Official Title of Study:

A Phase 3, Randomized, Open-label, Study of Subcutaneous Nivolumab + Relatlimab Fixed-dose Combination versus Intravenous Nivolumab + Relatlimab Fixed-dose Combination in Participants with Previously Untreated Metastatic or Unresectable Melanoma

NCT Number: NCT05625399

Document Date (Date in which document was last revised): 03 Mar 2026

CLINICAL PROTOCOL CA224127

A Phase 3, Randomized, Open-label, Study of Subcutaneous Nivolumab + Relatlimab Fixed-dose Combination versus Intravenous Nivolumab + Relatlimab Fixed-dose Combination in Participants with Previously Untreated Metastatic or Unresectable Melanoma

Compound: BMS-986213

Brief Title:

A Study of Subcutaneous Nivolumab + Relatlimab FDC in Previously Untreated Metastatic or Unresectable Melanoma (**RELA**TIVITY-127)

Protocol Amendment 04

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REGULATORY AGENCY IDENTIFIER NUMBER(S)

IND: 159987
EU Trial Number: 2022-500967-11-00
UTN: U1111-1274-0193

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Protocol Amendment 04	03-Mar-2026	The main purpose of Protocol Amendment 04 is to: • [redacted] • [redacted] • [redacted] • Add an option for less frequent tumor assessment imaging for qualifying participants. • Stop collection of clinical outcome assessments ([redacted] FACT-M, [redacted]), subsequent cancer therapy, [redacted] • Miscellaneous changes include update to sponsor name and address, study personnel and other clarification/editorial changes.
Administrative Letter 07	13-May-2025	Updated study personnel
Administrative Letter 06	01-May-2024	Updated study personnel
Protocol Amendment 03	05-Mar-2024	The main purpose of Protocol Amendment 03 is to: • Eliminate the [redacted]-day screening window. • [redacted] • Miscellaneous changes include country-specific requirements for Mexico in Appendix 10 and other clarification/editorial changes.
Protocol Amendment 02	16-Jun-2023	• Exclude participants who have not recovered from surgery in the interest of participant safety. • [redacted]

Document	Date of Issue	Summary of Change
		• Mandatory laboratory testing has been introduced at [redacted] to appropriately detect the late onset of any laboratory-based immune-related adverse events. • [redacted] • Other updates have been made to address country-specific requirements (Germany and Sweden). • [redacted] • Change was made from all treated participants to all randomized participants for all efficacy endpoints such as ORR, PFS, OS, DOR, and TTR to maintain consistency throughout the protocol. • Clarified the definition of 5 half-lives in Appendix 4. • Modified the renal function cut-off in the exclusion criteria [redacted]. • [redacted]
Administrative Letter 02	25-Aug-2022	Updated study personnel
Protocol Amendment 01	17-Jun-2022	The main purpose of Protocol Amendment 01 is to add the following elements: • [redacted] • [redacted] In addition, minor clarifications and editorial updates have been made throughout the protocol.

Document	Date of Issue	Summary of Change
Original Protocol	28-Apr-2022	Not applicable

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 04:

The purpose of this Protocol Amendment 04 is to: [redacted] add an option for less frequent tumor assessment imaging for qualifying participants; remove the collection of clinical outcomes assessments ([redacted] FACT-M [redacted]), subsequent cancer therapy, [redacted]

At the primary analysis database lock for the study (conducted on 02-Sep-2025), the primary endpoint of demonstrating PK non-inferiority for nivolumab + relatlimab FDC SC formulation versus nivolumab + relatlimab FDC IV formulation was met, while the key secondary efficacy endpoint of demonstrating non-inferiority of ORR by BICR for nivolumab + relatlimab FDC SC formulation versus nivolumab + relatlimab FDC IV formulation was not met. The overall safety profile was comparable between the treatment arms, with no new safety signals identified. [redacted]

Given the primary analysis result that the SC formulation did not demonstrate non-inferiority of ORR by BICR, further long-term data collection on the study is being minimized to reduce the burden of assessment for trial participants. [redacted] Tumor Assessment collection has been updated to include an option for less frequent image assessments for qualifying participants. Additionally, collection of Clinical Outcome Assessments ([redacted] FACT-M [redacted]), subsequent cancer therapy, [redacted] are being discontinued. These modifications do not impact patient safety. The [redacted] data collected at time of primary analysis was sufficient to adequately characterize the [redacted] and conduct statistical analysis to evaluate primary endpoints. [redacted]

This protocol amendment applies to all the participants in the study.

Minor editorial, formatting, and typographical corrections have been made and therefore have not been summarized. Additional changes are described in the table below.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	Updated the contact information of the clinical trial physician and removed contact information for the clinical scientist. Updated sponsor name and legal registered address	Administrative change.
Section 1: Protocol Summary	Updated to reflect changes made in the body of the protocol.	To align with protocol updates.
[redacted]		
Section 2: Schedule of Activities	Subsequent cancer therapy updated to no longer be collected on study	To reduce the burden of assessment for trial participants
Section 2: Schedule of Activities	Clinical outcome assessments ([redacted] FACT-M[redacted]) updated to no longer be collected on study	To reduce the burden of assessment for trial participants
[redacted]		
Section 5: Study Design	Section 5.1.2: [redacted] Also, updated that Clinical outcome assessments ([redacted] FACT-M[redacted]), [redacted] will no longer be collected on study	To align with protocol updates

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 9: Study Assessment and Procedures	Clinical outcome assessments ([redacted] FACT-M[redacted]), [redacted] collection will no longer be collected on study	To reduce the burden of assessment for trial participants
All	Formatting and typographical corrections.	Minor; therefore, have not been summarized.

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1 PROTOCOL SUMMARY

Protocol Title:

A Phase 3, Randomized, Open-label, Study of Subcutaneous Nivolumab + Relatlimab Fixed-dose Combination versus Intravenous Nivolumab + Relatlimab Fixed-dose Combination in Participants with Previously Untreated Metastatic or Unresectable Melanoma

Brief Title: A Study of Subcutaneous Nivolumab + Relatlimab FDC in Previously Untreated Metastatic or Unresectable Melanoma (RELATIVITY-127)

Rationale:

Relatlimab (BMS-986016) is a blocking antibody specific to the lymphocyte activation gene-3 (LAG-3) receptor. [redacted] The efficacy, safety, and pharmacokinetics (PK) of nivolumab and relatlimab have been well established in advanced (unresectable or metastatic) melanoma, as demonstrated in the CA224020 and CA224047 studies. Specifically, nivolumab and relatlimab have been shown to have encouraging clinical activity as combination therapy, with few overlapping toxicities. [redacted]

Furthermore, CA224047, a global, double-blind, randomized, Phase 2/3 study (N = 714) comparing the fixed-dose combination (FDC) of nivolumab 480 mg + relatlimab 160 mg intravenous (IV) every 4 weeks (Q4W) to nivolumab 480 mg IV Q4W in participants with unresectable or metastatic melanoma achieved its primary endpoint, demonstrating a statistically significant and clinically meaningful improvement in progression-free survival (PFS) by blinded independent central review (BICR). The Food and Drug Administration subsequently approved nivolumab + relatlimab-rmbw FDC (OPDUALAG™) for IV administration in adult and pediatric patients 12 years of age or older with unresectable or metastatic melanoma.

[redacted]

The coformulation of nivolumab 960 mg + relatlimab 320 mg FDC (BMS-986213) and rHuPH20 24,000 units will be referred to as nivolumab + relatlimab FDC SC, and the IV formulation of

nivolumab 480 mg + relatlimab 160 mg FDC (BMS-986213) will be referred to as nivolumab + relatlimab FDC IV.

