8%) participants that were reported with low-grade treatment-related AEs. Within the general disorders and administration site conditions SOC, there were 9 (25.0%) participants that were reported with low-grade treatment-related AEs. There were no reported treatment-related AEs leading to discontinuation or death.

Across treatment groups, ADAs were reported with nivolumab (BMS-986298) with and without rHuPH20 similar to what has been reported with the IV formulation. In Part C, 15 out of 67 participants had positive treatment-emergent ADA for nivolumab (7 out of 22 [31.8%]) participants in the nivolumab 720 mg with rHuPH20 group, 5 out of 18 (27.8%) participants in the nivolumab 720 mg without rHuPH20 group, and 3 out of 10 (30%) participants in the nivolumab 960 mg with rHuPH20 group; there was no treatment-emergent ADAs in the 17 participants who

received nivolumab 960 mg without rHuPH20 group. One out of 22 (4.5%) participants in the nivolumab 720 mg with rHuPH20 group was classified as persistent positive ADA. In Part D, 1 out of 26 (3.8%) participants developed treatment-emergent ADA; however, none were persistent positive. No neutralizing ADAs were detected in any part of the study and no association of anti-nivolumab antibody development with select AEs (ie, bronchospasm, hypersensitivity, infusion-related reactions) was reported. Data do not suggest that the presence of ADAs with SC nivolumab impacts clinical safety (eg, injection site or hypersensitivity reactions). Overall, the PK, safety, and immunogenicity data further support clinical development of additional dosing schedules [redacted] and 600 mg Q2W) of SC [redacted]nivolumab.

5.6 Clinical Pharmacology Summary

5.6.1 Clinical Pharmacology of Nivolumab

Nivolumab pharmacokinetics (PK) was assessed using a population PK approach for single-agent nivolumab.

Nivolumab as a single agent: The PK of single-agent nivolumab was studied in patients over a dose range of 0.1 to 20 mg/kg administered as a single dose or as multiple doses of nivolumab as a 60-minute intravenous infusion every 2 or 3 weeks. Nivolumab clearance (CL) decreases over time, with a mean maximal reduction (% coefficient of variation [CV%]) from baseline values of 24.5% (47.6%) resulting in a geometric mean steady-state clearance (CLss) (CV%) of 8.2 mL/h (53.9%) in patients with metastatic tumors; the decrease in CLss is not considered clinically relevant. Nivolumab clearance does not decrease over time in patients with completely resected melanoma, as the geometric mean population clearance is 24% lower in this patient population compared with patients with metastatic melanoma at steady-state. The geometric mean volume of distribution at steady-state (Vss) (CV%) is 6.8 L (27.3%), and geometric mean elimination half-life (t1/2) is 25 days (77.5%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg every 2 weeks, and systemic accumulation was 3.7-fold. The exposure to nivolumab increases dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks. The predicted exposure (Cavg and Cmax) of nivolumab after a 30-minute infusion is comparable to that observed with a 60-minute infusion.

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

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

Hepatic Impairment: The effect of hepatic impairment on the clearance of nivolumab was evaluated by population PK analyses in patients with HCC and in patients with other tumors with

mild hepatic impairment (total bilirubin [TB] less than or equal to the ULN and AST greater than ULN or TB greater than 1 to 1.5× ULN and any AST) and in HCC patients with moderate hepatic impairment (TB greater than 1.5 to 3× ULN and any AST). No clinically important differences in the clearance of nivolumab were found between patients with mild/moderate hepatic impairment.

Full details on the clinical pharmacology aspects of nivolumab can be found in the Investigator Brochure and product label.

Full details regarding approved nivolumab dosages in their associated indications may be found in the product label.

5.6.2 Clinical Pharmacology of Recombinant Human Hyaluronidase PH20

rHuPH20 may enable coadministered therapeutics to overcome administration time and volume barriers to SC drug delivery. Overall, data from a number of studies suggest that rHuPH20 can increase the utility of SC drug administration by improving ease of administration and the PK profile of concurrently administered large proteins. The half-life of rHuPH20 in skin is < 30 minutes, and the local permeability barrier in these tissues is restored to pre-injection levels within 24 hours to 48 hours after injection of hyaluronidase.[35,36] A study showed that rHuPH20 was not detectable systemically in healthy volunteers and patients following SC administration at doses of 10,000 U and 30,000 U with a currently marketed monoclonal antibody product.[37] Another study of the PK of rHuPH20 (Halozyme Study HALO-104-104) demonstrated that plasma concentrations of rHuPH20 rapidly declined, with a very short $t_{1/2}$ (≤ 10.4 minutes) and the plasma concentration became undetectable (< 0.03 ng/mL) within 1.5 hours after the end of the IV infusion for IV doses of 10,000 or 30,000 units of rHuPH20.[38]

As of Dec-2022, 1,592 participants were exposed to HYLENEX and other rHuPH20 DPs in 30 clinical studies conducted under Investigational New Drug 66,888 or in postmarketing Phase 4 studies. In these studies, the maximum duration of exposure was 12 weeks, and individual doses ranged from 15 U to 96,000 U rHuPH20. In partnered trials with co-administered therapeutics, more than 9,000 participants were exposed.[20]

In partnered trials, the maximum duration of participant exposure to rHuPH20 was up to 3.5 years (187.69 patient-years) in the combined pivotal and safety extension studies for HYQVIA® (Immune Globulin Infusion 10% [Human] With Recombinant Human Hyaluronidase). One Halozyme study evaluated rHuPH20 injected intradermally as a single agent, 28 studies evaluated rHuPH20 injected SC immediately prior to another agent or coadministered SC with another agent, and 13 studies evaluated rHuPH20 coformulated with recombinant human insulin (insulin-PH20) or rapid-acting insulin analogs (aspart-PH20 and lispro-PH20). One Halozyme IV dosing study was conducted using 10,000 U or 30,000 U of rHuPH20 in healthy volunteer participants. All but 2 Halozyme studies were conducted in adult populations; pediatric exposure (< 18 years of age) in 2 clinical studies included 139 participants with mild-to-moderate dehydration who received SC infusions of isotonic fluids.

Across all studies, SC injections of rHuPH20 were generally well tolerated in healthy participants, dehydrated pediatric participants, hospice and palliative care participants, participants with type 1

and 2 diabetes, and participants with rheumatoid arthritis. SC injections of rHuPH20 either alone or co-administered with lactated Ringer's, normal saline, co-injected drugs (morphine, ceftriaxone, insulin, and insulin analogues), or biologic products (immunoglobulin G and adalimumab) have been well tolerated in all clinical trials. Most AEs were mild, transient injection-site reactions, including erythema, pain, bruising, pruritus, burning, tenderness, edema, induration, irritation, paresthesia, numbness, and rash. Moderate injection-site reactions, which have occurred less frequently, included burning, erythema, pain, and numbness. Mild-to-moderate headache was also commonly reported. AEs in these trials have otherwise generally reflected the adverse reaction profiles of the co-administered drug or have been associated with the rapid introduction of a relatively large volume of fluid into the SC space.

Antibodies to rHuPH20 have been evaluated in several nonclinical and clinical studies. To date, no clinical signs or symptoms have been associated with positive binding or neutralizing antibodies titers in clinical trials with rHuPH20 and no confirmed rHuPH20-neutralizing antibody activity has been detected. In addition to these studies, a large clinical safety database exists for rHuPH20 as a tissue permeability enhancer co-administered with several approved products in the US and/or Europe (European Union), including:

- DARZALEX FASPRO™ (daratumumab and hyaluronidase-fihj);
- PHESGO™ (pertuzumab, trastuzumab, and hyaluronidase-zzxf; US only);
- HYQVIA® (Immune Globulin Infusion 10% [Human] with rHuPH20);
- Herceptin® SC/HERCEPTIN HYLECTATM (trastuzumab coformulated with rHuPH20);
- MabThera® SC/RITUXAN HYCELA® (rituximab coformulated with rHuPH20); and
- HYLENEX® (rHuPH20 alone; US only).

6 STUDY POPULATION

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

6.1 Inclusion Criteria

Not applicable per Protocol Amendment 01 (as of 24-Feb-2023, enrollment in this study has closed).

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

1) Signed Written Informed Consent

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

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

2) Type of Participant and Target Disease Characteristics

a) All participants must have been diagnosed with either Stage IIIA (> 1 mm tumor in lymph node)/B/C/D or Stage IV melanoma by AJCC 8th edition and have histologically confirmed melanoma (as documented in the pathology report) that is completely surgically resected (free of disease) with negative margins in order to be eligible. All melanomas, except uveal and mucosal melanoma, regardless of primary site of disease, will be allowed.

b) Participants are eligible if central nervous system (CNS) metastases have been resected and participants are neurologically stable.

   i) Prior resected CNS metastases must be without evidence of recurrence, as determined by magnetic resonance imaging (MRI) performed at least 4 weeks after resection is complete and within 28 days prior to randomization (Part 1) [redacted].

   ii) Participants must be off immunosuppressive doses of systemic steroids (>10 mg/day prednisone or equivalent) for at least 14 days prior to study drug administration and must have returned to neurologic baseline post-operatively.

   iii) For CNS lesion(s), a pathology report indicating that there has been complete resection of CNS lesion(s) will suffice as confirmation of negative margins.

c) Complete resection must be performed within 12 weeks prior to randomization (Part 1) [redacted] Management of residual lymph nodes after positive sentinel lymph node biopsy (ie, completion lymph node dissection) will be as per local standards and recommendations for the individual participant.

d) All participants must have disease-free status documented by a complete physical examination within 14 days prior to randomization (Part 1[redacted] and imaging studies within 28 days prior to randomization/treatment assignment. Imaging studies must include computed tomography (CT) scan of the chest; CT or MRI scans of the abdomen, pelvis, and all known sites of resected disease; and brain MRI or CT (brain CT allowable if MRI is contraindicated).

e) Participants must have an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 1 (Appendix 8).

f) [redacted]

3) Age of Participant

Participants must be ≥ 18 years of age or age of majority at the time of informed consent.

4) Reproductive Status

Investigators shall counsel women of child bearing potential (WOCBP) on the importance of pregnancy prevention, the implications of an unexpected pregnancy, and the potential of fetal toxicity occurring due to transmission of study intervention to a developing fetus.

The investigator shall evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

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

a) Female Participants:

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

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

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

(1) If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

iv) Additional requirements for pregnancy testing during and after study intervention are located in Section 2, Schedule of Activities.

v) 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.

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

vii) WOCBP are permitted to use hormonal contraception methods (as described in Appendix 4).

viii) 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 after the last dose and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction for the same time period

b) Male Participants:

No additional contraceptive measures are required to be used.

6.2 Exclusion Criteria

Not applicable per Protocol Amendment 01 (as of 24-Feb-2023, enrollment in this study has closed).

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

1) Medical Conditions

a) History of uveal or mucosal melanoma.

b) Untreated/unresected CNS metastases or leptomeningeal metastases.

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

d) Participants with serious or uncontrolled medical disorder within 4 weeks prior to screening.

   i) Additionally, in the case of prior SARS-CoV-2 infection, 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 investigational treatment.

e) Concurrent malignancy (present during screening) requiring treatment or history of prior malignancy active within 2 years prior to randomization (Part 1) [redacted] (ie, participants with a history of prior malignancy are eligible if treatment was completed at least 2 years before randomization/treatment assignment and the patient has no evidence of disease). Participants with history of prior early stage basal/squamous cell skin cancer or non-invasive or in situ cancers that have undergone definitive treatment at any time are also eligible.

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

g) Any condition that according to investigator makes participant ineligible from participation in the study, including but not limited to medical (including psychological, psychiatric), or social conditions; or conditions that can impact ability to comply with protocol requirements (eg, conditions that preclude the use of IV or SC route of study drug administration) or that can put the participant at risk. Participants with history of self-harm including suicidal attempts will be excluded from the study.

2) Prior/Concomitant Therapy

a) Prior immunotherapy treatments for any prior malignancies are not permitted (such as, but not limited to anti-PD-1, anti-PD-L1, anti-PD-L2, or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways).

b) Participants treated with anti-cancer therapy directed against the resected melanoma (for example, but not limited to, systemic, local, radiation, and radiopharmaceuticals) except:

   i) Surgery for the melanoma lesion(s)

   ii) Adjuvant radiation therapy after neurosurgical resection for CNS lesions

   iii) Prior adjuvant interferon completed ≥ 6 months prior to randomization (Part 1) [redacted]

c) Treatment with complementary medications (eg, herbal supplements or traditional Chinese medicines) to treat the disease under study within 2 weeks prior to randomization (Part 1) [redacted] Such medications are permitted if they are used as supportive care. Refer to Section 7.7.1 for prohibited therapies.

d) Participants currently in other interventional trials, including those for COVID-19, until the protocol specific washout period is achieved. If a study participant has received an investigational COVID-19 vaccine or other investigational product designed to treat or prevent COVID-19 prior to screening, enrollment must be delayed until the full dosing schedule of the vaccine has been completed and the biologic impact of the vaccine or investigational product is stabilized, unless the delay would compromise the participant's health or suitability for enrollment as determined by the investigator, and in discussion with the BMS Medical Monitor/designee.

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

f) Treatment with any live attenuated vaccine within 30 days of first study treatment (Vaccines that are not live attenuated are allowed, including COVID-19 vaccines). Details regarding COVID-19 vaccination are available in Section 7.7.

3) Physical and Laboratory Test Findings

a) Positive pregnancy test at enrollment or prior to administration of study medication.

Note for criteria 3b to 3e: May not transfuse, use growth factors, and/or coagulation factors within 14 days of randomization (Part 1) [redacted]

b) White blood cell count < 2000/µL.

c) Neutrophils < 1500/µL.

d) Platelets < $100*10^3$/µL.

e) Hemoglobin < 9.0 g/dL.

f) Blood creatinine > 2.0 × upper limit of normal (ULN), unless calculated creatinine clearance (CrCl) ≥ 30 mL/min (using the Cockcroft-Gault formula).

g) Aspartate transaminase (AST) / alanine aminotransferase (ALT) > 3.0× ULN.

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

i) Any positive test result for hepatitis B virus (HBV) indicating presence of virus (eg, Hepatitis B surface antigen [HBsAg, Australia antigen]) positive.

j) Any positive test result for hepatitis C virus (HCV) indicating presence of active viral replication (detectable HCV-ribonucleic acid [RNA]). Note: Participants with positive HCV antibody and an undetectable HCV RNA are eligible to enroll.

k) Known human immunodeficiency virus (HIV) positive with an AIDS defining opportunistic infection within the last year, or a current CD4 count < 350 cells/uL. Participants with HIV are eligible if:

i) they have received antiretroviral therapy (ART) for at least 4 weeks prior to randomization (Part 1) [redacted]

ii) they continue on ART as clinically indicated while enrolled on study.

iii) CD4 counts and viral load are monitored per standard of care by a local healthcare provider.

NOTE: Testing for HIV must be performed at sites where mandated locally. HIV positive participants must be excluded where mandated locally (see Appendix 10).

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

4) Allergies and Adverse Drug Reaction

a) History of allergy or hypersensitivity to study drug components [redacted]

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

5) Other Exclusion Criteria

a) Prisoners or participants who are involuntarily incarcerated. (Note: Under certain specific circumstances and only in countries where local regulations permit, a person who has been imprisoned may be included or permitted to continue as a participant. Strict conditions apply, and BMS approval is required.)

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 (Arm A Only)

6.3.1 Meals and Dietary Restrictions

Not applicable.

[redacted]

6.4 Screen Failures

Not applicable per Protocol Amendment 01 (enrollment closed).

Screen failures are defined as participants who consent to participate in the clinical study but who are not subsequently randomized (Part 1) [redacted] 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-in Period

Not applicable per Protocol Amendment 01 (enrollment closed).

Participant Re-enrollment: This study permits the re-enrollment of a participant who 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.

A participant who is a pre-treatment failure in Part 1 (participant has not been randomized/has not been treated) [redacted] If re-enrolled, the participant must be re-consented and assigned a new participant number.

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

The most current result prior to randomization (Part 1 [redacted] is the value by which study inclusion will be assessed, because it represents the participant's most current clinical state.

Laboratory parameters and/or assessments that are included in Table 2-1, Screening Procedural Outline, and Section 9.4.4, 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, for example by reverse transcriptase-polymerase chain reaction (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, participants may be considered eligible for the study after meeting all inclusion/exclusion criteria related to active infection, and after meeting the following criteria:

- At least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared or positive RT-PCR or viral antigen test result
- At least 24 hours have passed since last fever without the use of fever-reducing medications
- Acute symptoms (eg, cough, shortness of breath) have resolved
- In the opinion of the investigator, there are no COVID-19-related sequelae that may place the participant at a higher risk of receiving investigational treatment
- Negative follow-up SARS-CoV-2 RT-PCR or viral antigen test based on institutional, local, or regional guidelines

7 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

Study intervention includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational/Auxiliary [Medicinal] Product (Non-IP/Non-IMP/AxMP) as indicated in Table 7.1-1.

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

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

7.1 Study Interventions Administered

Table 7.1-1: Study Interventions

ARM Name	Arm A Nivolumab SC [redacted]	Arm B Nivolumab IV
Intervention Name	Nivolumab/rHuPH20 BMS-986298	Nivolumab BMS-936558
Type	[redacted]	Drug
Dose Formulation	SC injection	Solution for injection[a]
[redacted]		
Dosage Level(s)	Nivolumab 600 mg [redacted] Once Q2W for up to 52 weeks	Nivolumab 240 mg Q2W for 16 weeks (8 doses) Nivolumab 480 mg Q4W for 36 weeks (9 doses)
Route of Administration	SC injection	IV infusion
IMP and Non-IMP	IMP	IMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labeling	[redacted]	Study intervention will be provided in vial(s) in a carton. Each vial(s) and carton will be labeled as required per country requirement.
Current/Former Name(s) or Alias(es)	N/A - see intervention name	Opdivo

Abbreviations: [redacted]; IMP, investigational medicinal product; IV, intravenous; N/A; not applicable[redacted] Q2W, every 2 weeks; Q4W, every 4 weeks; rHuPH20, recombinant human hyaluronidase PH20 enzyme; SC, subcutaneous; U, units.

[a] "Concentrate for Solution for Infusion" is also being used for certain countries for dose formulation to align with the commercial Opdivo product.

7.1.1 Study Treatment Details for Intravenous Administration of Nivolumab

Participants randomized to Arm B will receive nivolumab at a dose of 240 mg over an approximately 30-minute IV infusion Q2W on Days 1 and 15 of the first 4 treatment cycles. Subsequently, participants will receive nivolumab at a dose of 480 mg over an approximately 30-minute IV infusion Q4W on Day 1 of each treatment cycle starting at Cycle 5, Day 1 until disease recurrence, unacceptable toxicity, withdrawal of consent, a maximum of 52 weeks of treatment from first dose, death, or the end of study, whichever occurs first. If needed, flush the intravenous line with an appropriate amount of diluent (eg, 0.9% Sodium Chloride or 5% Dextrose in water) to ensure that the complete dose is administered over approximately 30 minutes. Begin study treatment within 3 calendar days of randomization.

There will be no intra-participant dose escalations or reductions of nivolumab allowed. For Q2W dosing cycles, participants may be dosed no less than 12 days from the previous dose. The dosing window is ± 3 days. Premedications are not recommended for the first dose of nivolumab.

Monitor participants carefully for infusion-site reactions during nivolumab administration and assess the infusion site following the infusion during Cycle 1, Days 1 and 15. If an acute infusion reaction is noted, manage participants according to Section 7.4.5.

Doses of study drug(s) may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment. Dosing visits are not skipped, only delayed.

Please refer to the current Investigator Brochure and/or Pharmacy Manual for further details regarding storage, preparation, and administration of nivolumab.

Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

7.2 Method of Study Intervention Assignment

Before the study is initiated, designated site staff will receive log-in information and directions on how to access the IRT. Each participant will be assigned a unique participant number known as patient identification number (PID) after signing the consent. Participant's study information and data will be recorded only using the patient identification number. Participant numbers will not be reassigned. An IRT will be employed to manage participant randomization, treatment assignment, and dispensation of study drug. The investigator or designee will register the participant for enrollment by following the enrollment procedures established by BMS.