Objectives and Endpoints:

Objectives	Endpoints
Co-primary	
• To demonstrate PK non-inferiority for nivolumab + relatlimab FDC SC formulation versus nivolumab + relatlimab FDC IV formulation	• Cavgd28 of nivolumab • Cminss of nivolumab • Cavgd28 of relatlimab • Cminss of relatlimab
Secondary	
• To demonstrate the non-inferiority of ORR by BICR for nivolumab + relatlimab FDC SC formulation versus nivolumab + relatlimab FDC IV formulation	• ORR by BICR per RECIST v1.1
• To evaluate PK of nivolumab + relatlimab FDC SC formulation versus nivolumab + relatlimab FDC IV formulation	• Cmind28, Cmax1, Cmaxss, and Cavgss of nivolumab and relatlimab
• To evaluate other measures of efficacy for nivolumab + relatlimab FDC SC formulation versus nivolumab + relatlimab FDC IV formulation	• DOR, DCR, and TTR by BICR per RECIST v1.1 • ORR, DOR, DCR, and TTR by Investigator per RECIST v1.1 • PFS by BICR and Investigator per RECIST v1.1 • OS
• To assess the safety of nivolumab + relatlimab FDC SC formulation	• AEs, SAEs, AEs leading to discontinuation, IMAEs, OESIs, deaths, and laboratory abnormalities
• To characterize changes in melanoma-related symptoms and quality of life for participants treated with nivolumab + relatlimab FDC SC formulation versus nivolumab + relatlimab FDC IV formulation	• Mean changes from baseline for FACT-M (MS)

Abbreviations: AE, adverse event; BICR, blinded independent committee review; Cavgd28, time-averaged serum concentration over 28 days; Cavgss, time-averaged serum concentration at steady state; Cmax1, peak serum concentration after the first dose; Cmaxss, peak serum concentration at steady state, Cmind28, trough serum concentration at Day 28; Cminss, trough serum concentration at steady state; DCR, disease control rate; DOR, duration of response; FACT-M (MS), Functional Assessment of Cancer Therapy-Melanoma (Melanoma Subscale); FDC, fixed-dose combination; IMAE, immune-mediated adverse event; IV, intravenous; OESI, other events of special interest; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetic; RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1; SAE, serious adverse event; SC, subcutaneous; TTR, time to response.

Overall Design:

CA224127 is a Phase 3, open label, randomized, pharmacokinetic (PK) non-inferiority study of nivolumab + relatlimab FDC SC formulation versus nivolumab + relatlimab FDC IV formulation in adult and adolescent participants with previously untreated metastatic or unresectable melanoma. Participants will be randomized in a 1:1 ratio into 1 of 2 treatment groups [redacted]

[redacted]

Participants will be enrolled using Interactive Response Technology. After signing the informed consent form, participants will be evaluated based on the assessments outlined in the Schedule of Activities and inclusion and exclusion criteria.

An independent Data Monitoring Committee will be utilized in the study to ensure oversight of safety and provide necessary recommendations for the continued protection of participants considering the assessed benefit/risk profile.

[redacted]

Number of Participants:

Approximately [redacted] participants will be enrolled to randomize [redacted] participants [redacted]

[redacted]

Detailed criteria will be defined in the Pharmacometrics Analysis Plan.

Study Population:

The study population includes adults and adolescents ≥ 12 years of age with previously untreated unresectable or metastatic melanoma.

Key Inclusion Criteria

- Participants who are ≥ 12 years of age and < 18 years of age (adolescents) must weigh ≥ 40 kg at the time of signing the informed consent (assent).

  Except: Where local regulations and/or institutional policies do not allow for participants ≥ 12 and < 18 years of age (adolescent population) to participate. For those sites, the eligible participant population is ≥ 18 years of age.
- Participants must have an Eastern Cooperative Oncology Group performance status of ≤ 1 (for adults ≥18 years of age)/Lansky Performance Score ≥ 80% for adolescents (≥ 12 to < 18 years of age).
- Participants must have histologically confirmed Stage III (unresectable) or Stage IV (metastatic) melanoma, per the American Joint Committee on Cancer staging system (8th edition).
- Participants must be treatment-naïve (ie, no prior systemic anticancer therapy for unresectable or metastatic melanoma).

  [redacted]
- Participants must have measurable disease by computed tomography or magnetic resonance imaging per Response Evaluation Criteria In Solid Tumors version 1 (RECIST v1.1).

  [redacted]
- Participants with known BRAF V600 mutation status, or who consent to BRAF V600 mutation testing per local institutional standards during the Screening Period with the sample collected within 3 months prior to randomization. All BRAF statuses (ie, BRAF wild-type or BRAF 600 mutation positive) are eligible.

- A formalin-fixed paraffin-embedded tissue block [redacted] of tumor tissue from core biopsy, punch biopsy, excisional biopsy, or surgical specimen obtained during screening or collected [redacted] with an associated pathology report, must be sent to the central laboratory prior to randomization. Fine needle aspirates or other cytology samples are not acceptable. Biopsies of bone lesions that do not have a soft tissue component are not acceptable. [redacted]
- Participant Re-enrollment: This study permits the re-enrollment of a participant that has discontinued the study as a pre-treatment failure (ie, participant has not been randomized). If re-enrolled, the participant must re-consent.

Key Exclusion Criteria

- Participants must not have active brain metastases or leptomeningeal metastases. [redacted]

  Participants with brain disease treated with whole brain radiation are not eligible.
- Participants must not have ocular melanoma.
- Participants must not have an active, known, or suspected autoimmune disease. Participants may enroll with the following conditions:
  - Type 1 diabetes mellitus.
- Hypothyroidism only requiring hormone replacement therapy.
- Skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment.
- Conditions not expected to recur in the absence of an external trigger.
- Participants must not have a history of myocarditis, regardless of etiology.
- Participants must not have a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 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.

- Participants must not have a concurrent malignancy (present during screening) requiring treatment or history of prior malignancy active within 2 years prior to randomization (ie, participants with a history of prior malignancy are eligible if treatment was completed at least 2 years before randomization and the participant has no evidence of disease). Participants with history of prior early stage basal/squamous cell skin cancer or non-invasive or in situ cancers that have undergone definitive treatment at any time are also eligible.
- [redacted]
- Participant must not have had prior treatment with relatlimab or any other lymphocyte activation gene 3-targeted agents.
- Prior radiation therapy within 2 weeks prior to first study treatment. Participants must have recovered (ie, Grade ≤ 1 or at baseline) from radiation-related toxicities prior to first study treatment.
- Participant has not recovered adequately from toxicity and/or complications from surgery prior to starting study treatment.
- Participants who are pregnant or breastfeeding.
- [redacted]
- [redacted]

Study Intervention:

The study consists of 3 periods: screening, on treatment, and follow-up. After screening, participants will be randomized 1:1 to either nivolumab + relatlimab FDC SC or nivolumab + relatlimab FDC IV.

Treatment will be administered every 4 weeks until unacceptable toxicity, withdrawal of consent, lost to follow up, disease progression, death, or termination of the study by the Sponsor, whichever occurs first.

[redacted] Delay administration of nivolumab + relatlimab FDC SC or nivolumab + relatlimab FDC IV if any of the delay criteria are met. For participants who require a delay of dosing, re-evaluate weekly, or more frequently, if clinically indicated, and resume dosing when criteria to resume treatment are met. Continue tumor assessments per protocol even if dosing is delayed.

Study Intervention:

Study Interventions for CA224127		
Intervention Name	**Unit Dose Strength(s) (Dosage Level)**	**IP/Non-IP/AxMP**
relatlimab + nivolumab FDC IV [redacted] (BMS-986213 [relatlimab [redacted] mg/nivolumab [redacted] mg]	4 mg/mL, 12 mg/mL (relatlimab 160 mg/nivolumab 480 mg)	IP
Nivolumab + relatlimab FDC SC (nivolumab, relatlimab, rHuPH20 Injection)	[redacted] mg, [redacted] mg, [redacted] Units/mL (nivolumab 960 mg, relatlimab 320 mg, rHuPH20 24,000 Units)	IP

Abbreviations: AxMP, Auxiliary Medicinal Product; FDC, fixed-dose combination; IP, Investigational Product; IV, intravenous; rHuPH20, recombinant human hyaluronidase; SC, subcutaneous.