The following information is required for enrollment:

- Date that informed consent was obtained
- Year of birth
- Gender at birth

Participants who have met all eligibility criteria will be randomized in a 1:1 ratio and stratified by weight (< 80 kg vs ≥ 80 kg) and AJCC 8th edition staging (Stage IIIA/B vs Stage IIIC/D/IV).

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

7.3 Blinding

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

As this study is open-label, blinding is not applicable; however, the specific treatment will be assigned using IRT. The bioanalytical laboratory will receive treatment assignments in order to minimize unnecessary analysis of samples and/or to be able to determine dilutions.

7.4 Dosage Modification

7.4.1 Dose Delay Criteria for Nivolumab In-Clinic

Dose delay criteria apply for all drug-related adverse events. Delay administration of nivolumab (SC AI or IV) if any of the delay criteria in Table 7.4.2-1 are met. Delay nivolumab dosing for any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Dose must be delayed for SARS-CoV-2 infection either confirmed or suspected.

For participants who require delay of nivolumab, re-evaluate weekly, or more frequently, if clinically indicated and resume dosing when criteria to resume treatment are met. (see Section 7.4.3). Continue efficacy surveillance per protocol even if dosing is delayed.

No dose escalations or reductions for nivolumab are permitted.

[redacted]

Table 7.4.2-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Nivolumab

Drug-Related Adverse Event (AE) per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Gastrointestinal			
Colitis or Diarrhea	Grade 2	Delay dose	Dosing may resume when AE resolves to baseline
	Grade 3	Delay dose	Dosing may resume when AE resolves to baseline
	Grade 4	Permanently discontinue	
Renal			
Serum Creatinine Increased	Grade 2 or 3	Delay dose	Dosing may resume when AE resolves to Grade ≤ 1 or baseline value
	Grade 4	Permanently discontinue	
Pulmonary			
Pneumonitis	Grade 2	Delay dose	Dosing may resume after pneumonitis has resolved to ≤ Grade 1.
	Grade 3 or 4	Permanently discontinue	
Hepatic			
Aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin (T.bili) increased	AST or ALT > 3x and ≤5x upper limit of normal (ULN) or T.Bili >1.5x and ≤3x ULN, regardless of baseline value	Delay dose	Dosing may resume when laboratory values return to baseline.
	AST or ALT > 5 x ULN or T. bili > 3 x ULN, regardless of baseline value	Delay dose or permanently discontinue	In most cases of AST or ALT > 5 x ULN or T.bili >3x ULN, study treatment will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion between the investigator and the Medical Monitor/ designee must occur and approval from Medical Monitor prior to resuming therapy.

Table 7.4.2-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Nivolumab

Drug-Related Adverse Event (AE) per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
	Concurrent AST or ALT > 3 x ULN and T.bili > 2 x ULN, regardless of baseline value	Permanently discontinue	
Endocrinopathy			
Adrenal Insufficiency	Grade 2 adrenal insufficiency	Delay dose	Dosing may resume after adequately controlled with hormone replacement.
	Grade 3 or 4 adrenal insufficiency or adrenal crisis	Delay dose or permanently discontinue	Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If adrenal insufficiency resolves or is adequately controlled with physiologic hormone replacement, participant may not require discontinuation of study drug.
Hyperglycemia	Hyperglycemia requiring initiation or change in daily management (Grade 2 or 3)	Delay dose	Dosing may resume if hyperglycemia resolves to Grade ≤1 or baseline value, or is adequately controlled with glucose-controlling agents.
	Grade 4	Delay dose or permanently discontinue	Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If hyperglycemia resolves, or is adequately controlled with glucose-controlling agents, participant may not require discontinuation of study drug.
Hypophysitis/Hypopituitarism	Symptomatic Grade 1-3 that is also associated with corresponding abnormal lab and/or pituitary scan	Delay dose	Dosing may resume if endocrinopathy resolves to be asymptomatic, or is adequately controlled with only physiologic hormone replacement.
	Grade 4	Delay dose or permanently discontinue	Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If endocrinopathy resolves or is adequately controlled with physiologic hormone replacement, participant may not require discontinuation of study drug.
	Grade 2 or 3	Delay dose	Dosing may resume if endocrinopathy resolves to be asymptomatic, or is adequately controlled with only

Table 7.4.2-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Nivolumab

Drug-Related Adverse Event (AE) per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Hyperthyroidism or Hypothyroidism			physiologic hormone replacement or other medical management.
	Grade 4	Delay dose or permanently discontinue	Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If endocrinopathy resolves or is adequately controlled with physiologic hormone replacement or other medical management, participant may not require discontinuation of study drug.
Skin			
Rash	Grade 2 rash covering >30% body surface area or Grade 3 rash	Delay dose	Dosing may resume when rash reduces to ≤10% body surface area
	Suspected Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or drug reaction with eosinophilia and systemic symptoms (DRESS)	Delay dose	Dosing may resume if SJS, TEN, or DRESS is ruled out and rash reduces to is ≤10% body surface area
	Grade 4 rash or confirmed SJS,TEN, or DRESS	Permanently discontinue	
Neurological			
Guillain-Barre Syndrome (GBS)	Any Grade	Permanently discontinue	
Myasthenia Gravis (MG)	Any Grade	Permanently discontinue	
Encephalitis	Any Grade encephalitis	Delay dose	After workup for differential diagnosis, (ie, infection, tumor-related), if encephalitis is not drug related, then dosing may resume when AE resolves
	Any Grade drug-related encephalitis	Permanently discontinue	

Table 7.4.2-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Nivolumab

Drug-Related Adverse Event (AE) per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Myelitis	Any Grade myelitis	Delay dose	After workup for differential diagnosis, (ie, infection, tumor-related), if myelitis is not drug related, then dosing may resume when AE resolves
	Any Grade drug-related myelitis	Permanently discontinue	
Neurological (other than GBS, MG, encephalitis, or myelitis)	Grade 2	Delay dose	Dosing may resume when AE resolves to baseline
	Grade 3 or 4	Permanently discontinue	
Myocarditis			
Myocarditis	Symptoms induced from mild to moderate activity or exertion	Delay dose	Dosing may resume after myocarditis has resolved
	Severe or life threatening, with symptoms at rest or with minimal activity or exertion, and/or where intervention indicated.	Permanently discontinue	
Other Clinical AE			
Pancreatitis: Amylase or Lipase increased	Grade 3 with symptoms	Delay dose	Note: Grade 3 increased amylase or lipase without signs or symptoms of pancreatitis does not require dose delay. Dosing may resume when participant becomes asymptomatic.
	Grade 4	Permanently discontinue	
Uveitis	Grade 2 uveitis	Delay dose	Dosing may resume if uveitis responds to topical therapy (eye drops) and after uveitis resolves to Grade ≤ 1 or baseline. If participant requires oral steroids for uveitis, then permanently discontinue study drug.
	Grade 3 or 4 uveitis	Permanently discontinue	

Table 7.4.2-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Nivolumab

Drug-Related Adverse Event (AE) per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Other Drug-Related AE (not listed above)	Grade 2 non-skin AE, except fatigue	Delay dose	Dosing may resume when AE resolves to Grade ≤ 1 or baseline value.
	Grade 3 AE - First occurrence lasting ≤ 7 days	Delay dose	Dosing may resume when AE resolves to Grade ≤ 1 or baseline value.
	Grade 3 AE- First occurrence lasting > 7 days	Permanently discontinue	
	Recurrence of Grade 3 AE of any duration	Permanently discontinue	
	Grade 4 or Life-threatening adverse reaction	Permanently discontinue	
Other Lab abnormalities			
Other Drug-Related lab abnormality (not listed above)	Grade 3	Delay dose	Exceptions: No delay required for: Grade 3 lymphopenia Permanent Discontinuation for: Grade 3 thrombocytopenia > 7 days or associated with bleeding.
	Grade 4	Permanently discontinue	Exceptions: The following events do not require discontinuation of study drug: Grade 4 neutropenia ≤ 7 days Grade 4 lymphopenia or leukopenia Grade 4 isolated electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are responding to supplementation/appropriate management within 72 hours of their onset
Non-**drug related AEs**			
SARS-CoV-2 infection either confirmed or suspected	N/A	Delay Dose	Participants with SARS-CoV-2 infection (either confirmed or suspected) may resume treatment after:

Table 7.4.2-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Nivolumab

Drug-Related Adverse Event (AE) per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
			1) At least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared or positive test result (eg, RT-PCR or viral antigen) 2) Resolution of acute symptoms (including at least 24 hours 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 4) Consultation with the BMS Medical Monitor/designee For suspected cases, treatment may also resume if SARS-CoV-2 infection is ruled-out as per institutional policy for testing of SARS-CoV-2 and other criteria to resume treatment are met.
AEs, which in the judgement of investigator, require delaying dose	N/A	Delay Dose	
Infusion Reactions (manifested by fever, chills, rigors, headache, rash, pruritus, arthralgia, hypotension, hypertension, bronchospasm, or other allergic-like reactions.)			
Hypersensitivity reaction or infusion reaction	Grade 3 or 4	Permanently discontinue	Refer to Section 7.4.5 on Treatment of Related Infusion Reactions

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMS, Bristol-Myers Squibb; CTCAE, Common Terminology Criteria for Adverse Events; DRESS, drug reaction with eosinophilia and systemic symptoms; GBS, Guillain Barre syndrome; MG, myasthenia gravis; N/A, not applicable; RT-PCR, reverse transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SJS, Stevens-Johnson syndrome; T.bili, total bilirubin; TEN, toxic epidermal necrolysis; ULN, upper limit of normal; v5, version 5.

7.4.3 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 prednisone or equivalent, and meet the requirements per Table 7.4.2-1.

Prior to re-initiating treatment in a participant with a dosing delay as defined below, the Medical Monitor must be consulted.

- For Arm A, dosing delay > 6 weeks.
- For Arm B, dosing delay > 6 weeks (Cycles 1 to 4) and > 10 weeks (Cycles 5 to 13).

Continue tumor surveillance per protocol even if dosing is delayed. Continue periodic study visits to assess safety and laboratory studies every 4 weeks or more frequently if clinically indicated during such dosing delays.

Participants with SARS-CoV-2 infection (either confirmed or suspected) may resume treatment after **all of the following**:

- At least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared or positive test result (eg, RT-PCR or viral antigen)
- Resolution of acute symptoms (including at least 24 hours has passed since last fever without fever reducing medications)
- Evaluation by the investigator with confirmation that there are no sequelae that would place the participant at a higher risk of receiving investigational treatment
- Consultation by the Medical Monitor/designee. For suspected cases, treatment may also resume if SARS-CoV-2 infection is ruled-out and other criteria to resume treatment are met.

For additional criteria to resume treatment for dosing of [redacted] in the [redacted] setting, please refer to Appendix 5.

7.4.4 Management Algorithms for Nivolumab

Immuno-oncology (IO) agents are associated with AEs that can differ in severity and duration from AEs caused by other therapeutic classes. Nivolumab is considered an IO agent and the management algorithms in Appendix 7 provide guidance on assessing and managing the following groups of AEs:

- Gastrointestinal
- Renal
- Pulmonary
- Hepatic
- Endocrinopathy
- Skin

- Neurological
- Myocarditis

7.4.5 Treatment of Related Infusion- and Injection-Reactions

7.4.5.1 Systemic Reactions Occurring In-clinic

Since nivolumab contains only human immunoglobulin protein sequences, systemic hypersensitivity (allergic) reactions are unlikely. Although rare, if severe hypersensitivity were to occur, common manifestations might include fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, and/or bronchospasm. Report all Grade 3 or 4 hypersensitivity reactions within 24 hours as an SAE.

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

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

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

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

- Stop the study drug infusion/injection. Begin an IV infusion of normal saline and treat the participant with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor participant until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. For the participants receiving Nivo IV, 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 study medication will be administered at that visit.
- For participants in Arm A (Nivo SC) who need to receive 2 sequential injections for a full dose, do not administer the second injection if symptoms are noted with the first injection, and follow the treatment instructions mentioned above.
- For future infusions or injections, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg administered at least 30 minutes before nivolumab infusions or injections. 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 (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. Grade 4: Life-threatening consequences; urgent intervention indicated):

- Immediately discontinue infusion/injection of study drug. Begin an IV infusion of normal saline and treat the participant as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous or intramuscular administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Monitor participant until the investigator judges that the symptoms will not recur. Study drug will be permanently discontinued. Follow institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor participant until recovery of the symptoms.
- For participants in the Nivo SC arm (Arm A) who need to receive 2 sequential injections for a full dose, do not administer the second injection if symptoms are noted with the first injection, and follow the treatment instructions mentioned above.

[redacted]

7.4.5.3 Management of Local Infusion or Injection Site Reactions

In the clinical experience with Nivo IV, no tissue necrosis has been observed after accidental extravasations of Nivo IV. The use of oral medications (eg, antihistamines, acetaminophen/paracetamol) and topically applied therapies such as cold packs and steroid or antihistamine creams or gels is allowed for the treatment of local injection reactions due to Nivo SC [redacted](eg, swelling, erythema, pain, induration, local pruritus) and infusion local site reactions (local inflammation, necrosis due to drug extravasation) including those related to procedures (eg, hematoma). Local/institutional guidelines, if available, can be followed.

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).

[redacted]

7.5 Preparation/Handling/Storage/Accountability

Refer to the current version of the BMS-936558 IB for Nivo IV, the BMS-986298 IB for Nivo SC [redacted] and the Pharmacy Manual for complete information on storage, handling, dispensing, and administration information.

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

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

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

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

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

7.5.1 Retained Samples for Bioavailability/Bioequivalence/Biocomparability

At the time of receipt of the IP by the investigator or designee, BMS will specify the appropriate number of containers or units to select for retention, the conditions of sample storage, required duration of sample retention, and provisions for returning or disposing of the IP. When samples are selected, containers or units should be placed in packaging with a tamper-evident seal provided by BMS or sourced by the site. Package labeling should clearly identify the contents as retention samples and state that the IP should be stored in the restricted area with limited access.

Additional details regarding the retention process will be provided in a Pharmacy Manual or other written documentation.

7.6 Treatment Compliance

Study intervention compliance will be periodically monitored by drug accountability as well as the participant's medical record and CRF. Drug accountability should be reviewed by the site study

staff at each in-clinic visit to confirm treatment compliance. Sites should discuss discrepancies with the participant at each on-treatment study visit.

[redacted]

In addition, should the site identify a potential out-of-window dosing, the site must reach out to the participant and provide guidance on dosing, to be determined on a case-by-case basis (eg, to proceed immediately with dose, wait until the next dosing cycle, or delay the dose and resume treatment per investigator assessment).

A record of the quantity of [redacted] dispensed to and administered by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays, will also be recorded in the CRF (in-clinic dosings) [redacted]

7.7 Concomitant Therapy

7.7.1 Prohibited and/or Restricted Treatments

Prohibited and/or restricted medications taken prior to study treatment administration are described below. Medications taken within 30 days prior to the first dose of study treatment must be recorded on the CRF.

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

- 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 systemic anti-neoplastic therapy, including any concurrent adjuvant therapy for melanoma or for a new malignancy. Participants who develop a new non-melanoma fully resectable malignancy (examples include but are not limited to in situ bladder cancer, in situ gastric cancer, or in situ colon cancers; in situ cervical cancers/dysplasia; or breast carcinoma in situ; or prostate carcinoma) during the study may continue receiving study drugs if the only therapy required is hormonal therapy, surgery, and/or radiation (and the surgery or radiation site does not overlap with a previous primary melanoma or melanoma metastasis location). Consultation with the Medical Monitor is required once a new malignancy is detected.
- 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, live COVID-19 vaccines, varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella [MMR]) during treatment and until 100 days post last dose.
  - COVID-19 vaccines that are NOT live are permitted prior to study, during the study, and after the last dose of nivolumab. Please contact the medical monitor with any questions related to COVID-19 vaccines.
    - The following are NOT considered live vaccines and the decision to vaccinate should be made by the investigator and participant: inactivated vaccines (eg, heat-killed and formalin-killed vaccines), subunit vaccines, toxoid vaccines, nucleic acid vaccines that do not encode potentially infectious virus (Pfizer/BioNTech and Moderna COVID-19 vaccines) and replication-incompetent recombinant vector vaccines. If a study participant has received a live COVID-19 vaccine prior to screening, enrollment should be delayed until the impact of the vaccine is stabilized, UNLESS a delay would compromise participant health, as determined by the investigator in consultation with medical monitor. For COVID-19 vaccines requiring more than a single dose, the full series (eg, both doses of a 2-dose series) should be completed prior to enrollment when feasible, and when a delay in enrollment would not put the study participant at risk. Ideally, enrollment would occur after any acute reactions (eg, reactions occurring within 24 hours of vaccine administration) resolve.

Supportive care for disease-related symptoms may be offered to all participants on the trial.

7.7.2 Other Restrictions and Precautions

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

7.7.2.1 Imaging Restriction and Precautions

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

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

7.8 Continued Access to Study Intervention After the End of the Study

At the end of the study, BMS will not continue to provide BMS-supplied study intervention to participants/investigators unless BMS chooses to extend the study. The investigator should ensure that the participant receives appropriate standard of care to treat the condition under study.

8 DISCONTINUATION CRITERIA

8.1 Discontinuation From Study Intervention

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

- Participant's request to stop study intervention. Participants who request to discontinue study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by the participant to provide this information
- Any clinical AE, laboratory abnormality, or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant
- Termination of the study by BMS
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness. (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.)
- Disease recurrence (local, regional, or distant)
- Additional protocol-specified reasons for discontinuation (Section 8.1.1)
- Pregnancy (refer to Section 9.2.5)
- Significant noncompliance with protocol (eg, procedures, assessments, medications, etc.). The investigator should discuss such issues with the Medical Monitor.

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

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

If study intervention is discontinued prior to the participant's completion of the study, the reason for the discontinuation must be documented in the participant's medical records per local regulatory requirements in each region/country and entered on the appropriate CRF page.

8.1.1 Nivolumab Discontinuation

Nivolumab treatment must be permanently discontinued per criteria in Table 7.4.2-1 in Section 7.4. Discontinue nivolumab for any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the participant with continued nivolumab dosing.

Any event that leads to delay in dosing from the previous dose as described in Section 7.4.3 requires discontinuation of study treatment, with the following exceptions:

- Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events are allowed.
- Dosing delays lasting longer than those described in Section 7.4.3 that occur for non-drug-related reasons may be allowed if approved by the Medical Monitor (or designee).

8.1.2 Post-study Intervention Study Follow-up

Per Protocol Amendment 01, survival follow-up is not required. Participants will be followed for assessment of safety through 100 days (± 7 days) after the last dose of study treatment. Participants will not be followed for survival.

The following information refers to the original study design: In this study, overall survival is a key endpoint of the study. Post-study follow-up is of critical importance and is essential to preserving participant safety and the integrity of the study. Participants who discontinue study intervention must continue to be followed (in this study or a rollover study) for collection of outcome as required and in line with Section 5 until death or the conclusion of the study.

BMS may request that survival data be collected on all treated/randomized/assigned participants outside of the protocol defined window as defined in Section 2. At the time of this request, each participant will be contacted to determine their survival status unless the participant has withdrawn consent for all contact or is lost to follow-up.

Participants who discontinue study intervention may continue to be followed.

8.2 Discontinuation From the Study

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

- Participants should notify the investigator of the decision to withdraw consent from future follow-up.
- The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study intervention only or also from study procedures and/or post-treatment study follow-up, and entered on the appropriate CRF page.

- In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

8.2.1 Individual Discontinuation Criteria

- A participant may withdraw completely from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon. Stopping study intervention is not considered withdrawal from the study.
- At the time of discontinuing from the study, if possible, an early termination visit should be conducted, as shown in the Schedule of Activities. See the Schedule of Activities for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

8.3 Lost to Follow-up

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

- All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant.
- Lost to follow-up is defined by the inability to reach the participant after a minimum of **three (3)** documented phone calls, faxes, or emails, as well as lack of response by participant to one (1) registered mail letter. All attempts should be documented in the participant's medical records.
- If it is determined that the participant has died, the site will use permissible local methods to obtain date and cause of death.
- If the investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the participant's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining the participant's contact information or other public vital status data necessary to complete the follow-up portion of the study.
- The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information.
- If, after all attempts, the participant remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the participant's medical records.

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.
- Perform additional measures, including non-study required laboratory tests, as clinically indicated or to comply with local regulations. Laboratory toxicities (eg, suspected drug induced liver enzyme evaluations) will be monitored during the follow-up phase via on-site/local labs until all study drug-related toxicities resolve, return to baseline, or are deemed irreversible.
- Evaluate participant immediately to rule out cardiac or pulmonary toxicity if participant shows cardiac or pulmonary-related signs (hypoxia, abnormal heart rate or changes from baseline) or symptoms (eg. dyspnea, cough, chest pain, fatigue, palpitations).
- Some of the assessments referred to in this section may not be captured as data in the 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.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1 Imaging Assessments

9.1.1 Efficacy Assessment for the Study

Study evaluations will take place in accordance with Section 2, Schedule of Activities. Contrast-enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease is recommended to be performed; however, imaging per local standard of care is allowed.

- Imaging of extremities for resected melanomas located in the extremities is not a requirement and may be conducted per local standard of care. Extremity imaging should be conducted in the event of a suspected locoregional relapse that is not clinically unequivocal.
- If a PET-CT was obtained within 28 days prior to randomization and the site can document that a CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT

(with intravenous and oral contrast), then that CT portion of the PET-CT can be used for eligibility assessment.

Participants without a history of brain metastases should have brain imaging if clinically indicated. If a participant starts systemic therapy for melanoma recurrence or for a new non-melanoma tumor after study drug discontinuation, follow-up scans for this trial should be discontinued.

9.1.2 Imaging Assessment for the Study

Images are not required to be submitted to a central imaging vendor and will not undergo blinded independent central review. Prior to scanning first participant, sites should review and understand the image acquisition guidelines and submission process as outlined in the Imaging Manual provided by the central imaging vendor.

Screening and on study images should be acquired as outlined in Section 2, Schedule of Activities.

Tumor assessments at unscheduled time points and/or at an outside institution 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 central imaging vendor. X-rays and bone scans that clearly demonstrate recurrence of disease, for example most commonly as unequivocal lesions that are unmistakably new since the prior CT/MRI, should be submitted to central imaging vendor. Otherwise, they do not need to be submitted centrally.

Assessments for recurrence should preferably continue on the protocol-defined imaging schedule regardless if dosing is delayed or discontinued; however, imaging based on local standard of care is allowed. Assessment should be performed by the same investigator or designee at all time points and should continue until recurrence.

- For all participants: until local, regional, or distant recurrence, or up to the 100-day safety follow-up (whichever comes first), loss to follow-up, withdrawal of consent, or death.
- If a participant starts systemic therapy for melanoma recurrence or for a new non-melanoma tumor after study drug discontinuation, follow-up scans for this trial should be discontinued.

It is recommended that the same method of assessment used at Screening should be used for on-study time points. CT images should be acquired with slice thickness of 5 mm or less with no intervening gap (contiguous). In case of contraindication for CT or MRI (including intravenous contrast) it is strongly recommended to adhere to the following guidance:

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

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

Refer to Appendix 10: Country Specific Requirements for possible exceptions.

Other imaging may be collected per local standards, as clinically indicated.

- **Use of CT component of a PET-CT scanner:** Combined modality scanning such as with positron emission tomography-computed tomography (PET-CT) is increasingly used in clinical care, and is a modality/technology that is in rapid evolution; therefore, the recommendations outlined here may change rather quickly with time. At present, low-dose or attenuation correction CT portions of a combined PET-CT are of limited use in anatomically -based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast-enhanced CT scans for anatomically-based 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 intravenous and oral contrast), then the CT portion of the PET-CT can be used for measurements. In this specific study, for example, PET-CT can be used to support assessment of disease-free status in case CT or MRI are inconclusive.

9.1.3 Investigator Assessment of Baseline Disease Status

Participant eligibility must be confirmed by investigator prior to randomization.

9.1.3.1 Investigator Assessment of Recurrence

The same method of assessment used at Screening is recommended to be used for on-study time points. Post-baseline assessments will be performed until disease recurrence as confirmed by investigator, death, or withdrawal from the study.

- Tumor assessments for ongoing study treatment decisions will be completed by the investigator.
- Additional imaging of potential disease sites should be performed whenever disease recurrence or occurrence of a secondary malignancy is suspected.
- Brain CT or MRI with and without contrast or bone imaging during on-study treatment and follow-up periods should be obtained if clinically indicated.

9.1.3.2 General Considerations for Determining Recurrence

- The goal is to identify lesions suspicious for recurrence of melanoma. If it is believed that a lesion is NOT malignant in nature (eg, infection, trauma), it should be noted in the medical records. The specified minimum size criteria should be combined with radiographic appearance consistent with recurrent tumor in the assessment of all suspicious lesions.
- Non-melanoma primary cancer will be censored.

- Equivocal recurrence is upgraded to unequivocal recurrence (except in cases of CNS recurrence) by one or more of the following:
  - A subsequent scan not earlier than 4 weeks from the time when recurrence was first suspected demonstrates that the lesion size is ≥ 5 mm over the size previously recorded, or the radiographic appearance of the lesion has become consistent with tumor recurrence. If this occurs, the date of recurrence will be the date when the lesion was first suspected.
  - Positive histology/cytology
- Appearance of multiple new lesions in the same time point generally constitutes unequivocal recurrence, even though they may be from different organs (eg, one liver lesion, one lung lesion, and one enlarged lymph node).

Criteria for Diagnosing Recurrences is presented in Table 9.1.3.2-1.

Table 9.1.3.2-1: Criteria for Diagnosing Recurrence

Anatomic Sites	Criteria
Non-Nodal Soft Tissue	Equivocal lesions include: • Solitary lesion measuring < 10 mm in LD or with radiographic appearance equivocal for tumor recurrence. Unequivocal lesions include: • One or more new lesions > 10 mm in LD with radiographic appearance consistent with tumor recurrence. • Positive histology/cytology.
Bone Lesions	Equivocal lesions include: • Solitary lesion. • Lesions identified on radionuclide bone scan. Findings on radionuclide bone scan must be confirmed by CT, MRI, or plain films in order to be upgraded to unequivocal. Unequivocal lesions include: • Two or more new lesions consistent with tumor recurrence. • Positive histology/cytology.
Lymph Nodes[a]	Normal lymph nodes are defined as < 10 mm in the SAD. Equivocal lymph nodes include: • Lymph nodes measuring 10–14 mm SAD with radiographic appearance consistent with recurrence. • Lymph nodes ≥ 15 mm SAD without radiographic appearance consistent with recurrence. Unequivocal proof of nodal recurrence includes: • One or more previously normal or equivocal lymph nodes that enlarge to ≥ 15 mm SAD and with radiographic appearance consistent with recurrence. • Positive histology/cytology
Fluid Collections (eg, ascites, pleural/pericardial effusions)	• Presence of fluid alone, without pathological confirmation, does not constitute equivocal or unequivocal recurrence. • Unequivocal proof of recurrence is positive pathology of malignant cells from fluid(s).

Table 9.1.3.2-1: Criteria for Diagnosing Recurrence

Anatomic Sites	Criteria
CNS	Unequivocal recurrence is defined as any new CNS lesion of any size on CT or MRI with a radiographic appearance consistent with tumor recurrence.

Abbreviations: CNS, central nervous system; CT, computed tomography; LD, longest diameter; MRI, magnetic resonance imaging; SAD, short-axis diameter.

[a] For lymph node with short axis 10-15 mm, consider biopsy when lymph node is progressively enlarged as evidenced.

9.1.3.3 Definitions

Recurrence is defined as the appearance of one or more new melanoma lesions (except MMIS), which can be local, regional, or distant in location from the primary resected site.

Local Cutaneous Recurrence

Local recurrence is defined as tumor regrowth within 2 cm of the surgical incision following definitive excision of a primary melanoma with appropriate surgical margins. Lesions must be unequivocal. Local cutaneous recurrence after adequate excision of the primary melanoma is associated with aggressive tumor biologic features and is frequently a harbinger of metastases.

In Transit Metastasis Recurrence

Any skin or subcutaneous metastases more than 2 cm from the primary melanoma lesion, but not beyond the regional lymph node. When present, in transit metastases are usually multiple, evolve over time, and, as previously stated, are often the harbinger of subsequent systemic disease.

Regional Nodal Recurrences

Regional node failure, usually at the periphery of the prior surgical procedure. Lesions must be unequivocal as noted in Table 9.1.3.2-1.

Distant Recurrence

Any distant metastases with radiographic appearance consistent with tumor recurrence or positive histology/cytology (typically defined as any M except for M0). Distant metastases include node relapses beyond the anatomical compartment of the primary melanoma basin, a nodal basin situated in a different anatomical compartment beyond the primary melanoma lesion, or in 2 nodal basins (even if contiguous; ie, 2 pelvic nodal basins, 2 mediastinal nodal basins, etc).

Considerations for establishing distant recurrence on cross-sectional imaging:

- CT and MRI are an important part of the work-up to establish recurrence. Contrast-enhanced CT and MRI are the preferred imaging modalities. See Section 9.1.1 for details.
- Positron emission tomography (PET) alone will not be considered for the disease assessment. Complementary CT and/or MRI or biopsy must be performed in such cases.
- Cytology and/or histology are mandatory to confirm recurrence in solitary or in doubtful lesions, cutaneous, subcutaneous, or lymph node lesions. Histological or cytological evidence

of recurrence should be attempted in all cases (except for brain metastases) when safe and clinically feasible.

Clinically detected new lesions:

- The neoplastic nature of superficial cutaneous lesions must be confirmed by cytology/histology.
- Deep subcutaneous lesions and lymph node lesions should be documented by ultrasound, and histological/cytological evidence should be attempted. In absence of pathology report, lesion recurrence will be documented with a CT scan/MRI.
- Tumor markers or auto-antibodies alone cannot be used to assess recurrence.

9.1.3.4 Date of Recurrence

The first date when recurrence was observed is taken into account regardless of the method of assessment. Therefore, recurrence will be declared for any lesion when:

- Only imaging was performed and recurrence confirmed
- Only pathology was done and malignancy confirmed (in solitary or in doubtful lesions, cutaneous, subcutaneous, or lymph node lesions)
- Both pathology and imaging were done and recurrence/malignancy confirmed. In this case, the date of whichever examination comes first is considered the date of recurrence.

Pathology reports of biopsies confirming recurrence should be sent to a central vendor.

Note: For documentation, the date of recurrence is the date that the pathology and/or imaging confirms recurrence - not the date that the information was communicated to the participant.

9.1.4 Health Outcomes Assessments

Health outcomes assessment data will be collected using electronic data collection methods at designated times during treatment and in follow-up. If exceptional circumstances preclude the continued administration of measures using planned modalities, then alternate administration methods may be required, after consultation with Sponsor or the Sponsor's representative.

PRO data has been collected in Study CA2096GE. In this amendment, we are proposing to remove all PRO data collection in order to reduce participant and site burden now that this study is being stopped. The PRO data that has been collected will not be analyzed as part of the statistical analysis plan (SAP) due to the very limited amount of data; however, the data may be used internally at some point in the future to help develop PRO strategies in future clinical trials.

9.1.4.1 FACT-G7 (Part 1 Only)

Not applicable per Protocol Amendment 01. The following information refers to the original study design.

The FACT-G7 is a shortened, 7-item version of the FACT-G designed to quickly and effectively capture the most relevant issues to cancer patients in a valid and reliable manner.[39] The FACT-G7 consists of 3 subdomains: Physical well-being, Emotional well-being, and Functional well-being. Item responses for all 7 items use a 5-point Likert scale (from 0 "Not at all" to 4 "Very much"). The questions are phrased with a recall period of "over the past 7 days." The FACT-G7 can be used to rapidly assess top-rated symptoms and concerns for a broad spectrum of advanced cancers in clinical practice and research, as well as for quality reporting in cancer chemotherapy and radiation. The FACT-G7 will be completed by all participants in Part 1 of the study at every treatment cycle, safety follow-up, and survival follow-up (see Section 2 Schedule of Activities).

9.1.4.2 EQ-5D-5L (Part 1 Only)

Not applicable per Protocol Amendment 01. The following information refers to the original study design.

Participants' reports of general health status are assessed using the EuroQoL Group's 5-level EQ-5D (EQ-5D-5L) questionnaire.[40] The EQ-5D-5L has 2 components: a descriptive system and a visual analogue scale (VAS). The EQ-5D-5L descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels including no, slight, moderate, severe, and extreme or unable to. A dimension for which there are no problems is said to be at level 1, while a dimension for which there are extreme problems is said to be at level 5. Accordingly, the vectors 11111 and 55555 represent the best health state and the worst health state, respectively, described by the EQ-5D-5L. Altogether, the instrument describes 3,125 health states. Empirically derived weights can be applied to an individual's responses to the EQ-5D-5L descriptive system to generate a utility index measuring the value to society of his or her current health. In addition, the EQ-5D-5L VAS allows respondents to rate their own current health on a 101-point scale ranging from best imaginable to worst imaginable health.

The EQ-5D-5L has been shown to be a valid measure in a cancer patient population.[41] Currently there are no published MIDs for EQ-5D-5L index change scores for the EQ-5D-5L in a cancer population; however a change of 7 points on the EQ-5D VAS score is considered clinically meaningful.[42] All participants in Part 1 of the study will complete the EQ-5D-5L at every treatment cycle, safety follow-up, and survival follow-up (see Section 2 Schedule of Activities).

9.1.4.3 Modified CTSQ (Part 1 Only)

Not applicable per Protocol Amendment 01. The following information refers to the original study design.

The CTSQ assesses patient satisfaction and preference for cancer treatment. The original CTSQ contained 21 items spread across 5 domains, which was revised to a 16-item instrument measuring 3 domains during validation: Expectations of Therapy — 5 items, Feelings about Side Effects — 4 items, and Satisfaction with Therapy — 7 items.[43] All items are scored on a 1-5 scale, with a value of 1 associated with the worst response and a value of 5 representing the best response with a recall period of past 24 hours. For each domain, if the minimum item completion standard is met,

the domain is scored as (mean of completed item scores - 1) × 25; otherwise, a missing value was assigned. The linear transformation results in a score ranging from 0 to 100 for each domain, with a higher score associated with the best outcome on each domain. For the purposes of the clinical trial, the instructions will be modified to include the terminology IV/SC, rather than IV/pills, and only the Satisfaction domain (7 items) of the CTSQ will be completed by all participants in Part 1 of the study at selected time points during treatment (see Section 2 Schedule of Activities).

9.1.4.4 Modified TASQ (Part 1 Only)

Not applicable per Protocol Amendment 01. The following information refers to the original study design.

The TASQ was developed to assess patients' perceptions and satisfaction with subcutaneous (TASQ-SC) or intravenous (TASQ-IV) treatment administration. The questionnaire has been validated in a cancer patient population.[44] Each version of the TASQ (TASQ-IV and TASQ-SC) contains 19 items which comprise the 5 subdomains: Treatment satisfaction, Convenience, Physical impact, Psychological impact, and Impact on daily living. Although there is no specific recall period for either version of the TASQ, instructions provided indicate that the questionnaire should be completed after the most recent IV infusion or SC injection. Participants in Part 1 Arm B will complete the TASQ-IV and participants in Part 1 Arm A will complete the TASQ-SC. The questionnaire will be completed at specified time points during treatment (see Section 2, Schedule of Activities).

9.1.4.5 SIAQ (Part 1 Only)

Not applicable per Protocol Amendment 01. The following information refers to the original study design.

The SIAQ is a non-specific indication questionnaire that assesses patient overall experience with subcutaneous self-injection.[45] The measure contains 2 parts with pre- (7 items) and post-injection (21 items) questionnaire. The post-injection questionnaire captures 6 main subdomains: feelings about injections (3 items), self-image (1 item), self-confidence (3 items), pain, and skin reactions during or after the injection (2 items), ease of use of the self-injection [redacted] (5 items), and satisfaction with self-injection (7 items). To reduce patient burden and avoid capturing the same concept multiple times using different measures, only the self-confidence subdomain will be completed by participants. Each of the items in the self-confidence subdomain response options from 1 "Not at all" to 5 "Extremely". There is no specific recall period for the SIAQ; however the instructions state that the post-injection questionnaire must be answered by the participant after they self-inject. Therefore, if a caregiver or HCP administers the treatment, the participant would not complete the SIAQ. The SIAQ self-confidence subdomain will only be completed by participants who self-inject in Part 1 Arm A at specific time points during treatment. Caregivers/HCPs who administer treatment on behalf of the participant should not complete the SIAQ (see Section 2, Schedule of Assessments).

[redacted]

9.2 Adverse Events

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

AEs will be reported by the participant (or, when appropriate, by a caregiver or a surrogate).

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

Use CTCAE v5 definitions and grading for safety reporting of all AE and SAEs on the case report form.

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

[redacted]

[redacted]

Refer to Appendix 3 for SAE reporting.

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

All SAEs must be collected from the time of signing the consent, including those thought to be associated with protocol-specified procedures, and within 100 days following discontinuation of dosing. All AEs and SAEs, associated with confirmed or suspected SARS-CoV-2 infection must be collected from the date of the participant's written consent until 100 days following discontinuation of dosing.

Collect all nonserious adverse events (not only those deemed to be treatment-related) continuously during the treatment period and for a minimum of 100 days following discontinuation of dosing.

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

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

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

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

For participants who have been randomized or assigned to treatment and never treated with study drug, collect SAEs for 30 days from the date of randomization or treatment assignment.

For participants who are enrolled but not randomized, all SAEs and AEs/SAEs related to SARS-CoV-2 must be collected for 30 days from the date of signing consent.

9.2.2 Method of Detecting AEs and SAEs

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

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

AEs, including SAEs, occurring during the [redacted] period should be collected during in-clinic visits and reported as early as possible (within 24 hours of learning of the SAE).

9.2.3 Follow-up of AEs and SAEs

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

All SAEs and AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection will be followed until resolution, the condition stabilizes, the event is otherwise explained, the event is deemed irreversible, the participant is lost to follow-up (as defined in Section 8.3), or for suspected cases, until SARS-CoV-2 infection is ruled-out.

Beyond 100 days from the last dose of study therapy, participants will be followed for drug-related AEs/SAEs until resolution, returns to baseline, or is deemed irreversible, or until the participant is lost to follow-up or withdraws study consent.

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

9.2.4 Regulatory Reporting Requirements for SAEs

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

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

9.2.5 Pregnancy

If, following initiation of the study intervention, it is subsequently discovered that a participant is pregnant or may have been pregnant at the time of study exposure, including during at least for

5 months after study product administration, the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to the BMS designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Appendix 3.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information, must be reported on the Pregnancy Surveillance Form. Protocol-required procedures for study discontinuation and follow-up must be performed on the participant.

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

9.2.6 Laboratory Test Result Abnormalities

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

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

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

9.2.7 Potential Drug-Induced Liver Injury

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

Potential DILI is defined as:

- AT (aminotransferase) (ie, ALT or AST) elevation > 3 times upper limit of normal (ULN)
  AND
- Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)
  AND
- No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

9.2.8 Other Safety Considerations

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

9.3 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. Overdoses that meet the regulatory definition of SAE will be reported as an SAE (see Appendix 3).

Risk of intentional overdose in participants self-administering [redacted] is minimized based on the following considerations:

- CA2096GE will exclude participants with serious psychological and psychiatric disorders including participants with prior history of self-harm and suicidal attempts.
- Melanoma is not included among the main cancers with higher risk of suicide. In addition, clinical factors associated with suicidality such as substantial pain, insomnia, fatigue, loss of autonomy and independence are not considered prevalent among the study population (adjuvant melanoma).[46,47]
- The Pharmacy Manual details the required dose for Nivo [redacted] SC for the Q2W dosing frequency.

9.4 Safety

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

9.4.1 Physical Examinations

Refer to Schedule of Activities, Section 2.