[redacted]

Statistical Methods:

The aim of the study is to demonstrate PK non-inferiority of nivolumab + relatlimab FDC SC compared with nivolumab + relatlimab FDC IV.

[redacted]

[redacted]

Data Monitoring Committee: Yes

A Data Monitoring Committee will be used in the study.

Other Committee: No

Other review committee will not be used in the study.

Brief Summary:

The purpose of this study is to demonstrate the PK non-inferiority of nivolumab + relatlimab FDC SC compared with nivolumab + relatlimab FDC IV for Cavgd28 and Cminss in participants with previously untreated metastatic or unresectable melanoma. Study details include the following:

Study Duration: Screening procedures will occur from the time the participant signs the informed consent form to randomization. The Treatment Period begins at the time of randomization and will end at the beginning of the Follow-up Period. [redacted] Beyond the 135 days from the last dose of study intervention, participants will be followed for all drug-related adverse events (AEs) and serious AEs until resolution, [redacted]

Study Intervention Duration: Treatment will be administered until unacceptable toxicity, withdrawal of consent, lost to follow up, disease progression, death, or termination of the study by the Sponsor, whichever occurs first.

Study Visit Frequency: Treatment will be administered every 4 weeks. [redacted]

2 SCHEDULE OF ACTIVITIES

An overview of the schedule of major assessments in this study is provided in Table 2-1 (Screening), Table 2-2 (On-treatment), and Table 2-3 (Follow-up).

Table 2-1: Screening Procedural Outline (CA224127)

Procedure	Screening	Notes[a] All windows are based on calendar days
Eligibility Assessments		
Informed Consent Form	X	**Must be obtained prior to performing any screening procedures.** A participant is considered enrolled only when a protocol-specific IRB/IEC-approved informed consent (or assent) is signed and dated. The 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 Interactive Response Technology (IRT).
Informed Consent for Optional Sample Collection	X	See [redacted] Section 9.7.3.5 [redacted].
Informed Consent for Optional Future Research	X	This protocol will include residual sample storage for optional future research where allowed by local regulations (Section 9.8).
Contact IRT	X	Register in Interactive Response System to obtain participant number.
Inclusion/Exclusion Criteria	X	Must be confirmed prior to randomization. See Section 6 for further information.
Demography and Participant Characteristics	X	For US only. See Appendix 10 for further information.
Medical History	X	All medical history relevant to the disease under study.
Tumor Sample Submission	X	An FFPE tissue block (strongly preferred) [redacted] of tumor tissue from core biopsy, punch biopsy, excisional biopsy, or surgical specimen obtained during screening or collected [redacted] with an associated pathology report, must be sent to the central laboratory prior to randomization. Fine needle aspirates or other cytology samples are not acceptable. Biopsies of bone lesions that do not have a soft tissue component are not acceptable. [redacted]

Table 2-1: Screening Procedural Outline (CA224127)

Procedure	Screening	Notes[a] All windows are based on calendar days
		[redacted] See Section 9.7.3.5 for further information.
Baseline Tumor Assessment		
Body Imaging	X	Contrast-enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease [redacted]. See Section 9.1.1 for further information.
Brain Imaging	X	MRI of the brain without and with contrast is required for ALL participants during screening to rule out brain metastases [redacted]. CT of the brain (without and with contrast) can be performed if MRI is contraindicated. See Section 9.1.1 for further information.
Safety Assessments		
Physical Examination, Measurements, Vital Signs, and Performance Status	X	Height, weight, ECOG performance Status/Lansky Performance Score (Appendix 7), respiratory rate, seated blood pressure and heart rate, and body temperature. [redacted] Oxygen saturation by pulse oximetry at screening only. Must be collected within [redacted] days prior to randomization. If the screening physical examination is within 72 hours prior to Cycle 1 Day 1, then a single exam may count as both the screening and predose evaluation.
Assessment of Signs and Symptoms	X	Within [redacted] days prior to randomization.
Concomitant Medication Use	X	Within [redacted] days prior to randomization. Document live/attenuated vaccine use if within [redacted] days prior to first dose of study treatment. See Section 7.7 for further information.

Table 2-1: Screening Procedural Outline (CA224127)

Procedure	Screening	Notes[a] All windows are based on calendar days
Adverse Events (AEs) and Serious Adverse Events (SAEs) Assessment	X	**AEs/SAEs will be graded according to the NCI-CTCAE version 5.0.** All AEs and SAEs must be collected from the time of signing the informed consent. For participants who are enrolled but not randomized, SAEs must be collected during the screening period from the time of signing the informed consent. All AEs (SAEs or non-serious AEs) associated with SARS-CoV-2 infection must be collected from the time of signing the informed consent.
[redacted]		
Laboratory Tests		
Clinical Laboratory Assessments	X	On-site/local laboratory tests must be performed within [redacted] days prior to randomization. See Section 9.4.4 for list of laboratory tests to conduct. [redacted] For HIV: testing at sites where locally mandated; see Appendix 10. [redacted]

Table 2-1: Screening Procedural Outline (CA224127)

Procedure	Screening	Notes[a] All windows are based on calendar days
		[redacted]
[redacted]		
Pregnancy Test (Women of Childbearing Potential [WOCBP] [redacted]	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. If needed, the pregnancy test may be performed at a local laboratory provided the minimum sensitivity requirement is met. If so, the results of the test should be reported to the study site as well as the Sponsor in a timely manner.
FSH	X	Women only. If needed to document post-menopausal status, see Appendix 4.
Clinical Outcome Assessments		
FACT-M (MS)	X	To be administered using eCOA at the site. Adults (≥ 18 years) only at screening within [redacted] days prior to randomization.

Abbreviations: AE, adverse event; [redacted] CRF, case report form; [redacted] eCOA, electronic clinical outcome assessment; ECOG, Eastern Cooperative Oncology Group; FACT-M (MS), Functional Assessment of Cancer Therapy - Melanoma (Melanoma subscale); FFPE, formalin-fixed paraffin-embedded; FSH, follicle-stimulating hormone; [redacted] HIV, human immunodeficiency virus; IRB/IEC, independent regulatory board/independent ethics committee; IRT, interactive response technology; [redacted] MS, Melanoma Subscale; [redacted] NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events version 5.0; [redacted] SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; [redacted] 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 regulation.