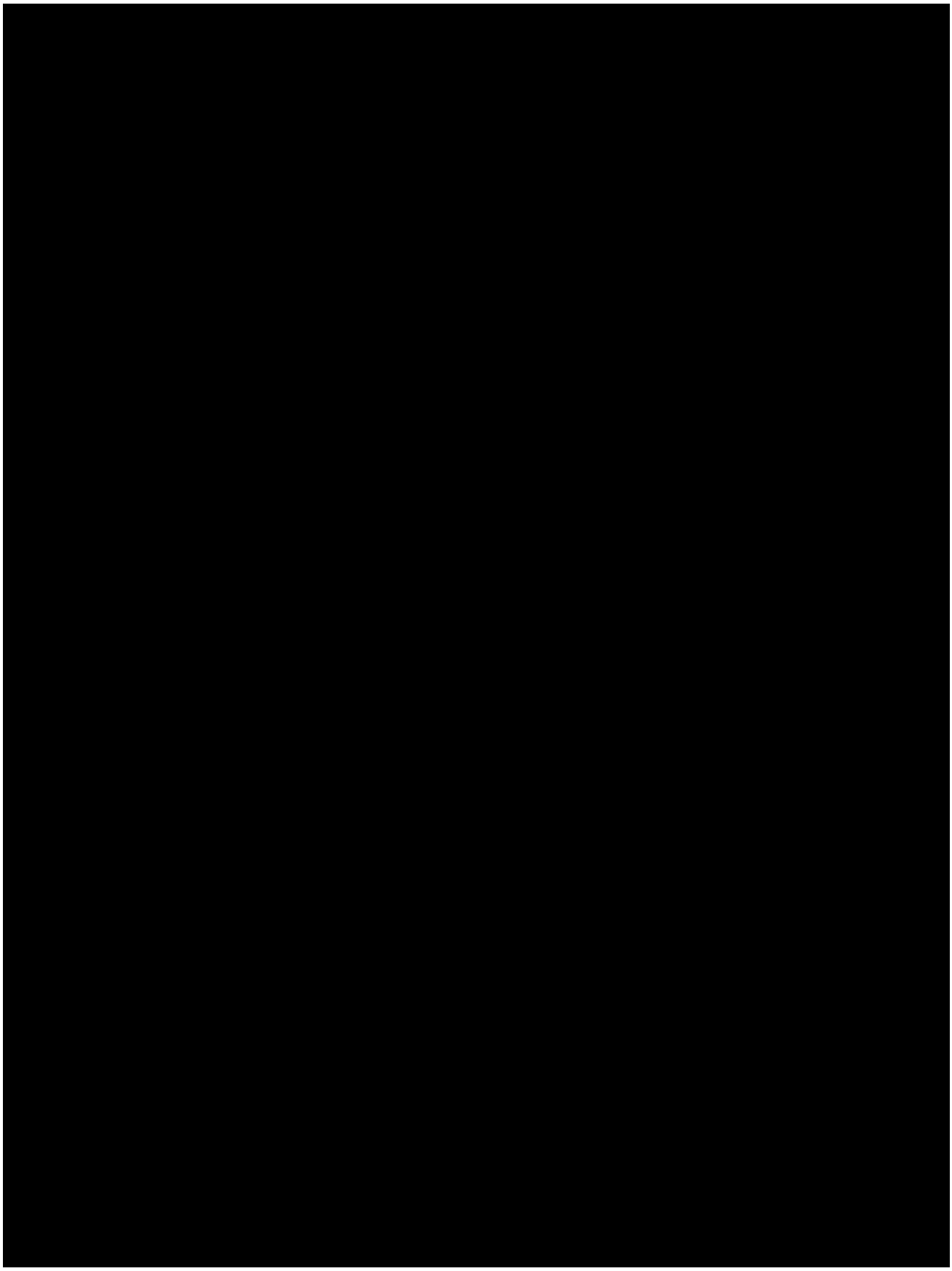
9.4.2 Vital Signs

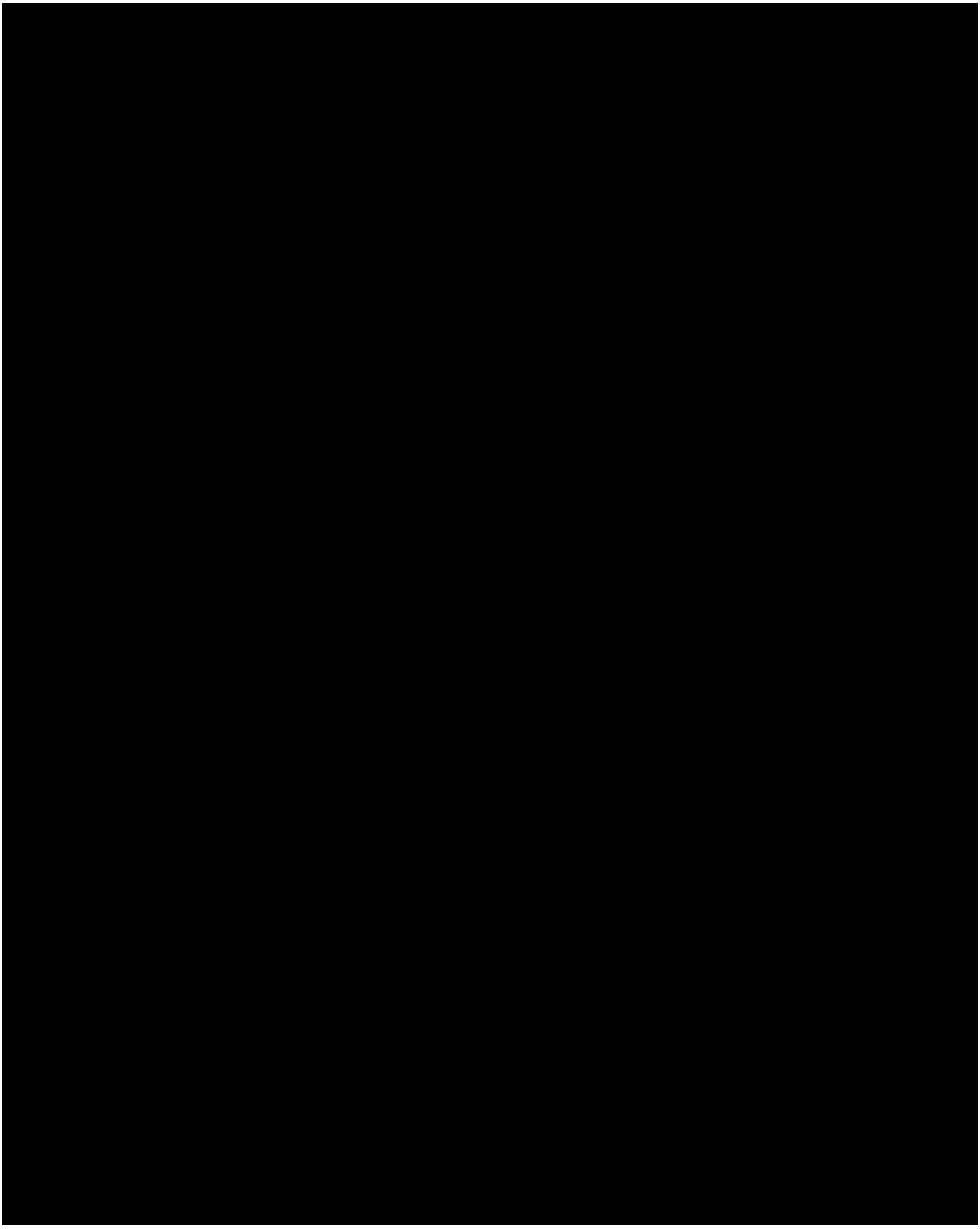
Refer to Schedule of Activities, Section 2.

9.4.3 Electrocardiograms

Refer to Schedule of Activities, Section 2.

[redacted]





[redacted]

9.4.6 Suicidal Risk Monitoring

Not applicable.

9.4.7 Imaging/Other Safety Assessment

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

9.5 Pharmacokinetics

Upon implementation of Protocol Amendment 01, sample collections for PK and ADAs are no longer necessary for any participant who is on study treatment. In the event samples are collected following implementation of Protocol Amendment 01, samples will be analyzed bioanalytically and reported as listings.

The following information refers to the original study design.

Actual times of sample collection will be used in all PK analyses.

The nivolumab exposure measures (PK endpoints) to be assessed in the study include the following:

- Cavgd28: time-averaged nivolumab serum concentration over the first 28 days
- Cminss: trough nivolumab serum concentration at steady-state
- Cmind28: trough nivolumab serum concentration on Day 28
- Cmax1: maximum nivolumab serum concentration after the first dose
- Tmax: time to Cmax1
- Cavgss: time-averaged nivolumab serum concentration at steady-state
- Cmaxss: maximum nivolumab serum concentration at steady-state

Individual co-primary (Cavgd28 and Cminss in Part 1; Cavgd28 in [redacted] and secondary (Cmind28, Cmax1, Tmax, Cavgss, and Cmaxss in Parts 1 and 2; Cminss in [redacted] PK endpoints will be determined using PPK analysis. Specifically, the structural, interindividual variability,

covariate, and residual error components of the previously developed combined SC and IV PPK model will be pre-specified and the population and individual PK parameters will be estimated using the data collected in this study. Individual PK exposure measures (ie, PK endpoints listed above) will be derived using the individual (empirical Bayes estimates) PK model parameters (eg, rate of absorption, bioavailability, clearance, volume of distribution) estimated by the model. The details of the PPK analysis will be presented in a pre-specified pharmacometrics analysis plan.

The co-primary PK endpoints in Part 1 (Cavgd28 and Cminss) will be used for non-inferiority assessment as described in Section 10.4.2.

9.5.1 Pharmacokinetics and Anti-Drug Antibody Sample Collection and Processing

Not applicable per Protocol Amendment 01. The following information refers to the original study design.

A detailed schedule of PK and ADA evaluations is found in Table 9.5.1-1, Table 9.5.1-2, and Table 9.5.1-3. Serial PK samples will be collected in all participants. All on-treatment PK time points are intended to align with days on which study treatment is administered. On-treatment PK samples are intended to be drawn relative to actual dosing days.

Predose samples should be collected just before the administration of nivolumab (preferably within 30 minutes). If it is known that a dose is going to be delayed, then collect the predose sample 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. In Part 1, Arm B, the end of the infusion (EOI) occurs when the entire nivolumab dose in the infusion bag is administered to the participant. If the site infuses the drug without a flush, then collect the EOI-PK sample within approximately 5 minutes after EOI. If a flush is administered to clear the IV lines of the drug and to ensure delivery of the entire drug dose, then draw the EOI-PK sample within approximately 5 minutes after the end of the flush. If the EOI is delayed to beyond the nominal infusion duration (30 minutes), the collection of the EOI-PK sample should be delayed accordingly.

Draw blood samples from a site other than the infusion site (ie, contralateral arm) on days of infusion for all predose and EOI-PK samples. Please ensure accurate documentation of the time and date of sample collection.

Samples will be evaluated for development of anti-drug antibodies (ADA). Samples may also be analyzed for neutralizing antibodies and PK samples may be used for ADA analysis in the event of insufficient volume, to complete immunogenicity assessment, or to follow-up on suspected immunogenicity-related AEs.

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

Immunogenicity of nivolumab will be assessed per the SAP. PK data for rHuPH20 will not be collected in this study; however, immunogenicity data for rHuPH20 will be collected and may be analyzed and reported separately, as appropriate.

Table 9.5.1-1: Pharmacokinetic and Immunogenicity Sampling Schedule for Part 1, Arm A (600 mg SC [redacted] Q2W)

Study Day of Sample Collection (1 Cycle = 28 Days)	Event	Time Relative to Nivolumab Dose (hr:min)	Nivolumab PK Serum Sample	Nivolumab IMG (ADA) Serum Sample	rHuPH20 IMG (ADA) Plasma Sample[a]
Cycle 1, Day 1	Predose[b]	0:00	X	X	X
Cycle 1, Day 4 (± 1 day)		72:00	X		
Cycle 1, Day 8 (± 1 day)		168:00	X		
Cycle 1, Day 15	Predose[b,c]	0:00	X	X	X
Cycle 1, Day 22 (± 1 day)		168:00	X		
Cycle 2, Day 1	Predose[b,c]	0:00	X	X	X
Cycle 3, Day 1	Predose[b]	0:00	X	X	X
Cycle 4, Day 1	Predose[b,c]	0:00	X		
Cycle 5, Day 1	Predose[b]	0:00	X	X	X
Cycle 9, Day 1	Predose[b]	0:00	X	X	X
Cycle 13, Day 1	Predose[b]	0:00	X	X	X
Follow-up 1 and 2[d]			X	X	X

Abbreviations: ADA, anti-drug antibody; [redacted] hr, hour; IMG, immunogenicity; min, minute; PK, pharmacokinetic; Q2W, every 2 weeks; rHuPH20, recombinant human hyaluronidase PH20 enzyme; SC, subcutaneous.

[a] rHuPH20 ADA predose samples on Cycle 1 Day 1 must be collected in all participants.

[b] Take all predose samples for nivolumab prior to the start of the first of 2 SC nivolumab injection (preferably within 30 minutes). 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 taken.

[c] Biomarker testing will be conducted using an aliquot of PK or ADA serum sample.

[d] If a participant discontinues study drug during the treatment/sampling period, move to sampling at the follow-up visits (Follow-up Visits 1 and 2 is 30 days and 100 days from date of last dose, respectively).

Table 9.5.1-2: Pharmacokinetic and Immunogenicity Sampling Schedule for Part 1 Arm B (240 mg IV Q2W for 4 Cycles then 480 mg IV Q4W)

Study Day of Sample Collection (1 Cycle = 28 Days)	Event	Time Relative to Nivolumab Dose (hr:min)	Nivolumab PK Serum Sample	Nivolumab IMG (ADA) Serum Sample
Cycle 1, Day 1	Predose[a]	0:00	X	X

Table 9.5.1-2: Pharmacokinetic and Immunogenicity Sampling Schedule for Part 1 Arm B (240 mg IV Q2W for 4 Cycles then 480 mg IV Q4W)

Study Day of Sample Collection (1 Cycle = 28 Days)	Event	Time Relative to Nivolumab Dose (hr:min)	Nivolumab PK Serum Sample	Nivolumab IMG (ADA) Serum Sample
	End of infusion[b]	See footnote	X	
Cycle 1, Day 8 (± 1 day)		168:00	X	
Cycle 1, Day 15	Predose[a,c]	0:00	X	
	End of infusion[b]	See footnote	X	
Cycle 1, Day 22 (± 1 day)		168:00	X	
Cycle 2, Day 1	Pre-dose[a,c]	0:00	X	X
Cycle 3, Day 1	Predose[a]	0:00	X	X
Cycle 4, Day 1	Predose[a,c]	0:00	X	
Cycle 5, Day 1	Predose[a]	0:00	X	X
Cycle 9, Day 1	Predose[a]	0:00	X	X
Cycle 13, Day 1	Predose[a]	0:00	X	X
Follow-up 1 and 2[c,d]			X	X

Abbreviations: ADA, anti-drug antibody; hr, hour; IMG, immunogenicity; min, minute; PK, pharmacokinetic; IV, intravenous; Q2W, every 2 weeks; Q4W, every 4 weeks.

[a] Take all predose samples for nivolumab prior to the start of nivolumab infusion (preferably within 30 minutes). 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 taken.

[b] Since the end of infusion-PK (EOI-PK) sample is drawn with the intent of accurately estimating the maximum concentration (Cmax) of the drug, draw the EOI-PK when all the study drug has been infused. If the site infuses drug without a flush, then collect the EOI-PK sample within approximately 5 minutes after end of infusion. If a flush is administered to clear the IV lines of the drug and to ensure delivery of the entire drug dose, then draw the EOI-PK sample within approximately 5 minutes after end of the flush. Do not draw EOI samples from the same IV access that the drug was administered.

[c] Biomarker testing will be conducted using an aliquot of PK or ADA serum sample.

[d] If a participant discontinues study drug during the treatment/sampling period, move to sampling at the follow-up visits (Follow-up Visits 1 and 2 is 30 days and 100 days from date of last dose, respectively).

[redacted]

9.5.2 Pharmacokinetic and Immunogenicity Sample Analyses

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

Concentration analyses for nivolumab will be performed by validated bioanalytical method(s).

Serum samples will be analyzed for nivolumab and anti-nivolumab ADAs, and plasma samples may be analyzed, as appropriate, for anti-rHuPH20 ADAs by validated immunoassays. Only samples that are positive for the presence of anti-nivolumab or anti-rHuPH20 binding antibodies will be analyzed as appropriate for anti-nivolumab and anti-rHuPH20 neutralizing activity.

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.)

Additionally, residual bioanalytical samples will be archived and may be used for potential exploratory bioanalysis (including, but not limited to, analysis of drug-ADA immune complexes, metabolite analyses, etc) and or for additional method purposes (including, but not limited to, cross-validation, ADA/PK selectivity, cutpoint, etc.)

9.6 Immunogenicity Assessments

Details regarding immunogenicity assessments can be found in Section 9.5.2.

9.7 Genetics

Please refer to Section 9.8.

9.8 Biomarkers

Not applicable per Protocol Amendment 01. The following information refers to the original study design.

Serum and whole blood collected at time points indicated in Table 9.8-1 and [redacted] may be used for but not limited to the measurement of deoxyribose nucleic acid (DNA) and protein biomarkers in the periphery. Features within the periphery have been established as pharmacodynamic biomarkers of nivolumab biological activity. These include increased soluble factors such as, but not limited to, chemokine (CXC) motif, CXC ligand-9 (CXCL9), and CXC ligand-10 (CXCL10). Pre- and on-treatment peripheral blood may be used to compare the pharmacodynamic activity between [redacted] and Nivo IV treatment arms. In addition to characterizing the pharmacodynamic activity of [redacted] and Nivo IV, data from these investigations may also be evaluated for associations with clinical efficacy and safety/toxicity (AE) data. To identify any potential imbalances in known prognostic factors in the tumor between SC [redacted] and IV treatment arms, baseline tumor biomarkers may be compared between arms (may include, but are not limited to, PD-L1, tumor mutational burden [TMB], mutational status, and tumor inflammation). Optional tumor biopsies will also be collected upon recurrence (see Table 9.8-1 and [redacted] Complete instructions on the collection, processing, handling, and shipment of all samples described herein will be provided in a separate Lab manual.

Table 9.8-1: Biomarker Sampling Schedule for Part 1 Arms A and B

Study Day of Sample Collection (1 Cycle = 28 Days)	Tumor Biopsy	Serum Biomarkers	SARS-CoV-2 Serology	Whole Blood DNA
Screening	X[a]			
Cycle 1 Day 1 (Predose)		X[b]	X[b]	X
Cycle 1 Day 15		X[c]		
Cycle 2 Day 1		X[c]		
Cycle 4 Day 1		X[c]		
Upon recurrence (optional)	X			

Abbreviations: DNA, deoxyribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a] Tissue availability must be determined during screening period. Submission of required tissue can occur during screening period (preferred); however, it must be submitted no later than 14 days post-randomization.

[b] A single blood draw will be used for serum biomarkers and SARS CoV-2 serology.

[c] Biomarker testing will be conducted using an aliquot of PK or ADA serum sample (see Table 9.5.1-1 and Table 9.5.1-2).

[redacted]

9.8.1 Tumor Acquisition

Not applicable per Protocol Amendment 01. The following information refers to the original study design.

Pre-treatment tumor samples are required from all participants. Sufficient, recent FFPE tumor tissue block, obtained from the recent resection (preferred) or from an archival biopsy conducted within 6 months prior to enrollment, must be submitted to the central laboratory. If an FFPE block is not available, a minimum of 15 unstained slides may be submitted. If despite best efforts, 15 unstained slides are not obtainable, submission of 5 unstained slides is acceptable. Tissue availability needs to be determined during the screening period. It is recommended that tissue is submitted during the screening period; however, it must be submitted no later than 14 days post-randomization/treatment assignment. Biopsies should be obtained from core biopsy, punch biopsy, excisional biopsy, or surgical specimen. Fine-needle aspirates or other cytology samples are not acceptable. Preferably, participants should not have received any systemic anticancer therapy between time of tissue acquisition and randomization/treatment assignment. Submission of tumor biopsy upon recurrence is highly recommended but optional. Refer to the Laboratory Manual for detailed biopsy collection instructions.