Table 2-2: On-treatment Procedural Outline (CA224127)

Procedure	Cycle 1 Day 1 (Cycle Duration = [redacted])	[redacted]	Notes[b] All windows are based on calendar days
Study Treatment			
IRT Drug Randomization/Dispense Study Drug	X		IRT contact for randomization into 1 of the 2 treatment arms should occur when eligibility criteria are met. First dose to be administered within 3 calendar days following randomization. [redacted]
Administer Study Drug	X	X	Treatment to continue until unacceptable toxicity, withdrawal of consent, lost to follow up, disease progression, death, or termination of the study by the Sponsor, whichever occurs first.
Safety Assessments			
[redacted]			

Table 2-2: On-treatment Procedural Outline (CA224127)

Procedure	Cycle 1 Day 1 (Cycle Duration = [redacted])	[redacted]	Notes[b] All windows are based on calendar days
Targeted Physical Examination, Measurements, Vital Signs, and Performance Status	X*	X	Weight, ECOG performance Status/Lansky Performance Score (Appendix 7), respiratory rate, seated blood pressure and heart rate, and body temperature within 3 days prior to each dosing. *If the screening physical examination is within 72 hours prior to Cycle 1 Day 1, then a single exam may count as both the screening and predose evaluation.
[redacted]			
Adverse Events (AEs) Assessment and Serious Adverse Events (SAEs)	Continuously		**AEs/SAEs will be graded according to the NCI-CTCAE version 5.0.** All AEs and SAEs must be collected from the time of signing the informed consent. Record at each visit. Collect continuously throughout the treatment period. All AEs (SAEs or non-serious AEs), including those associated with SARS-CoV-2 infection, must be collected continuously during the treatment period from the time of signing the informed consent.
Concomitant Medication Use	Continuously		Record at each visit.
[redacted]			
Laboratory Tests (See Section 9.4.4)			

Table 2-2: On-treatment Procedural Outline (CA224127)

Procedure	Cycle 1 Day 1 (Cycle Duration =)		Notes[b] All windows are based on calendar days
Clinical Laboratory Assessments	X*	X	Perform on site/local laboratory testing within 72 hours prior to each dose. *For the first treatment visit, laboratory testing need not be repeated if performed within 72 hours and the results are available and have been reviewed for eligibility. See Section 9.4.4 for the list of laboratory tests to be conducted.

Table 2-2: On-treatment Procedural Outline (CA224127)

Procedure	Cycle 1 Day 1 (Cycle Duration =)		Notes[b] All windows are based on calendar days
Pregnancy Test (WOCBP)	X	See Notes	Serum or urine within 24 hours prior to first dose and then every (± 1 week) irrespective of dosing schedule. If needed, the pregnancy test may be performed at a local laboratory provided the minimum sensitivity requirement is met. If so, the results of the test should be reported to the study site as well as the sponsor in a timely manner.
Efficacy Assessments			
Body Imaging	See Notes	See Notes	Contrast enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease .

Table 2-2: On-treatment Procedural Outline (CA224127)

Procedure	Cycle 1 Day 1 (Cycle Duration =)		Notes[b] All windows are based on calendar days
			Note: Imaging method used at baseline should be maintained throughout the study. See Section 9.1.1 for further details.
Brain Imaging	See Notes	See Notes	Participants with a history of brain metastasis or symptoms should have a surveillance MRI (without and with contrast) per standard of care . CT of the brain (without or with contrast) can be performed if MRI is contraindicated. See Section 9.1.1 for further details.

Table 2-2: On-treatment Procedural Outline (CA224127)

Procedure	Cycle 1 Day 1 (Cycle Duration =)		Notes[b] All windows are based on calendar days
Clinical Outcome Assessments			
FACT-M	X	X	To be administered to adults (≥ 18 years) using eCOA at the site. Each assessment should be completed prior to each dosing. See Section 9.1.2 for further details. Post Protocol Amendment 04, FACT-M will no longer be administered or collected on study.

Table 2-2: On-treatment Procedural Outline (CA224127)

Procedure	Cycle 1 Day 1 (Cycle Duration =)		Notes[b] All windows are based on calendar days

Abbreviations: AE, adverse event; CRF, case report form; CT, computed tomography; eCOA, electronic clinical outcome assessment; ECOG, Eastern Cooperative Oncology Group; FACT-M, Functional Assessment of Cancer Therapy - Melanoma; hCG, human chorionic gonadotropin; IRT, interactive response technology; MRI, magnetic resonance imaging; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events version 5.0; SAE, serious adverse event; WOCBP, women of childbearing potential.

[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 regulation.

Table 2-3: Follow-up Assessments (CA224127)

Procedure	[redacted]		Note[c] All windows are based on calendar days
Safety Assessments			
Targeted Physical Examination, Measurements, Vital signs, and Performance Status	X		Weight, ECOG performance Status/Lansky Performance Score, respiratory rate, seated blood pressure and heart rate, and body temperature.
[redacted]			
Adverse Event (AE) Assessment and Serious Adverse Events (SAE)	See Notes		**AEs/SAEs will be graded according to the NCI-CTCAE version 5.0.** Record at each visit. Collect continuously throughout the treatment period from the time of signing the informed consent and for a minimum of 135 days following discontinuation of dosing. Beyond 135 days from the last dose of study therapy, participants will be followed for drug-related AEs/SAEs until resolution, [redacted]
Concomitant Medication Use	X	See Notes	Record at each visit. All medications with a start date within [redacted] days of the last dose date of study intervention are considered concomitant.

Table 2-3: Follow-up Assessments (CA224127)

Procedure	[redacted]		**Note[c]** **All windows are based on calendar days**
			Corticosteroids and other immune-modulating medications beyond [redacted] days of the last dose are to be collected for [redacted]
Subsequent Cancer Therapy	X	X	Include documentation of subsequent cancer therapy (ie, systemic therapy, tumor-directed surgery, or radiation therapy). Post Protocol Amendment 04, subsequent cancer therapy will no longer be collected on study
Laboratory Tests (See Section 9.4.4)			
Clinical Laboratory Assessments	X		To be performed at [redacted]. See Section 9.4.4 for the list of laboratory tests to perform. Laboratory toxicities (eg, suspected drug induced liver enzyme elevations) will be monitored during the follow-up phase, based on results from on-site/local labs, until all study intervention related toxicities resolve, return to baseline, or are deemed irreversible
[redacted]			
Pregnancy Test (WOCBP [redacted])	X		Serum or urine If needed, the pregnancy test may be performed at a local laboratory provided the minimum sensitivity requirement is met. If so, the results of the test should be reported to the study site as well as the sponsor in a timely manner.
Efficacy Assessments			
Body Imaging	See Notes		[redacted]

Table 2-3: Follow-up Assessments (CA224127)

Procedure	[redacted]	**Note[c]** **All windows are based on calendar days**
		[redacted] Contrast enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease to be performed at all subsequent assessments. Note: Imaging method used at baseline should be maintained throughout the study. See Section 9.1.1 for further details.
Brain Imaging	See Notes	Participants with a history of brain metastasis or symptoms should have surveillance MRIs (without and with contrast) [redacted] CT of the brain (without or with contrast) can be performed if MRI is contraindicated. See Section 9.1.1 for further details. See Section 9.1.1 for instructions on the performance of scans in participants with contrast allergies.

Table 2-3: Follow-up Assessments (CA224127)

Procedure	[redacted]		**Note[c]** **All windows are based on calendar days**
Survival Status	X	X	During Safety Follow-up [redacted] and every [redacted] months [redacted]
Clinical Outcome Assessments			
[redacted]			
FACT-M	X		Each assessment should be completed by adults (≥ 18 years) for [redacted]. See Section 9.1.2 for further details. Post Protocol Amendment 04, FACT-M will no longer be administered or collected on study.
FACT-M (MS)		X	For survival visits, MS questionnaire should be completed by [redacted]. Post Protocol Amendment 04, FACT-M (MS) will no longer be administered or collected on study.