Pre-treatment tumor samples will be assessed for PD-L1 expression using the Dako PD-L1 immunohistochemistry 28-8 pharmDx validated assay. PD-L1 stained tissue sections will be assessed by a pathologist, and membranous PD-L1 expression will be scored in tumor and immune cells if a minimum of 100 evaluable tumor cells are present. Samples with < 100 evaluable tumor cells or inadequate sample will be characterized as PD-L1 unevaluable. Indeterminate PD-L1 tumor expression is defined as membrane staining that is obscured by high cytoplasmic staining or melanin content. To identify any potential imbalances in known prognostic factors between SC[redacted] and IV treatment arms, baseline biomarkers including, but not limited to, PD-L1, TMB, tumor inflammation, will be descriptively compared between arms. Tumor biopsy submitted upon recurrence will be similarly evaluated. For TMB analysis, tumor tissue may be evaluated by targeted and/or whole exome or whole genome sequencing (WES). Exploratory analyses of mRNA may be completed using RNA isolated from tumor tissue. Targeted and/or whole transcriptome RNA-seq and/or similar methodologies may be used to assess gene expression signatures, such as but not limited, to those associated with inflammatory processes and/or immune-related signaling.

9.8.2 Serum

Not applicable per Protocol Amendment 01. The following information refers to the original study design.

Pre- and on-treatment serum may be assessed by enzyme-linked immunosorbent assay, seromics, metabolomics, and/or other relevant multiplex-based protein assay methods for immune-related factors that will predict for SC [redacted] and Nivo IV benefit or AEs and to evaluate pharmacodynamic activity of SC[redacted] and Nivo IV. Potential serum-based biomarkers currently under investigation may include, but are not limited to, levels of cytokines and chemokines. Changes from baseline in biomarkers will be descriptively compared between SC [redacted] and IV treatment arms.

Serum will be collected for potential future measurements of anti-SARS-CoV-2 antibodies by serology (anti-SARS-CoV-2 total or IgG) at baseline to explore potential association with safety, efficacy, and/or immune biomarkers.

9.8.3 Germline Control Whole Blood Analysis by Genomics

Not applicable per Protocol Amendment 01. The following information refers to the original study design.

Whole blood will be collected from all participants prior to treatment for genomic DNA isolation. Blood DNA sequencing data generated using Next Generation Sequencing technologies to enable WES may be used as a control in order to improve the accuracy of mutational analyses from tumor samples. Germline mutations from blood samples will be inferred from the WES data to consider somatic mutations for TMB assessment.

9.9 Additional Research

Not applicable per Protocol Amendment 01. The following information refers to the original study design.

This protocol will include both sample collection and residual sample storage for additional research (AR).

For All US sites:

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

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

For non-US Sites:

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

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

Sample Collection and Storage

Residual PK, immunogenicity, blood (or blood derivatives) or tumor tissue (recent, archival, or fresh biopsy and extracted RNA/deoxyribonucleic acid [DNA]) from tumor biopsy and biomarker collections (see Table 9.9-1 below) will also be retained for additional research purposes.

Samples kept for future research will be stored at the BMS Biorepository in New Jersey, USA 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 9.9-1: Residual Sample Retention for Additional Research Schedule

Sample Type	Time points for which residual samples will be retained
PK	All
Immunogenicity	All
Serum	All
Tumor Biopsy	All
Isolated DNA/RNA	All
Whole blood DNA	All

Abbreviations: DNA, deoxyribonucleic acid; PK, pharmacokinetics; RNA, ribonucleic acid.

9.10 Other Assessments

9.10.1 Investigational Site Training

BMS will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to Good Clinical Practice, AE reporting, [redacted] study details and procedures, eCRFs, study documentation, informed consent, and enrollment of WOCBP.

9.11 Health Economics OR Medical Resource Utilization and Health Economics

Not applicable per Protocol Amendment 01. The following information refers to the original study design.

Healthcare Resource Use data associated with medical encounters will be collected in the CRF by the investigator and study-site personnel for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

The data collected may be used to conduct exploratory economic analyses and will include the following:

- 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

Per Protocol Amendment 01, only safety analyses will be conducted. Summary tables and listings for baseline characteristics, disposition, safety, and efficacy data will be provided to support the Clinical Study Report (CSR). Additional summaries (as appropriate for small sample size) will be planned in the SAP to support study data disclosure on original study objectives.

10.1 Statistical Hypotheses

Not applicable per Protocol Amendment 01. The following information refers to the original study design.

Part 1 of the study will be subjected to statistical hypothesis testing.

[redacted]

Research Hypothesis (Part 1 - Randomized Study)

Nivolumab exposures following [redacted] (BMS-986298) 600 mg administered Q2W are non-inferior to exposures following nivolumab (BMS-936558) 240 mg IV Q2W for the adjuvant treatment of melanoma.

10.2 Sample Size Determination

The aim of the study is to assess the safety and tolerability of [redacted] and Nivo IV. This has changed from the original protocol's study objective of PK. Sample size calculations are not based on statistical considerations. There were 14 participants randomized and treated at the time of Protocol Amendment 01.

[redacted]

[redacted]

10.3 Analysis Sets

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

Population	Description
All Enrolled Participants	All participants who signed an ICF and are registered into the IRT. This is the primary dataset for disposition.
All Randomized Participants	All participants who are randomized to any treatment group. This is the primary dataset for analyses of demography, protocol deviations, baseline characteristics, efficacy, and outcome research for the randomized part of the study.
All Treated Participants	All participants who receive at least 1 dose of nivolumab. This is the primary dataset for dosing and safety analyses. Data will be analyzed based on randomized treatment, except if a participant received the same incorrect treatment throughout the study, then the participant will be analyzed based on treatment received.

Abbreviations: ICF, informed consent form; IRT, interactive response technology.

10.4 Statistical Analyses

The SAP will be finalized prior to primary endpoint database lock (DBL), and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including the primary endpoint.

A description of the participant population will be included in the clinical study report, including subgroups of age, gender, race and other study specific populations and demographic characteristics. A description of participant disposition will also be included in the clinical study report.

10.4.1 General Considerations

A summary of the planned statistical analysis is described below in subsequent paragraphs.

10.4.2 Primary Endpoint(s)

Safety is the primary endpoint. See Table 10.4.2-1 for details.

Table 10.4.2-1: Primary Endpoint

Primary Endpoint	Description	Timeframe
• AEs/SAEs, treatment-related AEs/SAEs for each treatment group.	• Incidence of all AEs/SAEs, treatment-related AEs/SAEs for each treatment group.	• Up to 100 days after the last treatment of study intervention or up to discontinuation of study treatment.

Abbreviations: AE, adverse event; IMAE, immune-mediated adverse event; SAE, serious adverse event.

All safety analyses will be performed using the All Treated participants population.

The frequency of AEs, SAEs, and treatment-related AEs/SAEs will be tabulated by treatment arm. IMAEs, AEs, and SAEs leading to discontinuation of study drug, infusion/injection-related AEs, [redacted] deaths, and abnormalities in specific clinical laboratory assessments will be presented as listings by treatment arm.

The safety summary will be presented by severity where applicable. Analyses will be conducted using the 30 and/or 100-day safety window from the day of last dose received. AEs will be coded using the most recent Medical Dictionary for Regulatory Activities (MedDRA) version available during the conduct of the study. AEs and laboratory values will be graded for severity according to the NCI CTCAE version 5.0.

10.4.2.1 Part 1 PK Co-Primary Endpoints

Not applicable per Protocol Amendment 01. The following information refers to the original study design.

Table 10.4.2.1-1: Part 1 PK Co-Primary Endpoint

Co-Primary Endpoint	Description	Timeframe
Cavgd28	Time averaged nivolumab serum concentration over the first 28 days	First 28 days of treatment
Cminss	Minimum nivolumab serum concentration at steady-state	17 weeks after the start of treatment

Abbreviations: Cavgd28, time averaged nivolumab serum concentration over the first 28 days; Cminss, minimum nivolumab serum concentration at steady-state, PK, pharmacokinetics.

For Primary PK Endpoints analysis, a linear fixed effect model with treatment and stratification factors (defined in the study design) as fixed effects will be fitted to the log-transformed Cavgd28 and Cminss for use in estimation of treatment effects and construction of CIs. To assess non-inferiority of [redacted] to Nivo IV, point estimate and the 2-sided 90% CIs for treatment differences on the log scale will be exponentiated to obtain estimates for ratio of geometric means and respective 90% CIs for Cavgd28 and Cminss on the original scale.

Non-inferiority of [redacted] to Nivo IV will be concluded if the lower limit of the 2-sided 90% CIs for the ratio of geometric means for nivolumab Cavgd28 and Cminss is not lower than 0.8.

[redacted]

10.4.3 Secondary Endpoint(s)

Per Protocol Amendment 01, secondary endpoints [redacted] of the study have been removed. Efficacy, patient-reported outcomes (PROs), and biomarker analyses will not be completed. Samples already collected for PK and immunogenicity assessments will be analyzed bioanalytically for nivolumab concentrations and anti-drug antibodies (ADAs) and reported as listings. Further collections for PK, ADAs, biomarkers, and PROs will be discontinued. The following information refers to the original study design.

10.4.3.1 Part 1 Secondary Endpoint(s)

Not applicable per Protocol Amendment 01. The following information refers to the original study design.

Table 10.4.3.1-1: Part 1 Secondary Endpoints

Secondary Endpoints	Description	Timeframe
Key Secondary		
Incidence of all AEs/SAEs, treatment-related AEs, including IMAEs, SAEs, AEs [redacted] eading to discontinuation or death, and laboratory abnormalities for each treatment group	Incidence of all AEs/SAEs, treatment-related AEs, including IMAEs, SAEs, AEs [redacted] leading to discontinuation or death, and laboratory abnormalities for each treatment group	Up to 100 days after the last treatment of study intervention or up to discontinuation of study treatment
OS rate	Time from randomization to death due to any cause	Until death, up to 36 months
RFS (per investigator) rate	Time between the date of randomization and the date of first recurrence (local, regional, or distant metastasis), new primary melanoma, or death (whatever the cause), whichever occurs first	Until recurrence event, up to minimum follow-up of 12 months from last participant randomized in the study or death whichever is earlier

Table 10.4.3.1-1: Part 1 Secondary Endpoints

Secondary Endpoints	Description	Timeframe
Other Secondary		
Cmind28; Cmax1, Tmax, Cmaxss, and Cavgss	Minimum nivolumab serum concentration at Day 28; maximum nivolumab serum concentration after the first dose; time of maximum nivolumab serum concentration after the first dose; maximum nivolumab serum concentration at steady-state; time-averaged nivolumab serum concentration at steady-state	First 28 days of treatment; 17 weeks after the start of treatment
Percentage of participants who develop anti-nivolumab antibodies and neutralizing antibodies, if applicable, and the impact of anti-nivolumab antibodies on AEs, administration-related reactions, and events within MedDRA SMQ Anaphylactic reactions	Percentage of participants who develop anti-nivolumab antibodies and neutralizing antibodies, if applicable, and the impact of anti-nivolumab antibodies on AEs, administration-related reactions, and events within MedDRA SMQ Anaphylactic reactions	Up to 100 days after the last study treatment or up to discontinuation of study treatment
Mean CTSQ Satisfaction domain scores and score change from baseline at each assessment time point	Mean CTSQ Satisfaction domain scores and score change from baseline at each assessment time point	At each assessment time point

Abbreviations: AE, adverse event; Cavgss, time-averaged nivolumab serum concentration at steady-state; Cmax1, maximum nivolumab serum concentration after the first dose; Cmaxss, maximum nivolumab serum concentration at steady-state; Cmind28, minimum nivolumab serum concentration on Day 28; CTSQ, Cancer Treatment Satisfaction Questionnaire; IMAE, immune mediated-adverse event; MedDRA, Medical Dictionary for Regulatory Activities; OS, overall survival; RFS, recurrence-free survival; SAE, serious adverse event; SMQ, standard MedDRA query; Tmax, time to maximum nivolumab serum concentration after the first dose.

The ratio of geometric means and its 90% CI of the relevant secondary PK endpoints of Cmind28, Cmax1, Cmaxss, and Cavgss endpoints will also be tabulated similar to the PK primary endpoint but will not be used for concluding non-inferiority. Medians and ranges will be presented for Tmax by treatment group. Summary statistics by treatment group will be provided for each nivolumab PK parameter together with subject listing. Geometric means and coefficients of variation will be presented by treatment group together with N, mean, SD, median, minimum, and maximum.

Safety, immunogenicity, biomarkers, outcome research, and efficacy endpoints will be analyzed descriptively.

RFS will be programmatically determined based on the disease recurrence date provided by the investigator and is defined as the time between the date of randomization and the date of first recurrence (local, regional, or distant metastasis), new primary melanoma (including melanoma in situ), or death (whatever the cause), whichever occurs first. A participant who dies without reported recurrence will be considered to have recurred on the date of death. For participants who remain alive and whose disease has not recurred, RFS will be censored on the date of last evaluable disease assessment. For those participants who remain alive and have no recorded post-

randomization disease assessment, RFS will be censored on the day of randomization. Censoring rules are presented in Table 10.4.3.1-2 below.

Table 10.4.3.1-2: Censoring Scheme for Primary Definition of Recurrence-Free Survival

Situation	Date of Event or Censoring	Outcome
Recurrence (local, regional, distant, new primary melanoma, including melanoma in situ)	Date of first recurrence	Event
Death without recurrence	Date of death	Event
No baseline disease assessment	Date of randomization	Censored
No on-study disease assessments and no death	Date of randomization	Censored
No recurrence and no death	Date of last evaluable disease assessment	Censored
Second non-melanoma primary cancer (excluding BCC and/or SCC) reported prior or on the same day of disease assessment	Date of last evaluable disease assessment prior to or on the same date of diagnosis of second non-melanoma primary cancer	Censored

Abbreviations: BCC, basal cell carcinoma; SCC, squamous cell carcinoma.

In Part 1, RFS distributions will be descriptively compared between treatment groups and hazard ratios, and corresponding 95% CIs will be estimated using a Cox proportional hazards (CPH) model, with treatment group as a single covariate, stratified by the protocol-specified factors.

RFS curves will be estimated using Kaplan-Meier (K-M) product-limit methodology. Median RFS with 2-sided 95% CIs using the log-log transformation will be computed.

RFS rates at 12, 18, 24, and 36 months (and yearly after depending on follow-up) with 2-sided 95% CIs using the log-log transformation will be computed.

For RFS, a supplemental analysis will be performed using a while on study treatment estimand strategy to handle the intercurrent events of start of new anticancer therapy, tumor-directed radiotherapy, or tumor-directed surgery (excluding basal cell carcinoma [BCC]/squamous cell carcinoma [SCC] removal). Under this strategy, RFS will be censored on the date of last evaluable disease assessment prior to or on the same date of initiation of new anticancer therapy, tumor-directed radiotherapy, or tumor-directed surgery (excluding BCC/SCC removal).

For the supplemental descriptive analysis, the RFS curves will be estimated using Kaplan-Meier (K-M) product-limit methodology. Median RFS with 2-sided 95% CIs using the log-log transformation will be computed.

OS is defined as the time from randomization to the date of death from any cause. For participants that are alive (ie, without documentation of death), 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 randomization for subjects who were randomized but had no follow-up. OS will be followed continuously while participants are on the study drug and every 3 months via in-person or phone contact after participants discontinue the study drug.

In Part 1 OS distributions will be descriptively compared between treatment groups, hazard ratio, and corresponding 95% CIs will be estimated using a CPH model, with treatment group as a single covariate, stratified by the protocol-specified factors.

OS curves will be estimated using K-M product-limit methodology. Median OS with 2-sided 95% CIs using the log-log transformation will be computed.

OS rates at 12, 18, 24, and 36 months with 2-sided 95% CIs using the log-log transformation will be computed.

All safety analyses will be performed using the All Treated participants population. Descriptive statistics of safety will be presented using NCI CTCAE v5 by treatment group. AEs will be coded using the most recent Medical Dictionary for Regulatory Activities (MedDRA) version available during the conduct of the study.

Frequency distribution of treated participants with AE using the worst CTC grade will be presented. Participants will only be counted (1) once at the preferred term (PT) level, (2) once at the system organ class (SOC) level, and (3) once in the "total participant" row at their worst CTCAE grade, regardless of SOC or PT.

10.4.4 Exploratory Endpoint(s)

Exploratory analyses will be described in the SAP that will be finalized before the database lock.

10.4.5 Other Analyses

10.4.5.1 Exposure-Response Analyses

Not applicable per Protocol Amendment 01. The following information refers to the original study design.

Model-determined nivolumab exposures may be used for exposure-response (E-R) analyses. If E-R analyses are conducted, the methods and results would be reported in a separate pharmacometrics report.

10.4.5.2 Immunogenicity Analyses

Not applicable per Protocol Amendment 01. The following information refers to the original study design.

All immunogenicity analyses will be performed using the Immunogenicity Evaluable Participants population.

A listing will be provided for all available immunogenicity data. A baseline ADA positive participant is defined as a participant with positive seroconversion detected in the last sample before initiation of treatment. An ADA-positive participant is a participant with at least 1 ADA-positive sample relative to baseline after initiation of the treatment. For each drug, frequency distribution of baseline ADA-positive participants and ADA-positive participants after initiation of the treatment will be summarized. To examine the potential relationship between

immunogenicity and safety, a table summarizing the frequency and type of AEs of special interest may be explored by immunogenicity status.

In addition, potential relationships between immunogenicity and efficacy and/or PK may also be explored.

10.4.5.3 Outcomes Research

Not applicable per Protocol Amendment 01. The following information refers to the original study design.

Unless otherwise specified in the SAP, the analysis of Outcome Research endpoints will be performed on the All Treated participants population and will be restricted to treated participants who have an assessment at baseline and at least 1 post-baseline assessment for the given questionnaire (where applicable). Descriptive statistics will be provided.

10.4.5.4 Biomarkers

Not applicable per Protocol Amendment 01. The following information refers to the original study design.

For biomarker participants, descriptive summary statistics of biomarker assessments will be presented at baseline and at each on-study time point described in Section 9.8, unless otherwise specified.

10.4.6 Study Analyses Timeframe

The following DBLs will be performed:

10.4.6.1 Part 1

Not applicable per Protocol Amendment 01. The following information refers to the original study design.

Primary lock for Part 1 will be performed after all randomized participants in both arms have completed PK evaluation for the co-primary endpoints (Week 17). Subsequent database lock(s) will occur at 18 and 36 months after last participant is randomized (minimum follow-up of 18 and 36 months for all randomized participants) to assess for longer safety and efficacy secondary endpoint of RFS.

[redacted]

10.4.6.3 Final Analysis

The DBL will occur approximately 100 days after the last participant last treatment or earlier as applicable due to participant death or lost to follow-up.

10.5 Interim Analyses

Not applicable.

11 REFERENCES

[1] Shah SC, Kayamba V, Peek Jr RM, et al. Cancer control in low- and middle-income countries: is it time to consider screening? J Glob Oncol 2019;5:1-8.

[2] Jemal A, Torre L, Soerjomataram I, et al. The Cancer Atlas. 3rd ed. New York: The American Cancer Society, Inc.; 2019. pp. 36-8.

[3] Ferlay J, Ervik M, Lam F, et al. Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available from URL: https://gco.iarc.fr/today.

[4] Ambroggi M, Biasini C, Del Giovane C, et al. Distance as a barrier to cancer diagnosis and treatment: review of the literature. Oncologist 2015;20:1378-85.

[5] Hanly P, Céilleachair AÓ, Skally M, et al. How much does it cost to care for survivors of colorectal cancer? Caregiver's time, travel and out-of-pocket costs. Support Care Cancer 2013;21:2583-92.

[6] De Cock E, Pivot X, Hauser N, et al. A time and motion study of subcutaneous versus intravenous trastuzumab in patients with HER2-positive early breast cancer. Cancer Med 2016;5:389-97.

[7] Sait MK, Aguam AP, Mohidin S, et al. Intravenous site complications for patients receiving chemotherapy: an observational study. Ann Short Rep 2019;2:1032.

[8] Narducci F, Jean-Laurent M, Boulanger L, et al. Totally implantable venous access port systems and risk factors for complications: a one-year prospective study in a cancer centre. Eur J Surg Oncol 2011;37:913-8.

[9] Pandey M, Sarita GP, Devi N, et al. Distress, anxiety, and depression in cancer patients undergoing chemotherapy. World J Surg Oncol 2006;4:68.

[10] Suwankhong D, Liamputtong P. Early detection of breast cancer and barrier to screening programmes amongst Thai migrant women in Australia: a qualitative study. Asian Pac J Cancer Prev 2018;19:1089-97.

[11] Bluethmann SM, Mariotto AB, Rowland JH. Anticipating the “silver tsunami”: prevalence trajectories and comorbidity burden among older cancer survivors in the United States. Cancer Epidemiol Biomarkers Prev 2016;25:1029-36.

[12] US Food and Drug Administration. FDA’s Home Use Medical Device Initiative, slide 16 https://www.fda.gov/media/88981/download.

[13] Opdivo® Annex I Summary of Product Characteristics. Bristol-Myers Squibb Company; 2020.

[14] OPDIVO (nivolumab) US Prescribing Information. Bristol-Myers Squibb, Princeton, NJ. March 2020.

[15] Ossio R, Roldan-Marin R, Martinez-Said H, et al. Melanoma: a global perspective. Nat Rev Cancer 2017;17:393-4.

[16] Saginala K, Barsouk A, Aluru JS, et al. Epidemiology of melanoma. Med Sci (Basel) 2021;9:63.

[17] SEER data. Cancer Stat Facts: Melanoma of the skin. Available from URL: https://seer.cancer.gov/statfacts/html/melan.html.

[18] BMS-936558: A phase 3, randomized, double-blind study of adjuvant immunotherapy with nivolumab versus ipilimumab after complete resection of Stage IIIB/C or Stage IV melanoma in subjects who are at high risk for recurrence (CheckMate 238: CHECKpoint pathway and nivoluMAb clinical trial evaluation 238). Bristol-Myers Squibb Company; 2020. Document Control No. 930155919.

[19] BMS-936558: A phase 3, randomized study of adjuvant immunotherapy with nivolumab combined with ipilimumab versus nivolumab monotherapy after complete resection of stage IIIB/C/D or stage IV melanoma (CheckMate 915: CHECKpoint pathway and nivoluMAb clinical trial evaluation 915). Bristol-Myers Squibb Company; 2020. Document Control No. 930162406.

[20] Recombinant Human Hyaluronidase PH20 (rHuPH20) Investigator's Brochure. Halozyme, Inc.; 2023. Document Control No. 930124324.

[redacted]

[redacted]

30 Rosengren S, Dychter SS, Printz MA, et al. Clinical immunogenicity of rHuPH20, a hyaluronidase enabling subcutaneous drug administration. AAPS J 2015;17:1144-56.

[redacted]

34 Nivolumab (BMS-936558) Investigator Brochure. Bristol-Myers Squibb Company; 2022. Document Control Number 930038243.

35 Bookbinder LH, Hofer A, Haller MF, et al. A recombinant human enzyme for enhanced interstitial transport of therapeutics. J Control Release 2006;114:230-41.

36 Bywaters EGL, Holborow EJ, Keech MK. Reconstitution of the dermal barrier to dye spread after hyaluronidase injection. Br Med J 1951;2:1178-83.

37 Kirschbrown WP, Wynne C, Kågedal M, et al. Development of a subcutaneous fixed-dose combination of pertuzumab and trastuzumab: results from the phase Ib dose-finding study. J Clin Pharmacol 2019;59:702-16.

38 Printz MA, Dychter SS, DeNoia EP, et al. A phase I study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of recombinant human hyaluronidase PH20 adminstered intravenously in healthy volunteers. Curr Ther Res Clin Exp 2020;93:100604.

39 Yanez B, Pearman T, Lis CG, et al. The FACT-G7: a rapid version of the Functional Assessment of Cancer Therapy – General (FACT-G) for monitoring symptoms and concerns in oncology practice and research. Ann Oncol 2013;24:1073-8.

40 EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy 1990;16:199-208.

41 Pickard AS, De Leon MC, Kohlmann T, et al. Psychometric comparison of the standard EQ-5D to a 5 level version in cancer patients. Med Care 2007;45:259-63.

42 Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. Health Qual Life Outcomes 2007;5:70.

43 Trask PC, Tellefsen C, Espindle D, et al. Psychometric validation of the cancer therapy satisfaction questionnaire. Value Health 2008;11:669-79.

[44] Theodore-Oklota C, Humphrey L, Wiesner C, et al. Validation of a treatment satisfaction questionnaire in non-Hodgkin lymphoma: assessing the change from intravenous to subcutaneous administration of rituximab. Patient Prefer Adherence 2016;10:1767-76.

[45] Keininger D, Coteur G. Assessment of self-injection experience in patients with rheumatoid arthritis: psychometric validation of the Self-Injection Assessment Questionnaire (SIAQ). Health Qual Life Outcomes 2011;9:2.

[46] Hughes MK. Suicide screening in the oncology population. J Adv Pract Oncol 2016;7:101-4.

[47] National Comprehensive Cancer Network. NCCN Distress Management Guidelines. Version 2.2023. Available from URL: https://www.nccn.org/docs/default-source/patient-resources/nccn_distress_thermometer.pdf.

12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
ADA	anti-drug antibody
AE	adverse event
[redacted]	[redacted]
AIDS	acquired immunodeficiency disease
AJCC	American Joint Committee on Cancer
ALT	alanine transaminase
AR	additional research
ART	antiretroviral therapy
AST	aspartate transaminase
AT	aminotransferase
AxMP	Auxiliary Medicinal Product
BCC	basal cell carcinoma
BLA	biologics license application
BMS	Bristol-Myers Squibb
BP	blood pressure
BRAF	B-Raf proto-oncogene
C	cycle
Cavgd28	time-averaged nivolumab serum concentration on Day 28
Cavgss	time-averaged nivolumab serum concentration at steady-state
CBC	complete blood count
CD	cluster of differentiation
cHL	chronic Hodgkin's lymphoma
CHO	Chinese hamster ovary
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CL	nivolumab clearance

Term	Definition
CLss	geometric mean steady-state clearance
Cmax1	maximum nivolumab serum concentration after first dose
Cmaxss	maximum nivolumab serum concentration at steady-state
Cmind28	minimum nivolumab serum concentration on Day 28
Cminss	minimum nivolumab serum concentration at steady-state
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus 2019
CPH	Cox proportional hazard
CRC	colorectal cancer
CRF	case report form
CSR	clinical study report
CT	computed tomography
CTAg	clinical trial agreement
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T lymphocyte associated antigen 4
CTSQ	Cancer Treatment Satisfaction Questionnaire
CV%	% coefficient of variation
CXC	chemokine
D	day
DBL	database lock
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DP	drug product
DPD	dihydropyrimidine dehydrogenase
[redacted]	[redacted]

Term	Definition
DRESS	drug reaction with eosinophilia and systemic symptoms
[redacted]	[redacted]
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EOI	end of infusion
EQ-5D-5L	EuroQol-5 Dimension-5 Level
EQ-VAS	EuroQol-5 Dimension-5 Level visual analogue scale
E-R	exposure-response
EU	European Union
F	bioavailability
FACT-G7	Functional Assessment of Cancer Therapy - General 7
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin embedded
FSH	follicle-stimulating hormone
fT3	free T3
fT4	free T4
FU	follow up
GBS	Guillain-Barre Syndrome
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCG	human chronic gonadotropin
HCP	health care provider

Term	Definition
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	hazard ratio
HRQoL	health-related quality of life
HRT	hormone replacement therapy
HuMAb	human monoclonal antibody
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IFU	Instructions for Use
IgG	immunoglobulin
IHC	immunohistochemistry
IMAE	immune-mediated adverse event
IMG	immunogenicity
IMP	Investigational Medicinal Product
IO	immuno-oncology
IP	Investigational Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUS	intrauterine hormone-releasing system
IV	intravenous
Ka	model-determined population mean absorption rate constant
K-M	Kaplan-Meier
LAM	lactational amenorrhea method

Term	Definition
LD	longest diameter
LDH	lactate dehydrogenase
LLN	lower limit of normal
MCB	master cell bank
MedDRA	Medical Dictionary for Regulatory Activities
MEK	mitogen-activated protein kinase
MG	myasthenia gravis
MMIS	malignant melanoma in situ
MMR	measles, mumps, rubella
MRI	magnetic resonance imaging
N	number of participants
NAb	neutralizing antibody
NCI	National Cancer Institute
Nivo	nivolumab
[redacted]	[redacted]
NSAID	non-steroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
OS	overall survival
PD-1	programmed death-1
PD-L1	programmed death-ligand 1
PD-L2	programmed death-ligand 2
PET-CT	positron emission tomography-computed tomography
PFS	pre-filled syringe
PK	pharmacokinetics
PPK	population pharmacokinetics
PT	preferred term
Q2W	every 2 weeks

Term	Definition
Q4W	every 4 weeks
QoL	quality of life
[redacted]	[redacted]
R&D	research and development
RCC	renal cell carcinoma
RFS	recurrence-free survival
rHuPH20	recombinant human hyaluronidase PH20 enzyme
RNA	ribonucleic acid
RT	radiation therapy
RT-PCR	reverse transcriptase-polymerase chain reaction
SAD	short-axis diameter
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous
SCC	squamous cell carcinoma
SCCHN	squamous cell carcinoma of the head and neck
SCLC	small cell lung cancer
SD	standard deviation
SIAQ	Self-Injection Assessment Questionnaire
SJS	Stevens-Johnson syndrome
SLN	sentinel lymph node
SmPC	summary of product characteristics
SMQ	standardized MedDRA query
SOA	Schedule of Activities
SOC	system organ class
SSC	Study Steering Committee

Term	Definition
SUSAR	suspected, unexpected serious adverse reaction
T.bili	total bilirubin
T3	triiodothyronine
T4	thyroxine
TASQ	Treatment Administration Satisfaction Questionnaire
TB	total bilirubin
TEN	toxic epidermal necrolysis
TMB	tumor mutational burden
TRAE	treatment-related adverse event
TSH	thyroid-stimulating hormone
U	unit
ULN	upper limit of normal
US	United States
USA	United States of America
USPI	United States prescribing information
v5	version 5
VAS	visual analogue scale
Vss	geometric mean volume of distribution at steady state
WBC	white blood cells
WES	whole exome syndrome
WOCBP	women of childbearing potential

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

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

REGULATORY AND ETHICAL CONSIDERATIONS

This study will be conducted in accordance with:

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

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

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

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

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

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

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

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

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

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

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

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

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

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

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

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

FINANCIAL DISCLOSURE

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

INFORMED CONSENT PROCESS

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

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

The investigator or his/her representative must:

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

Obtain an ICF signed and personally dated by participant and by the person who conducted the informed consent discussion.

- Include a statement in 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 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.

If informed consent is initially given by a participant's 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.

BMS COMMITMENT TO DIVERSITY IN CLINICAL TRIALS

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

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

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

DATA PROTECTION, DATA PRIVACY, AND DATA SECURITY

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

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

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

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

adverse effects. Furthermore, BMS Information Technology has defined 6 principles to protect our digital resources and information:

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

SOURCE DOCUMENTS

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

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

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

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

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

STUDY INTERVENTION RECORDS

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

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

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

CASE REPORT FORMS

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

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

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

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

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

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

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

MONITORING

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

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

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

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

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

RECORDS RETENTION

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

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

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

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

RETURN OF STUDY TREATMENT

BMS-936558 - NIVOLUMAB IV

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.

BMS-986298 - [redacted]

For this study, study intervention (those supplied by BMS or its vendors) containers, vials, and syringes related to [redacted] may be destroyed by the site/responsible Study Monitor or follow local regulations.

Study interventions supplied by BMS or its vendors associated with any product complaints (eg, study intervention defect, [redacted] malfunction, or unsuccessful administration) will be arranged for return to BMS by the site/responsible Study Monitor or follow local regulations.

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:

- External Principal Investigator designated at protocol development
- National Coordinating Investigator
- Study Steering Committee chair or their designee
- Participant recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Regional representation (eg, among top quartile of enrollers from a specified region or country)
- 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, electrocardiograms, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Note that abnormal lab tests or other safety assessments should only be reported as AEs if the final diagnosis is not available. Once the final diagnosis is known, the reported term should be updated to be the diagnosis.
- Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration, even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose, as a verbatim term (as reported by the investigator), should not be reported as an AE/serious adverse event (SAE) unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae and should specify "intentional overdose" as the verbatim term.

Events NOT Meeting the AE Definition

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

DEFINITION OF SAE

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

SERIOUS ADVERSE EVENTS

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

[redacted]

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.

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

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

All SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

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

SAE Email Address: [redacted]

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

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

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

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

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP:

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

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

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

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

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

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

End of Relevant Systemic Exposure

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

METHODS OF CONTRACEPTION

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

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

- 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.

A vasectomy is a highly effective contraception method provided that the participant 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 7.7.1 PROHIBITED AND/OR RESTRICTED TREATMENTS of the protocol.

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

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

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

COLLECTION OF PREGNANCY INFORMATION

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

[redacted]

APPENDIX 6 PARAMETER ESTIMATES FROM PPK MODEL USED FOR SIMULATIONS

Table 1: Parameter Estimates from the PPK Model Used For Simulations

Parameters (Units)	Estimate
Fixed Effects	
CL [mL/h]	10.8
VC [L]	4.01
Q [mL/h]	28.7
VP [L]	2.78
CL_{BBWT}	0.6
CL_{GFR}	0.12
CL_{SEX}	-0.14
CL_{PS}	0.17
VC_{BBWT}	0.55
VC_{SEX}	-0.153
CL_{EMAX}	-0.292
CL_{T50}	1.36
CL_{HILL}	2.74
CL_{RAAA}	0.0147
CL_{RAAS}	-0.0731
CL_{OTH}	-0.0268
CL_{NSCLC}	-0.0361
CL_{ADJM}	-0.514
KA	0.0132
F	0.7
Random Effects	
ω2CL [-]	0.0965
ω2VC [-]	0.139
ω2VP [-]	0.223
ω2EMAX [h]	0.095
ω2KA	0.115
ω2F	0.565
ω2CL: ω2VC	0.0368
ω2KA:F	0.22

Table 1: Parameter Estimates from the PPK Model Used For Simulations

Parameters (Units)	Estimate
Residual Error	
Proportional Error	0.22

Abbreviations: CL [mL/h], clearance milliliters per hour]); *CLADJM,*, effect of adjuvant melanoma on clearance; *CLBBWT*, effect of baseline body weight on clearance; *CLEMAX*, estimate of the maximal change in clearance; *CLGFR*, effect of estimated glomerular filtration rate on clearance; *CLHILL,* effect of sigmoidicity (Hill coefficient) on clearance; *CLNSCLC,* effect of non-small cell lung cancer on clearance; *CLOTH,* effect of other tumor types on clearance; *CLPS,* effect of performance status on clearance; *CLRAAA,* effect of African American race on clearance; *CLRAAS,* effect of Asian race on clearance; *CLSEX,* effect of sex on clearance*; CLT50,* time at which the change in clearance is 50% of the maximal change in clearance*;* F, bioavailability; *KA*, first order absorption rate constant; *Q* [mL/h], inter-compartmental clearance (milliliters per hour); *VC* [L], central volume of distribution (liters)*; VCBBWT,* effect of baseline body weight on central volume of distribution;*;VCSEX,* effect of sex on central volume of distribution; *VP* [L], peripheral volume of distribution (liters); *ω2CL* [-], random effects for clearance; *ω2CL: ω2VC,* random effects for correlated parameters clearance and central volume of distribution*; ω2EMAX* [h,], random effects for maximal change in clearance (hours); *ω2F,* random effects for bioavailability*; ω2KA,* random effects for first order absorption rate constant; *ω2KA:F,* random effects for correlated parameters first order absorption rate constant and bioavailability; *ω2VC* [-], random effects for central volume of distribution; *ω2VP* [-], random effect for peripheral volume of distribution.

APPENDIX 7 MANAGEMENT ALGORITHMS FOR STUDIES UNDER CTCAE VERSION 5.0

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

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

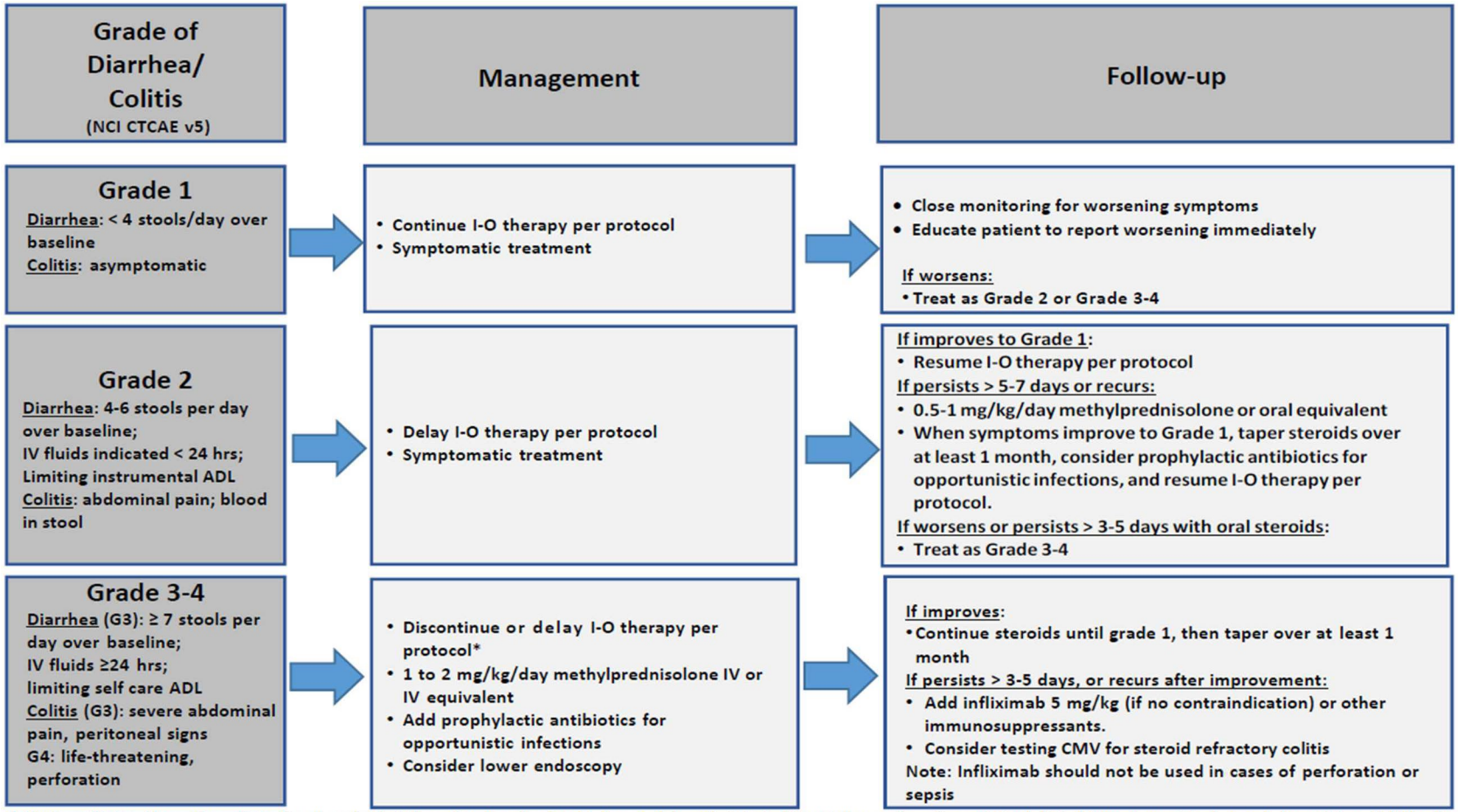
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the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