Table 2-3: Follow-up Assessments (CA224127)

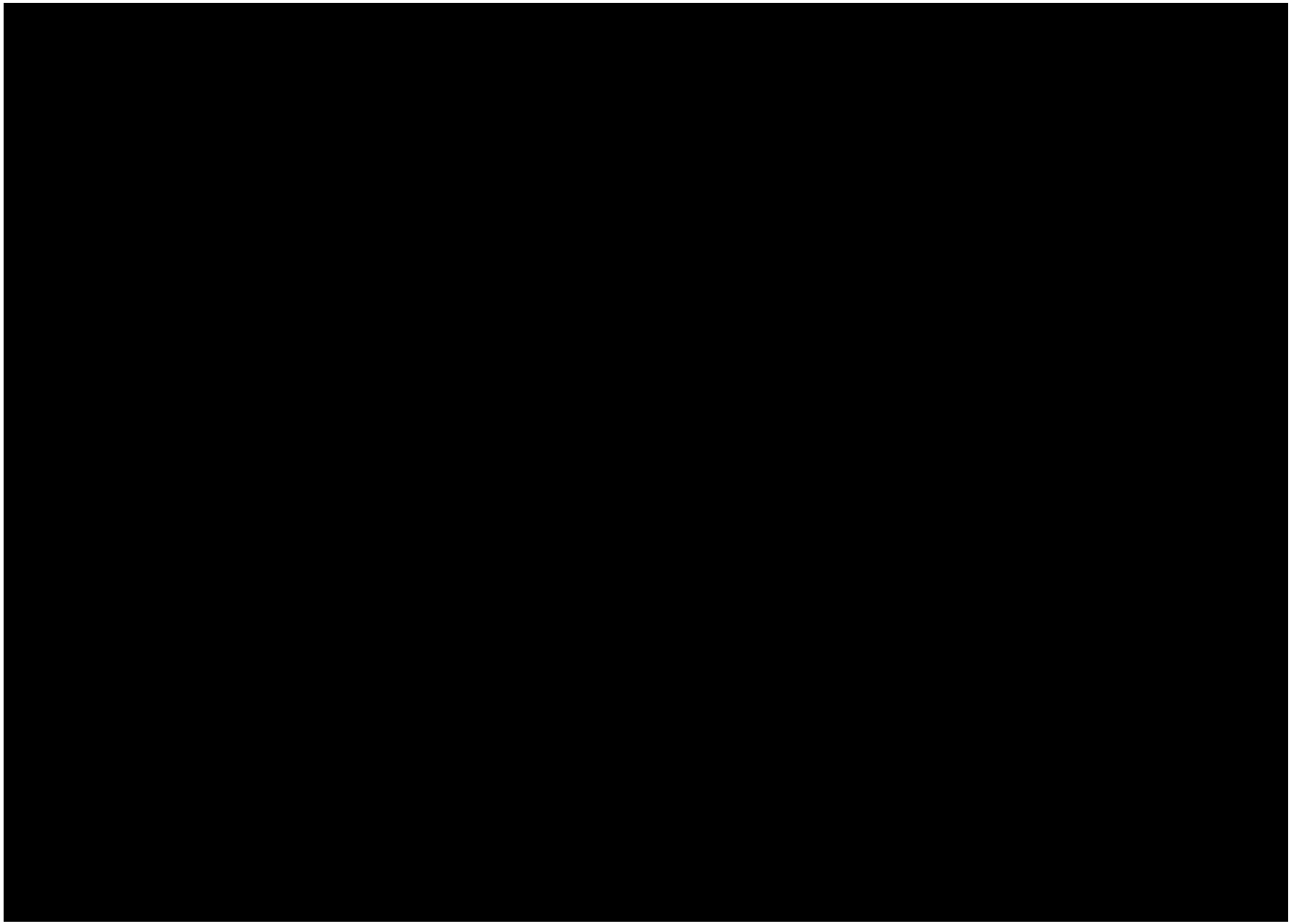
Procedure	[redacted]	Note[c] All windows are based on calendar days
[redacted]		

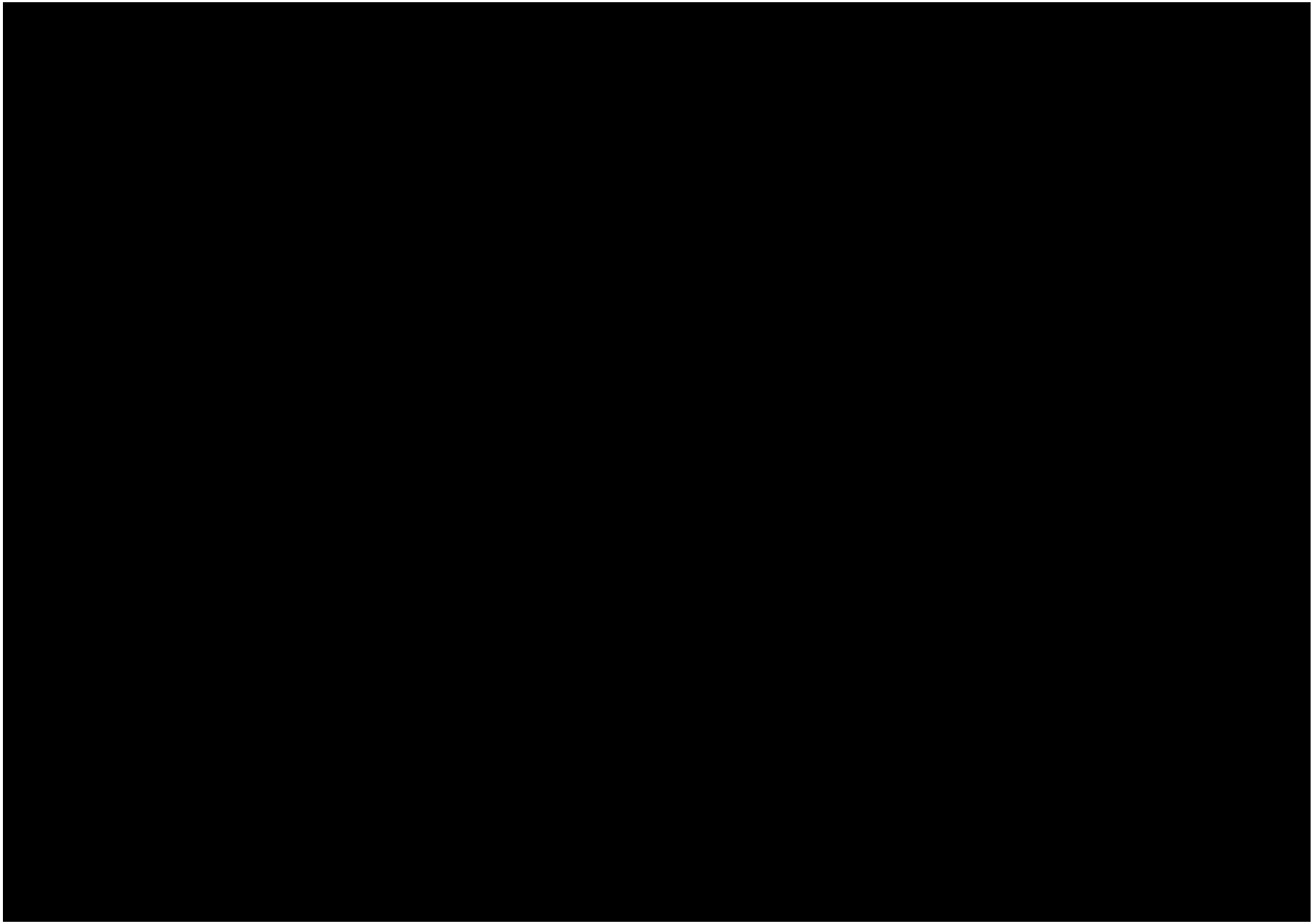
Abbreviations: AE, adverse event; CRF, case report form; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; [redacted] FACT-M (MS), Functional Assessment of Cancer Therapy - Melanoma (Melanoma subscale); hCG, human chorionic gonadotropin; [redacted] MS, Melanoma Subscale; MRI, magnetic resonance imaging; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events version 5.0; [redacted] SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; [redacted] WOCBP, women of childbearing potential.