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

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

GI Adverse Event Management Algorithm

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



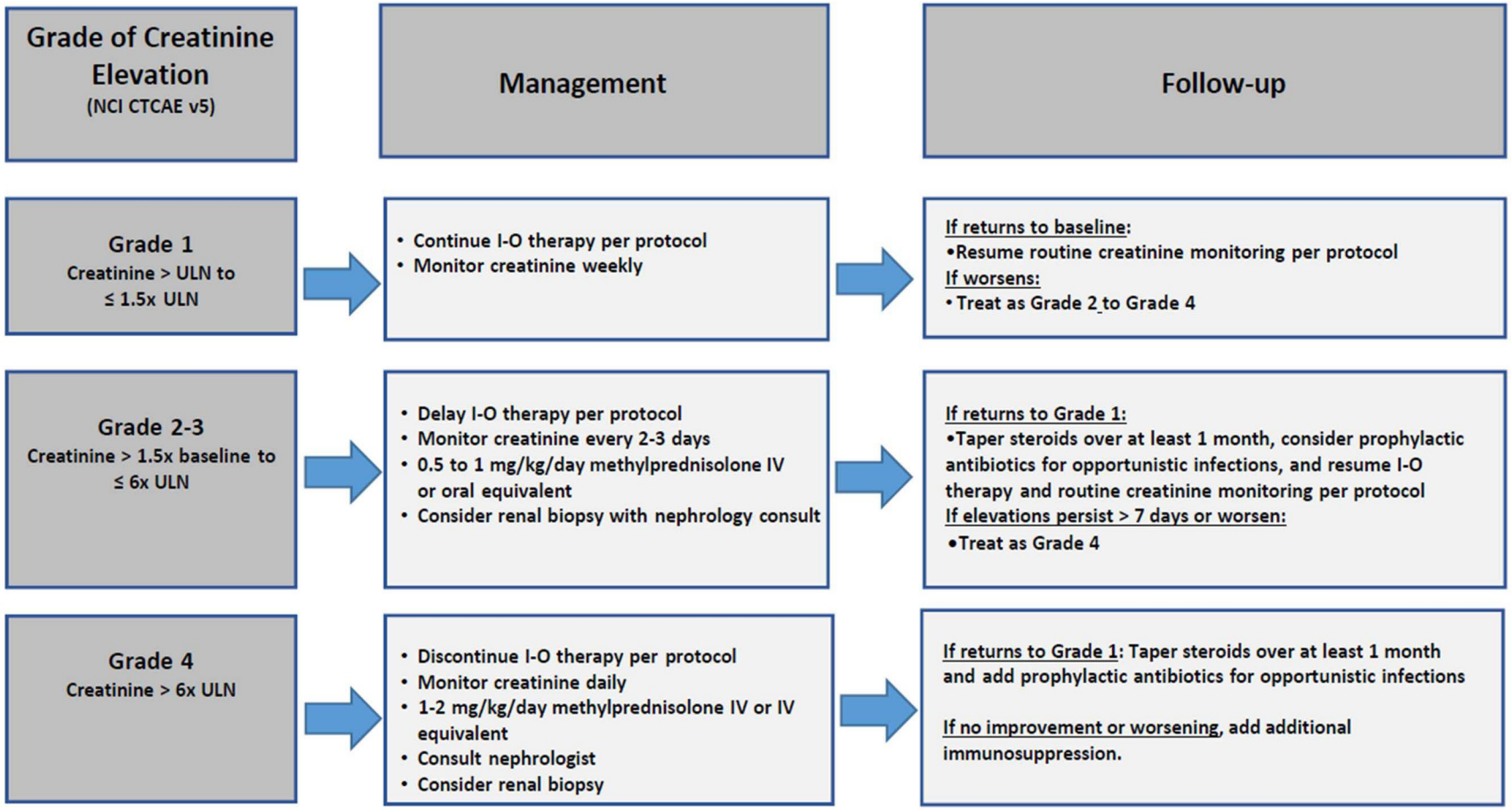
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

28-Sep-2020

Renal Adverse Event Management Algorithm

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

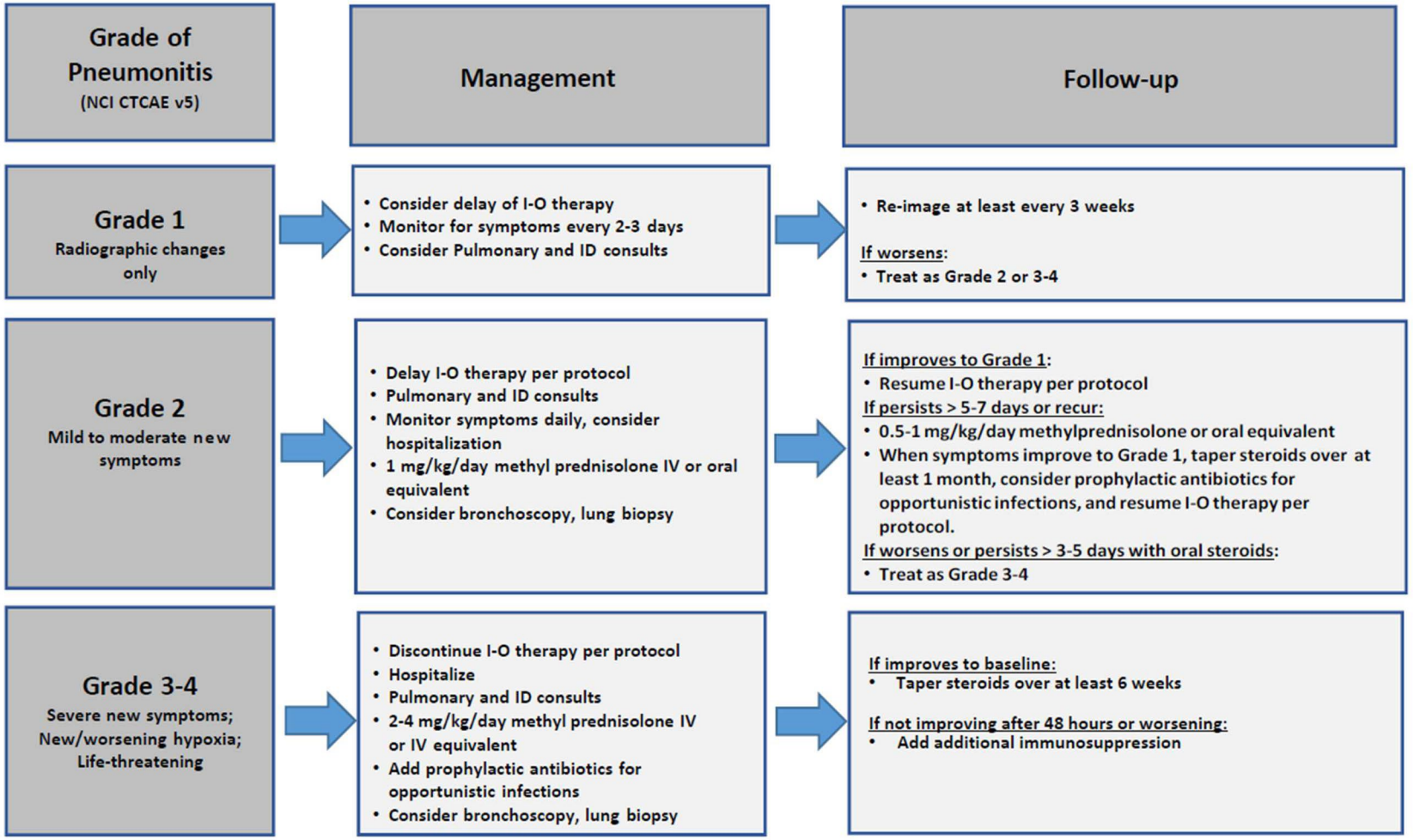


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

28-Sep-2020

Pulmonary Adverse Event Management Algorithm

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

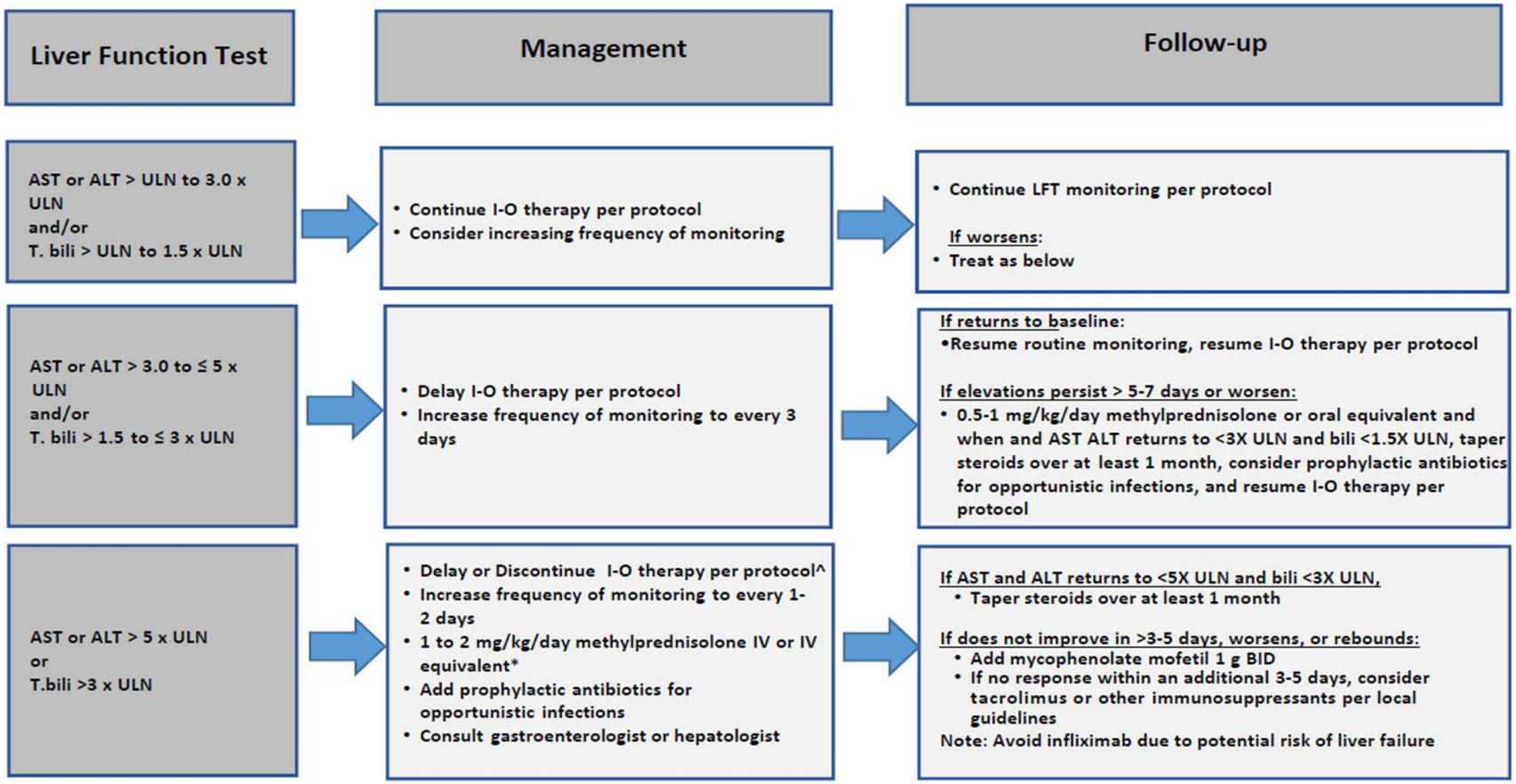


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

28-Sep-2020

Hepatic Adverse Event Management Algorithm

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



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

28-Sep-2020

Endocrinopathy Adverse Event Management Algorithm

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

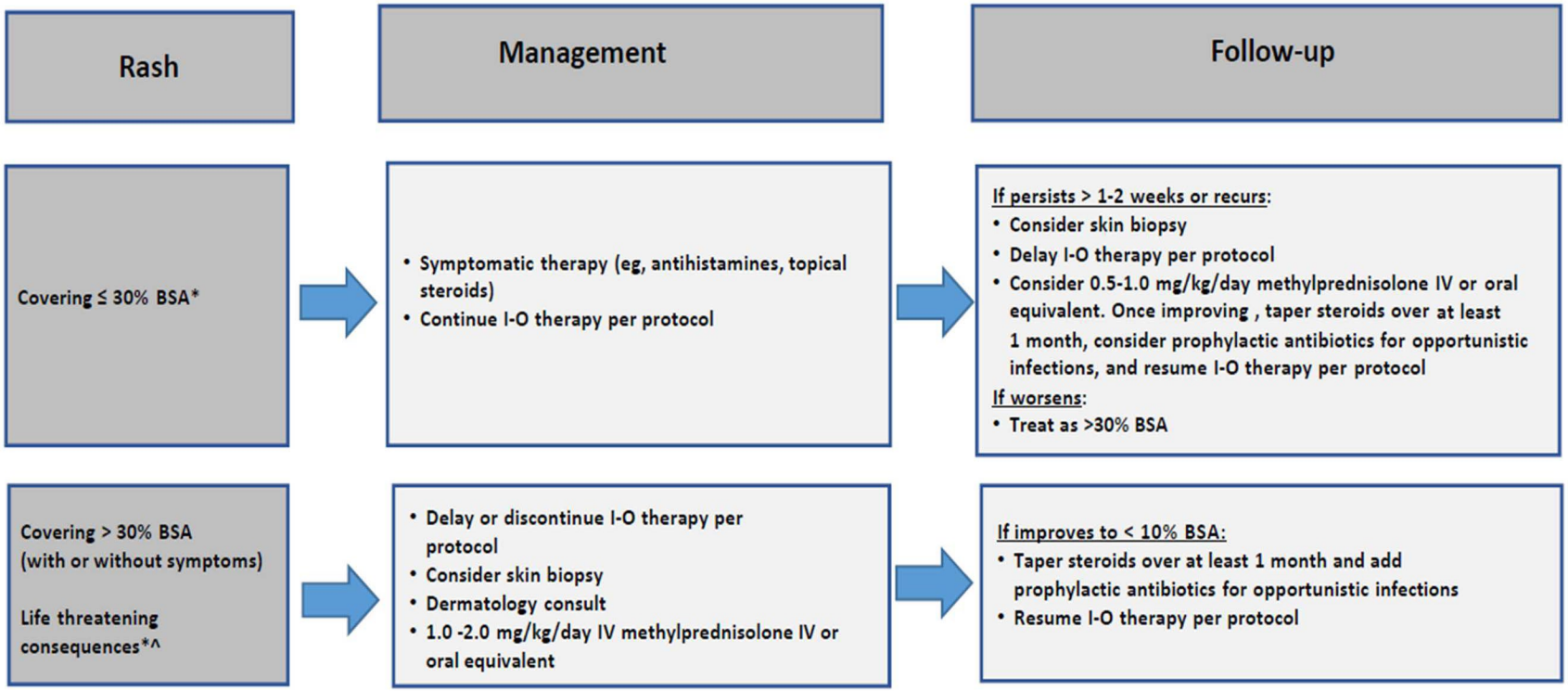
Endocrinopathy	Management	Follow-up
Asymptomatic TSH abnormality or Hyperglycemia requiring no medical intervention	• Continue I-O therapy per protocol • If TSH < 0.5 x LLN, or TSH > 2 x ULN, or consistently out of range in 2 subsequent measurements: o include fT4 at subsequent cycles as clinically indicated; o consider endocrinology consult	• Monitor TSH as per protocol • Monitor blood sugar • If symptomatic or blood sugar requiring initiation of treatment or change in management, manage as below
Symptomatic endocrinopathy or hyperglycemia requiring initiation of treatment or change in daily management or work up	• Evaluate endocrine function; consider endocrinology consult • Consider pituitary scan Symptomatic with abnormal lab/pituitary scan: • Delay I-O therapy per protocol • 1-2 mg/kg/day methylprednisolone IV or PO equivalent for hypophysitis • Initiate appropriate hormone/medical therapy No abnormal lab/pituitary MRI scan but symptoms persist: • Continue IO therapy. Repeat labs in 1-3 weeks /MRI in 1 month Hyperglycemia: Screen for Diabetic Ketoacidosis (DKA). If negative, continue IO and treat diabetes. If DKA hold IO, admit, manage DKA. Steroids not recommended for DKA/hyperglycemia	If improves (with or without hormone replacement): • Taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections • Resume I-O therapy per protocol • Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component
Suspicion of adrenal crisis (eg, severe dehydration, hypotension, shock out of proportion to current illness)	• Delay or discontinue I-O therapy per protocol • Rule out sepsis • Stress dose of IV steroids with mineralocorticoid activity • IV fluids • Consult endocrinologist	• Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component • If adrenal crisis resolves and patient is adequately controlled with physiologic hormone replacement, patient can resume IO therapy per protocol.

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

28-Sep-2020

Skin Adverse Event Management Algorithm

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



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

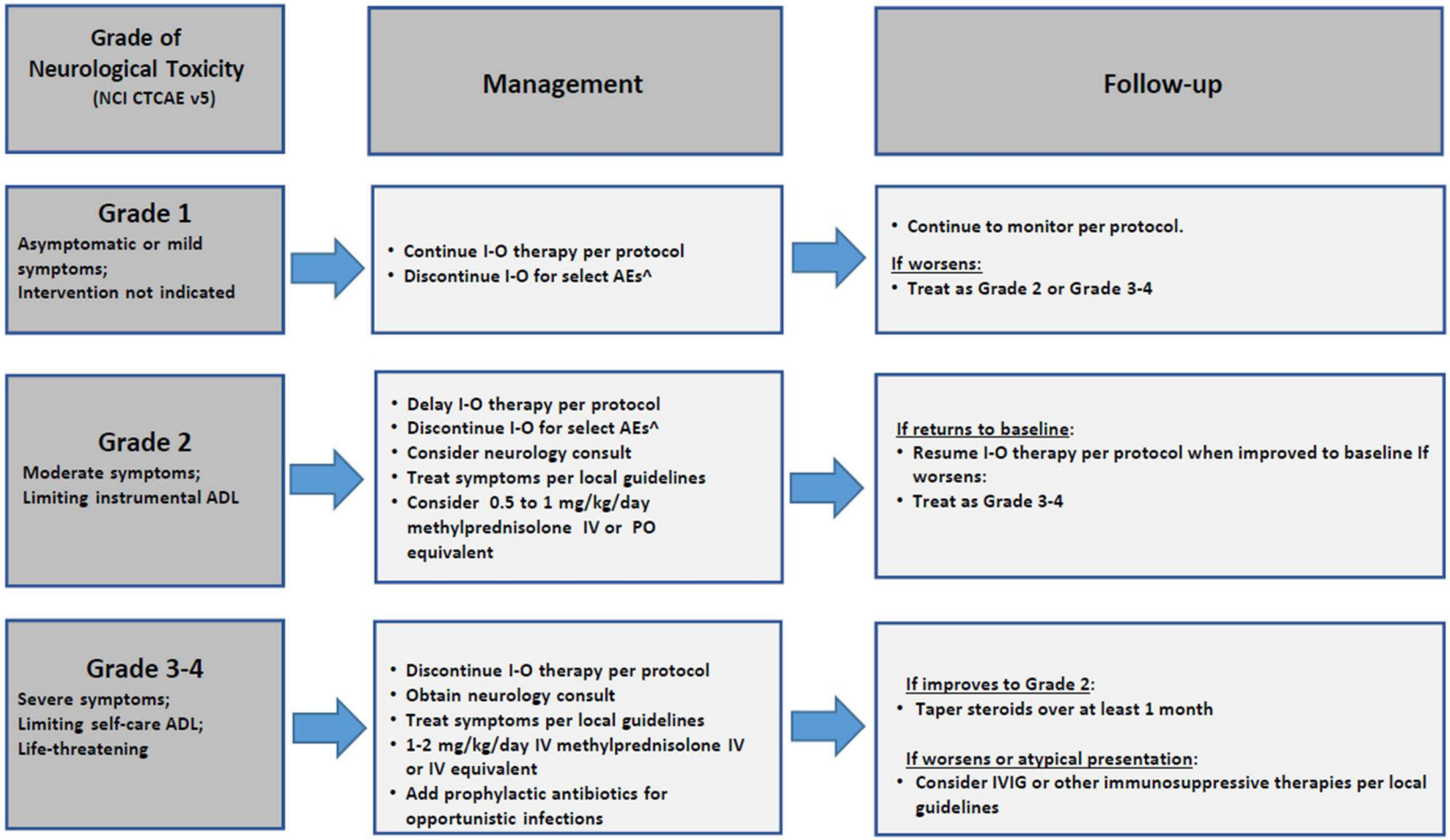
*Refer to NCI CTCAE v5 for term-specific grading criteria.

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

28-Sep-2020

Neurological Adverse Event Management Algorithm

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



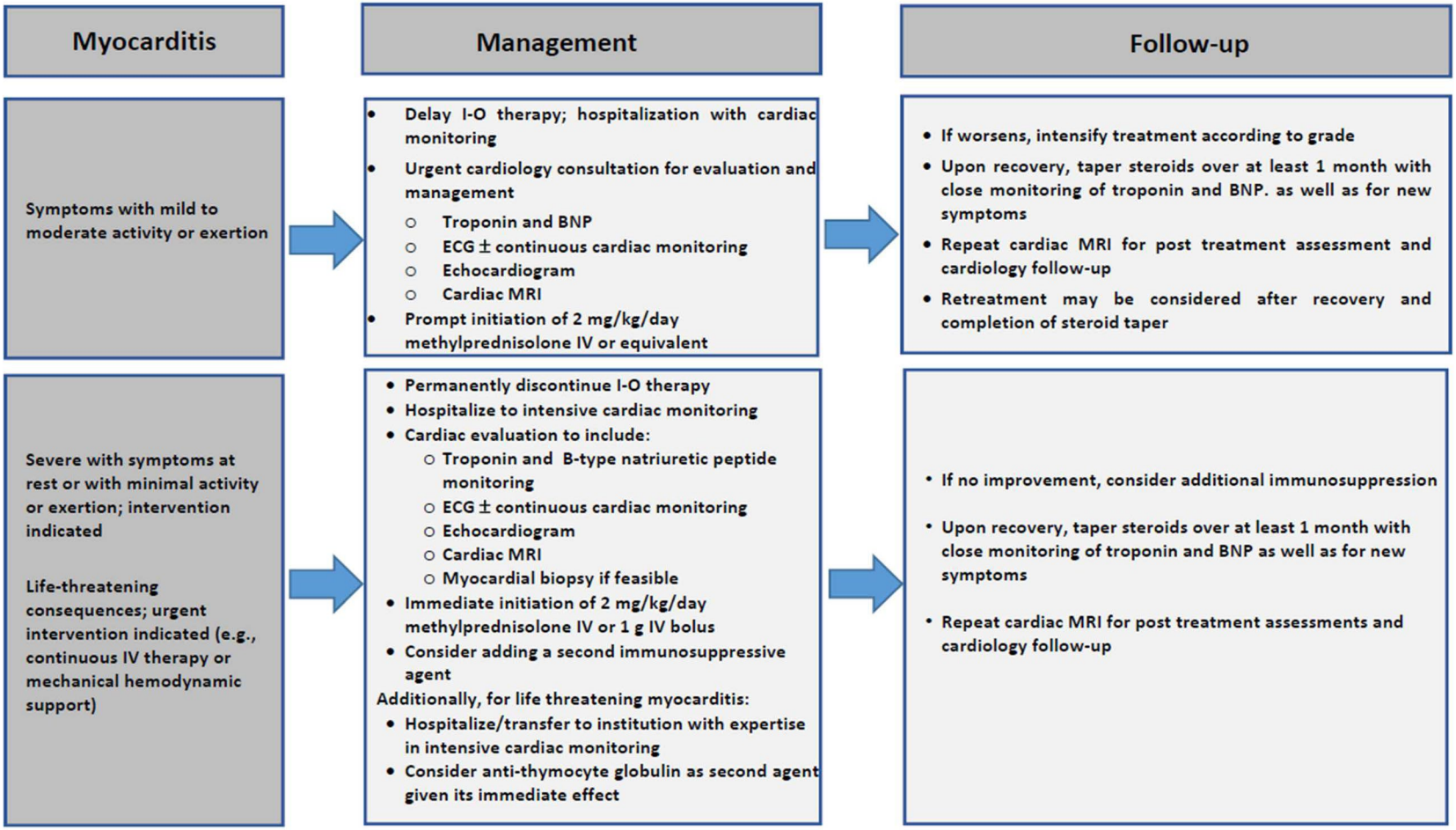
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

28-Sep-2020

Myocarditis Adverse Event Management Algorithm

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



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

28-Sep-2020

APPENDIX 8 ECOG PERFORMANCE STATUS

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

Reference: Oken MM, Creech RH, et al. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5: 649-655.

APPENDIX 9 AJCC MELANOMA STAGING (CANCER STAGING MANUAL 8TH EDITION)

Definition of Primary Tumor (T)

T Category	Thickness	Ulceration Status
TX: primary tumor thickness cannot be assessed (e.g., diagnosis by curettage)	Not applicable	Not applicable
T0: no evidence of primary tumor (e.g., unknown primary or completely regressed melanoma)	Not applicable	Not applicable
Tis (melanoma *in situ*)	Not applicable	Not applicable
T1	≤1.0 mm	Unknown or unspecified
T1a	<0.8 mm	Without ulceration
T1b	<0.8 mm 0.8-1.0 mm	With ulceration With or without ulceration
T2	>1.0-2.0 mm	Unknown or unspecified
T2a	>1.0-2.0 mm	Without ulceration
T2b	>1.0-2.0 mm	With ulceration
T3	>2.0-4.0 mm	Unknown or unspecified
T3a	>2.0-4.0 mm	Without ulceration
T3b	>2.0-4.0 mm	With ulceration
T4	>4.0 mm	Unknown or unspecified
T4a	>4.0 mm	Without ulceration
T4b	>4.0 mm	With ulceration

Definition of Distant Metastasis (M)

M Category	Anatomic site	LDH level
M0	No evidence of distant metastasis	Not applicable
M1	Evidence of distant metastasis	See below
M1a	Distant metastasis to skin, soft tissue including muscle, and/or non-regional lymph node	Not recorded or unspecified
M1a(0)		Not elevated
M1a(1)		Elevated
M1b	Distant metastasis to lung with or without M1a sites of disease	Not recorded or unspecified
M1b(0)		Not elevated
M1b(1)		Elevated
M1c		Not recorded or unspecified
M1c(0)		Not elevated

M Category	Anatomic site	LDH level
M1c(1)	Distant metastasis to non-CNS visceral sites with or without M1a or M1b sites of disease	Elevated
M1d	Distant metastasis to CNS with or without M1a, M1b, or M1c sites of disease	Not recorded or unspecified
M1d(0)		Not elevated
M1d(1)		Elevated
Suffixes for M category: (0) LDH not elevated; (1) LDH elevated. No suffix is used if LDH is not recorded or is unspecified.		

Definition of Regional Lymph Node (N)

N Category	Number of tumor-involved regional lymph nodes	Presence of in-transit, satellite, or microsatellite metastases
NX	Regional nodes not assessed (e.g., SLN biopsy not performed, regional nodes previously removed for another reason) **Exception**: pathological N category is not required for T1 melanomas, use cN	No
N0	No regional metastases detected	No
N1	One tumor-involved node or in-transit, satellite, and/or microsatellite metastases with no tumor-involved nodes	
N1a	One clinically occult (i.e., detected by SLN biopsy)	No
N1b	One clinically detected	No
N1c	No regional lymph node disease	Yes
N2	Two or three tumor-involved nodes or in-transit, satellite, and/or microsatellite metastases with one tumor-involved node	
N2a	Two or three clinically occult (i.e., detected by SLN biopsy)	No
N2b	Two or three, at least one of which was clinically detected	No
N2c	One clinically occult or clinically detected	Yes
N3	Four or more tumor-involved nodes or in-transit, satellite, or microsatellite metastases with two or more tumor-involved nodes, or any number of matted nodes with or without in-transit, satellite, and/or microsatellite metastases	
N3a	Four or more clinically occult (i.e., detected by SLN biopsy)	No
N3b	Four or more, at least one of which was clinically detected, or presence any number of matted nodes	No
N3c	Two or more clinically occult or clinically detected, and/or presence any number of matted nodes	Yes

AJCC Prognostic Stage Groups

Clinical (cTNM)

Clinical stage includes microstaging of the primary melanoma and clinical/radiologic/biopsy evaluation for metastases. By convention, clinical staging should be used after biopsy of the primary melanoma, with clinical assessment for regional and distant metastases. Note that pathological assessment of the primary melanoma is used for both clinical and pathological classification. Diagnostic biopsies to evaluate possible regional and/or distant metastasis also are included. Note there is only one stage group for clinical Stage III melanoma.

When T is....	And N is.....	And M is....	The clinical stage is...
Tis	N0	M0	0
T1a	N0	M0	IA
T1b	N0	M0	IB
T2a	N0	M0	IB
T2b	N0	M0	IIA
T3a	N0	M0	IIA
T3b	N0	M0	IIB
T4a	N0	M0	IIB
T4b	N0	M0	IIC
Any T, Tis	≥N1	M0	III
Any T	Any N	M1	IV

PATHOLOGICAL (pTNM)

Pathological staging includes microstaging of the primary melanoma, including any additional staging information from the wide excision (surgical) specimen that constitutes primary tumor surgical treatment and pathological information about the regional lymph nodes after SLN biopsy or therapeutic lymph node dissection for clinically evident regional lymph node disease.

When T is....	And N is.....	And M is....	The pathological stage is...
Tis	N0	M0	0
T1a	N0	M0	IA
T1b	N0	M0	IA
T2a	N0	M0	IB
T2b	N0	M0	IIA
T3a	N0	M0	IIA
T3b	N0	M0	IIB
T4a	N0	M0	IIB

When T is....	And N is.....	And M is....	The pathological stage is...
T4b	N0	M0	IIC
T0	N1b, N1c	M0	IIIB
T0	N2b, N2c, N3b or N3c	M0	IIIC
T1a/b-T2a	N1a-N2a	M0	IIIA
T1a/b-T2a	N1b/c or N2b	M0	IIIB
T2b/T3a	N1a-N2b	M0	IIIB
T1a-T3a	N2c or N3a/b/c	M0	IIIC
T3b/T4a	Any N ≥N1	M0	IIIC
T4b	N1a-N2c	M0	IIIC
T4b	N3a/b/c	M0	IIID
Ant T, Tis	Any N	M1	IV
Pathological Stage 0 (melanoma *in situ*) and T1 do not require pathological evaluation of lymph nodes to complete pathological staging; use cN information to assign their pathological stage.			

Adapted from: American Joint Committee on Cancer. Melanoma of the Skin. In: Amin MB, Edge SB, Greene FL, et al., editors. AJCC Cancer Staging Manual. 8th ed. Chicago: Springer International Publishing AG; 2018 pp 577-8.

APPENDIX 10 COUNTRY SPECIFIC REQUIREMENTS

Country	Section number and Title	Original Language	Country-specific language or differences
Argentina, Czech Republic, Germany, Romania, and Any Other Countries Where Exclusion of HIV Positive Participants is Locally Mandated	Section 2, Flow Chart/Time and Events Schedule, Table 2-1: Screening Assessments-Laboratory Tests		Add "HIV" to the list of laboratory tests
Argentina, Czech Republic, Germany, Romania and Any Other Countries Where Exclusion of HIV Positive Participants is Locally Mandated	Section 6.2, Exclusion Criteria, Exclusion criterion 3) k)	Known human immunodeficiency virus (HIV) positive with an AIDS defining opportunistic infection within the last year, or a current CD4 count < 350 cells/uL. Participants with HIV are eligible if: i) they have received antiretroviral therapy (ART) for at least 4 weeks prior to randomization as clinically indicated while enrolled on study ii) they continue on ART as clinically indicated while enrolled on study iii) CD4 counts and viral load are monitored per standard of care by a local health care provider. iv) inclusion of participants with HIV should be based on Investigator clinical judgement and in consultation with the Medical Monitor NOTE: Testing for HIV must be performed at sites where mandated locally. HIV positive participants must be excluded where mandated locally (see Appendix 10)	Positive test for HIV
Germany	Section 2, Flow Chart/Time and Events Schedule,	Contrast enhanced CT of the chest (if CT contrast is contraindicated, then non-contrast CT should be acquired). CT/MRI of the abdomen, pelvis, and all other	Contrast enhanced CT of the chest (if CT contrast is contraindicated, then non-contrast CT should be acquired). CT/MRI of the abdomen, pelvis, and all

Country	Section number and Title	Original Language	Country-specific language or differences
	Table 2-1: Screening Procedural Outline	known and/or suspected sites of disease, within 28 days prior to randomization. See Section 9.1.1 for further details.	other known and/or suspected sites of disease, within 28 days prior to randomization. See Section 9.1.1 for further details. MRI may be used as an alternative imaging modality to chest CT at screening, during treatment and in follow-up.
Germany	Section 2, Flow Chart/Time and Events Schedule, Table 2-2: On Study Treatment Procedural Outline (Arm A) Table 2-3, On Study Treatment Procedural Outline (Arm B)	Contrast enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease should occur every 12 weeks (± 7 days) starting from date of first dose until investigator assessed local, regional, or distant recurrence (whichever comes first) for Stage IV participants and until distant recurrence for Stage III participants. See Section 9.1.1 for further details. If a participant starts systemic therapy for melanoma recurrence, or for a new non-melanoma tumor after study drug discontinuation, follow-up scans for this trial should be discontinued.	Contrast enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease should occur every 12 weeks (± 7 days) starting from date of first dose until investigator assessed local, regional, or distant recurrence (whichever comes first) for Stage IV participants and until distant recurrence for Stage III participants. See Section 9.1.1 for further details. MRI may be used as an alternative imaging modality to chest CT at screening, during treatment and in follow-up. If a participant starts systemic therapy for melanoma recurrence, or for a new non-melanoma tumor after study drug discontinuation, follow-up scans for this trial should be discontinued.
Germany	Section 2, Flow Chart/Time and Events Schedule, Table 2-5: Follow-up Assessments	Contrast enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease should occur every 12 weeks (± 7 days) starting from date of first dose until investigator assessed local, regional, or distant recurrence (whichever comes first) for Stage IV participants and until distant recurrence for Stage III participants. See Section 9.1.1 for further details. If a	Contrast enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease should occur every 12 weeks (± 7 days) starting from date of first dose until investigator assessed local, regional, or distant recurrence (whichever comes first) for Stage IV participants and until distant recurrence for Stage III

Country	Section number and Title	Original Language	Country-specific language or differences
		participant starts systemic therapy for melanoma recurrence, or for a new non-melanoma tumor after study drug discontinuation, follow-up scans for this trial should be discontinued.	participants. See Section 9.1.1 for further details. MRI may be used as an alternative imaging modality to chest CT at screening, during treatment and in follow-up. If a participant starts systemic therapy for melanoma recurrence, or for a new non-melanoma tumor after study drug discontinuation, follow-up scans for this trial should be discontinued.
Germany	Section 9.1.1, Efficacy Assessment for the Study	Contrast enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease must be performed every 12 weeks (± 7 days) from date of first dose until investigator assessed local, regional, or distant recurrence (whichever comes first) for Stage IV participants and until distant recurrence for Stage III participants.	Contrast enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease must be performed every 12 weeks (± 7 days) from date of first dose until investigator assessed local, regional, or distant recurrence (whichever comes first) for Stage IV participants and until distant recurrence for Stage III participants. MRI may be used as an alternative imaging modality to chest CT at screening, during treatment and in follow-up.
France, Italy	Section 8.1, Discontinuation From Study Intervention		Add to discontinuation criteria item for discontinuation due to product inefficacy.
France:	Section 8.1, Discontinuation From Study Intervention		Add to discontinuation criteria item for discontinuation due to severe infection.

Country	Section number and Title	Original Language	Country-specific language or differences
Canada	Appendix 3, Adverse Evens		**Canada Phase IV AE reporting requirement:** The Division 8 of the Food and Drug Regulations in Canada require that any cases of Unusual Failure in Efficacy occurring in Canada be reported to the Canadian Health Authorities in an expedited manner. Canadian sites will record single cases of Unusual Failure in Efficacy as an Adverse Event. This reporting requirement is specific for Canadian sites only. This AE is required to be reported to BMS within 24 hours by the Investigator/site staff becoming aware of the report For transmission purposes, report this AE using the paper SAE form. For reporting information, refer to **Appendix 3 Adverse Events and Serious Adverse Event: Definitions and Procedures for Recording, Evaluating, Follow up and Reporting**, the section on *Reporting of SAEs to Sponsor or Designee.*
France	Section 6.2, Exclusion Criteria, Exclusion criterion 3) m)		Testing of DPD deficiency prior to treatment with 5-FU: not include patients with DPD deficiency blood uracil greater than or equal to 150ng/ml.
France	Table 7.4.2-1 under Hepatic Appendix 8, Hepatic Adverse Event Management Algorithm		The following phrase “delay dose” is deleted and the revised protocol language will state: “AST or ALT > 5x ULN or T.bili > 3x ULN, regardless

Country	Section number and Title	Original Language	Country-specific language or differences
			of baseline value: permanently discontinue". The following phrases are deleted: "In most cases" and "If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion between the investigator and the Medical Monitor/ designee must occur and approval from Medical Monitor prior to resuming therapy." The revised protocol language will state: "In all cases of AST or ALT > 5x ULN, study treatment will be permanently discontinued." A footnote is added to the algorithm which states: "AST or ALT > 5x ULN or T.bili > 3x ULN: Permanently discontinue I-O therapy per protocol."

APPENDIX 11 PRODUCT QUALITY ISSUES

DEFINITIONS: [redacted] STUDY INTERVENTION DEFECTS (IE, PRIOR TO USE OF [redacted] AND STUDY INTERVENTION MALFUNCTIONS

Study intervention defects may be related to component, product, or packaging and labeling issues prior to or during use. The list below includes, but is not limited to, descriptions of product complaints in these 3 categories that should be reported as a defect:

- Component Issue: Defect in container or dosing mechanism of the investigational product (IP). The component defect may be damaged, missing, or broken. Component examples include the [redacted] and the prefilled syringe housed within the [redacted]
- Product Issue (related to drug appearance, solution): Defect in the product itself. The product appearance has visual imperfections such as foreign particles, crystallization, discoloration, turbidity, insufficient volume, or anything that is not consistent to the product description in the IFU.
- Packaging/Labeling Issue: Defect in the packaging or labeling of the [redacted] The packaging (carton or tamper-evident seal) or labeling defects may be damaged or unreadable, or the label may be missing.

Study intervention malfunctions [redacted]

- An [redacted] ([redacted] malfunction is when the [redacted] appears normal during verification of shipment and then does not work during administration (eg, the [redacted] activated prematurely, failed to activate, the [redacted] stalled or did not expel the full volume, needle guard safety feature did not deploy, glass syringe breakage, needle bent, or broke upon use.

REPORTING PRODUCT QUALITY ISSUES (FOR [redacted] and IV)

Issues that call into question study intervention defects or study intervention [redacted] malfunctions (eg, IMP safety, purity, potency, quality, and identity [eg, evidence of suspected tampering of product]), [redacted] failed to activate, labelling issues) must be reported to the Sponsor using the following email: IMPQualityComplaints@bms.com within one business day and no longer than three calendar days (upon clinical site's identification or time of receipt from study participants receiving treatment [redacted]).

This includes suspected quality issues of components co-packaged with the drug, labelling, IMP [redacted] drug combination products, and [redacted]

In the event of a suspected product quality issue, the immediate action to be taken by the site is to quarantine the affected product. Do not dispose of the product unless retention presents a risk to personnel (eg, cytotoxic, risk of injury from broken glass or sharps). When reporting, provide as much product information as possible. Suspected IMP quality issues will be investigated, and a response will be provided back to the investigational site.

Site staff will be asked to send back malfunctioning [redacted] to the depot or local sponsor company according to local guidance/regulations.