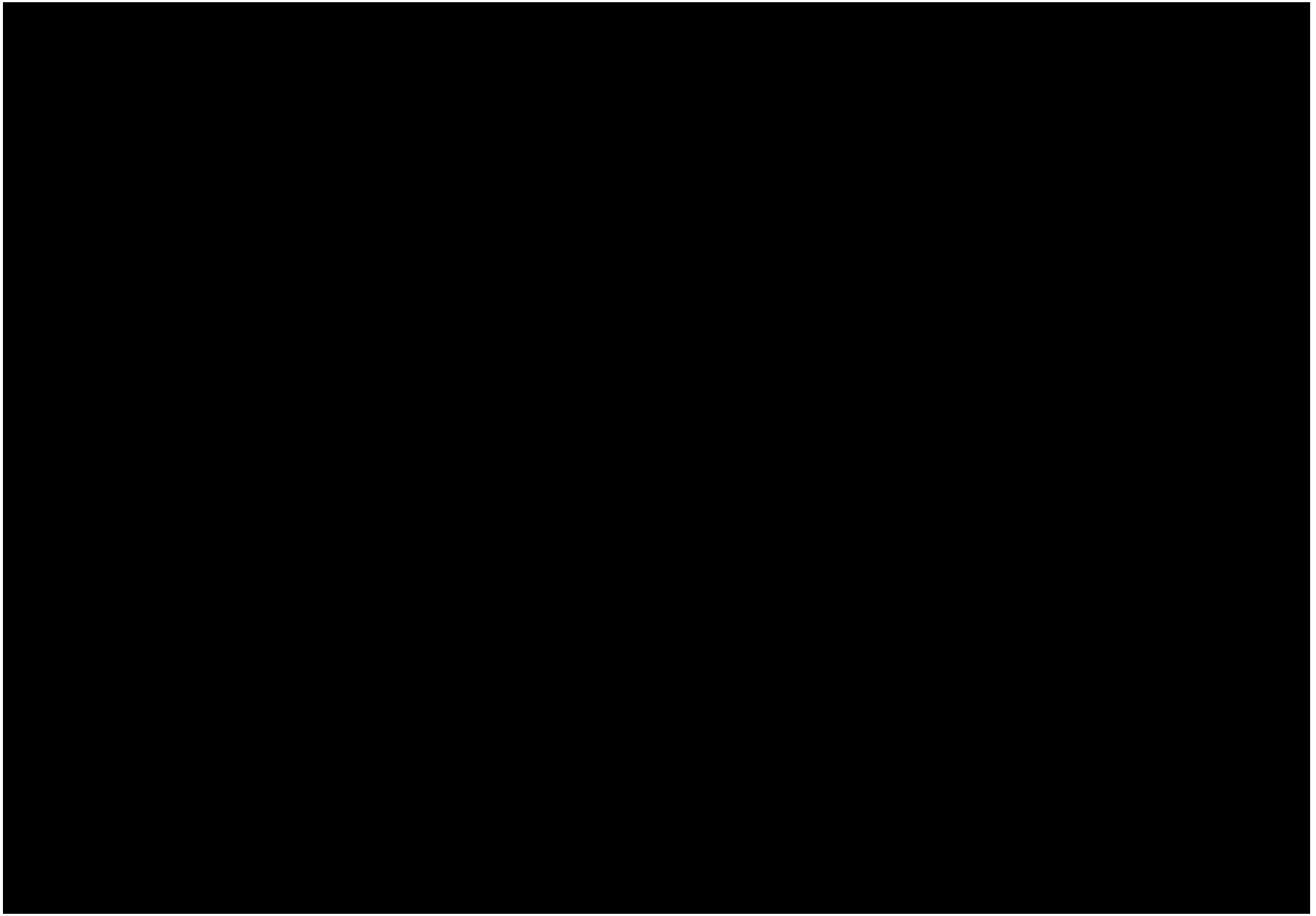
[redacted] Participants must be followed for at least 135 days (± 7 days) after last dose of study treatment. [redacted]

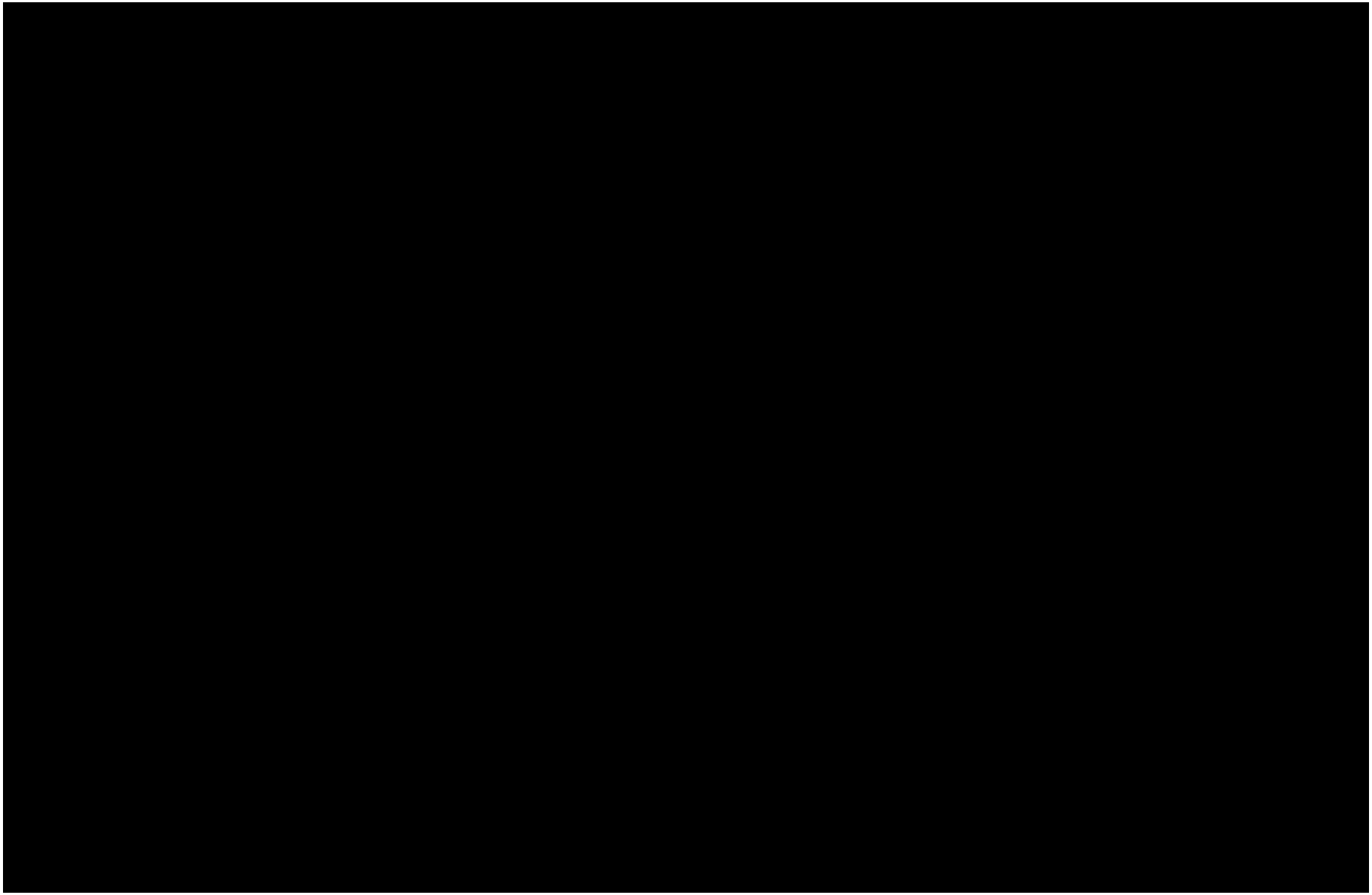
[redacted]

[c] 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 indicated.









In the event that multiple procedures are required at a single time point, the following is a list of procedures from highest to low priority:

- PK sampling
- Safety [redacted]
- Safety (clinical labs)

Note: Safety assessments in response to adverse events (AEs) are not impacted by this priority list.

3 INTRODUCTION

CA224127 is a Phase 3, randomized, open-label study in participants with previously untreated metastatic or unresectable melanoma that primarily will evaluate the non-inferiority of PK for nivolumab + relatlimab fixed-dose combination (FDC) co-formulated with recombinant human hyaluronidase PH20 (rHuPH20) administered subcutaneously (SC) versus nivolumab + relatlimab FDC administered intravenously (IV). In addition, the non-inferiority of objective response rate (ORR) will be evaluated for the SC versus IV formulation of the nivolumab + relatlimab FDC.

Throughout the protocol, the coformulation of nivolumab 960 mg + relatlimab 320 mg FDC (BMS-986213) and rHuPH20 24,000 units will be referred to as nivolumab + relatlimab FDC SC, and the IV formulation of nivolumab 480 mg + relatlimab 160 mg FDC (BMS-986213) will be referred to as nivolumab + relatlimab FDC IV.

[redacted]

3.1 Study Rationale

Relatlimab (BMS-986016) is a blocking antibody specific to the lymphocyte activation gene-3 (LAG-3) receptor. [redacted] The efficacy, safety, and PK of nivolumab and relatlimab have been well established in advanced (unresectable or metastatic) melanoma, as demonstrated in the CA224020 and CA224047 studies. Specifically, nivolumab and relatlimab have been shown to have encouraging clinical activity as combination therapy, with few overlapping toxicities.[11] [redacted]

Furthermore, CA224047, a global, double-blind, randomized, Phase 2/3 study (N = 714) comparing the FDC of nivolumab 480 mg + relatlimab 160 mg IV every 4 weeks (Q4W) to nivolumab 480 mg IV Q4W in participants with unresectable or metastatic melanoma achieved its primary endpoint, demonstrating a statistically significant and clinically meaningful improvement in progression-free survival (PFS) by blinded independent central review (BICR).[14] The Food and Drug Administration subsequently approved nivolumab + relatlimab-rmbw FDC (OPDUALAG™) for IV administration in adult and pediatric patients 12 years of age or older with unresectable or metastatic melanoma.[15]

[redacted]

3.1.1 Research Hypothesis

Treatment with nivolumab 960 mg + relatlimab 320 mg FDC SC formulation will show non-inferior PK compared to nivolumab 480 mg + relatlimab 160 mg FDC IV formulation.

3.2 Background

Melanoma, the most serious form of skin cancer, is the 5th most common cause of cancer in the United States (US)[16] and accounts for approximately 1% to 2% of all cancer deaths and approximately 5% of all new cases of cancer in the US with a historical 5-year survival rate of

18% for late-stage disease.[17] While rare in the pediatric population, melanoma is the second leading cause of cancer in adolescents and young adults over the age of 15, with an incidence of over 10 per million in 15- to 19-year-olds.[18] In the era of immuno-oncology (IO) therapy, the expected 5-year survival rate for metastatic melanoma has a lower bound of approximately 35% and could be as high as 50% for the nivolumab + ipilimumab combination among patients who would meet criteria for clinical trials.[19]

Prior to 2011, approved therapies for the treatment of metastatic melanoma were limited and included chemotherapy (dacarbazine) and immunotherapy (interleukin 2 [IL-2]). Since then, 3 new therapeutic classes have been added to the treatment armamentarium and include 7 new drugs administered as monotherapy or in combination. These drugs include 1) ipilimumab, an anti-cytotoxic T-lymphocyte-associated protein 4 (anti-CTLA-4)-blocking antibody, 2) drugs targeting the tyrosine kinase pathways including BRAF and MEK, which include vemurafenib, dabrafenib, trametinib, and cobimetinib, and 3) mAbs that bind to the PD-1 receptor, which include nivolumab and pembrolizumab. Though many of these therapies have demonstrated an overall survival (OS) benefit in Phase 3 studies, there are still areas of high unmet medical need for this population. Many patients relapse within months of initiating treatment[20,21,22] or are not eligible for treatment due to tumor mutation status requirements (eg, BRAF V600 mutation is present in approximately 50% of melanoma tumors).[23,24] [redacted]

3.2.1 Relatlimab Mechanism of Action

Relatlimab is a fully human antibody specific for human LAG-3 that was isolated from immunized transgenic mice expressing human immunoglobulin (Ig) genes.[11] It is expressed as an IgG4 isotype antibody that includes a stabilizing hinge mutation (S228P) for attenuated Fc receptor binding in order to reduce or eliminate the possibility of antibody- or complement-mediated target cell killing. Relatlimab binds to a defined epitope on LAG-3 with high affinity (dissociation constant, 0.25-0.5 nM) and specificity and potently blocks the interaction of LAG-3 with its known ligands, major histocompatibility complex (MHC) Class II (half maximal inhibitory concentration [IC50], 0.7 nM) and fibrinogen-like protein 1 (FGL-1). [redacted]

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^{TM}) 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 Recombinant Human Hyaluronidase PH20 Enzyme

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 an anionic, nonsulfated glycosaminoglycan that consists of a polymer of N-acetyl-glucosamine and glucuronic acid subunits. It 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 IB).[25] [redacted]

3.2.4 Nivolumab Clinical Activity

Nivolumab has demonstrated durable responses exceeding 6 months as monotherapy in several tumor types, including non-small cell lung cancer (NSCLC), melanoma, renal cell carcinoma (RCC), classic Hodgkin lymphoma, small cell lung cancer (SCLC), gastric cancer, squamous cell cancer of the head and neck (SCCHN), urothelial cancer, hepatocellular carcinoma (HCC), and colorectal cancer (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 US Package Insert (USPI) and Summary of Product Characteristics (SmPC).

3.2.5 Relatlimab Combined with Nivolumab Pre-clinical Activity

LAG-3 has been shown to be expressed in tumor-infiltrating lymphocytes (TILs) of several tumor types, including melanoma; HCC; and breast, ovarian, and lung cancers, often in connection with increased PD-1+ T cells.[26] Preclinical data presented in recent years illustrate a clear synergy

between the inhibitory receptors LAG-3 and PD-1 in controlling immune homeostasis, preventing autoimmunity, and enforcing tumor-induced tolerance.[11,27] Importantly, combined treatment of mice with blocking antibodies against both receptors resulted in more robust immune responses than either single-treated group in these studies, and analyses of *Lag3−/−Pdcd1−/−* double knockout mice revealed a cooperative requirement for LAG-3 and PD-1 in maintaining immune homeostasis.

The single agent anti-tumor activity of anti-LAG-3 antibody (19C7) was evaluated in the immunogenic Sa1N fibrosarcoma tumor model.[28] Compared with the isotype control group, all doses between 1 mg/kg and 30 mg/kg of anti-LAG-3 clone 19C7 demonstrated anti-tumor efficacy leading to between 30% and 60% of the mice being rendered tumor-free at the end of study.

Combined anti-PD-1 and anti-LAG-3 activity was also assessed in the Sa1N model. In 2 different studies, an anti-LAG-3 antibody, C9B7W, inhibited the growth of Sa1N tumors in mice when administered as monotherapy and when combined with anti-PD-1 antibody, 4H2.[29,30] The combination of these 2 antibodies resulted in 80% to 90% tumor-free mice and reductions in median tumor volumes superior to that of anti-PD-1 or anti-LAG-3 antibody monotherapy alone.[11]

Similarly, greater anti-tumor effect was also demonstrated for combined anti-PD-1 and anti-LAG-3 in the MC38 colon adenocarcinoma models than with either agent alone.[11]

3.2.6 Relatlimab Combined with Nivolumab Clinical Activity

Clinical efficacy of relatlimab as monotherapy and in combination with nivolumab has been studied in CA224020 and CA224022 at different doses and schedules. As monotherapy, relatlimab demonstrated activity in hematologic malignancies in the Phase 1/2a Study CA224022. Objective responses were observed in participants with relapsed or refractory marginal zone lymphoma, Hodgkin lymphoma, and mantle cell lymphoma.[11]

The Phase 1/2a Study CA224020 is investigating the safety, tolerability, and effectiveness of relatlimab, with and without nivolumab, to treat various solid tumors. [redacted] As of the cutoff date of 25-Feb-2021 for Part C of Study CA224020, objective responses in the range of 5.3% to 47% were achieved with nivolumab + relatlimab combination therapy in participants with IO-refractory and first-line (1L) advanced melanoma, IO-naive bladder cancer, IO-refractory/relapsed and 1L NSCLC, IO-naive renal cell carcinoma (RCC), IO-naive gastric cancer (GC), IO-naive hepatocellular cancer (HCC), and IO-naive squamous cell carcinoma of the head and neck.[11]

Additionally, in Parts D1, D2, and E, objective responses were achieved in participants with IO-refractory melanoma treated with nivolumab + relatlimab. Part D1 included heavily pretreated participants with advanced melanoma (with a high proportion of participants treated with 2 or

more prior lines of therapy including anti-CTLA-4 and/or anti-PD-1) and with a number of additional poor prognostic factors such as primary resistance to prior anti-PD-1 Stage IV disease with liver metastasis and high lactate dehydrogenase (LDH) who experienced disease progression. Part D1 provided supportive evidence of the anti-tumor activity of nivolumab + relatlimab at doses equivalent to nivolumab 480 mg and relatlimab 160 mg every 4 weeks (Q4W), with long-term clinical benefit as demonstrated by blinded independent central review (BICR)-confirmed overall response rate of 11.8% (22/186 response evaluable) and a meaningful number of complete responses (8) and durability of these responses. In advanced melanoma participants with progression on prior IO therapies in Part E treated with nivolumab 480 mg + relatlimab 480 mg coadministered Q4W, the ORR by BICR was 11.7%. With a minimum follow-up of 11.3 months, the median duration of response (DOR) was not reached (95% confidence interval [CI]: 3.06, non-estimable). Refer to the [redacted] and relatlimab + nivolumab IB[31] [redacted] for further information.

CA224047, a global, double-blind, randomized, Phase 2/3 study comparing a fixed-dose combination (FDC) formulation of nivolumab 480 mg + relatlimab 160 mg FDC Q4W to nivolumab 480 mg Q4W in participants with previously untreated advanced melanoma demonstrated a statistically significant and clinically meaningful benefit by dual inhibition of the LAG-3 and PD-1 pathways. The study achieved its primary endpoint, demonstrating statistically significant improvement in progression-free survival (PFS) by BICR with nivolumab + relatlimab FDC [redacted] compared to nivolumab monotherapy in all randomized participants (N = 714) (PFS hazard ratio [HR] = 0.75 [95% CI: 0.62, 0.92], P-value = 0.0055). With a median follow-up of 13.2 months, the median PFS in the nivolumab + relatlimab FDC [redacted] group was 10.1 months (95% CI, 6.4–15.7) compared to 4.6 months (95% CI, 3.4-5.6) in the nivolumab monotherapy arm. PFS rates at 12 months were 47.7% (95% CI, 41.8–53.2) and 36.0% (95% CI, 30.5–41.6) for nivolumab + relatlimab FDC [redacted] and nivolumab monotherapy, respectively. The PFS benefit of nivolumab + relatlimab FDC [redacted] was consistent across key prespecified subgroups.[31,32] The secondary endpoint of overall survival (OS) showed clinically meaningful improvement with nivolumab + relatlimab FDC over nivolumab monotherapy (median OS non estimable (34.20, not reached [NR]) versus 34.1 months (25.23, NR); HR = 0.80 [0.64-1.01]); p = 0.0593) in all randomized participants but was not statistically significant.[31,32]

[redacted]

The Food and Drug Administration subsequently approved nivolumab + relatlimab-rmbw FDC (OPDUALAG™) for IV administration in adult and pediatric patients 12 years of age or older with unresectable or metastatic melanoma.[15]

3.2.7 Nivolumab SC Monotherapy Clinical Safety

Clinical experience with SC nivolumab (BMS-986298), which incorporates rHuPH20, in humans is currently being assessed with preliminary data available from the ongoing PK study CA2098KX in solid tumors and Study CA20967T in renal cell carcinoma.[34]

[redacted]

3.2.8 Relatlimab Monotherapy Clinical Safety

[redacted]

The Phase 1/2a Study CA224022 evaluated the safety and tolerability of relatlimab administered to participants with relapsed or refractory B-cell malignancies. Of the 38 participants treated with relatlimab monotherapy, drug-related adverse events (AEs) were reported in 18 (47.4%) participants. [redacted]

In the Phase 1/2a Study CA224020, of the 25 participants treated with relatlimab monotherapy (Part A), drug-related AEs were reported in 15 (60.0%) participants. [redacted] In both studies, most drug-related AEs were Grades 1 or 2. Drug-related serious adverse events (SAEs) occurred only at the monotherapy dose of 800-mg relatlimab Q2W in Study CA224020 and were reported as Grade 2 pneumonitis and Grade 3 drug hypersensitivity. All events resolved. There was no apparent relationship in the incidence, severity, or causality of AEs to relatlimab at the tested dose levels of relatlimab monotherapy. More information can be found in [redacted]

3.2.9 Nivolumab Combined with Relatlimab Clinical Safety

The Phase 1/2a Study CA224020 enrolled the highest number of participants treated with the combination therapy of nivolumab + relatlimab in dose-escalation (Part B) and expansion cohorts in Parts C, D, and E tested in every 2-week (Q2W) and every 4-week (Q4W) dosing intervals. Refer to IB Table 5.5.1-1 for details of the dose levels tested across a range of solid tumor cohorts in Part B and dose-limiting toxicities (DLTs) observed.[11] The safety profile was acceptable at all dose levels tested up to 1440-mg relatlimab in combination with nivolumab 480 mg given Q4W,

with the MTD not reached at this dose level. Part C included expansion cohorts with multiple tumor types and Parts D and E included advanced melanoma participants (1L and progressed on prior-PD-1 therapy). [redacted]

As of a database lock of [redacted] in Study CA224020, 1415 participants have been treated with nivolumab + relatlimab across Parts B, C, D, and E demonstrating that the combination was well tolerated across multiple tumor types.[11] Based on an analysis of AEs in the all-combination group, 1374 (97.1%) participants experienced at least 1 event and 1164 (82.3%) participants experienced at least 1 event occurring in ≥ 5% of participants (refer to [redacted] for details). Across Parts B, C, D, and E, drug-related AEs were reported in 960 (67.8%) participants, with the most commonly reported (≥ 5% of participants) being fatigue (16.7%), pruritus (12.2%), diarrhea (8.6%), rash (8.8%), hypothyroidism (7.9%), arthralgia (7.4%), asthenia (7.3%), increased lipase and nausea (6.9% each), and dry mouth (5.4%). Most drug-related AEs were Grades 1-2. Grade 3-4 drug-related AEs were reported in 230 (16.3%) participants and the most frequently reported included lipase increased (3.7%), and 2 (0.1%) participants reported Grade 5 events (dyspnea and pulmonary fibrosis). Refer to the IBs for [redacted] nivolumab + relatlimab FDC (Section 5.5.1)[31] for details of drug-related AEs analyzed separately for Part D1, which included 82 heavily-pretreated participants with advanced melanoma, who had poor prognostic factors and were treated with nivolumab 480 mg + relatlimab 160 mg FDC.

Drug-related SAEs were reported in 179 of the 1415 (12.7%) participants with Grade 3-4 drug related SAEs occurring in 130 (9.2%) participants and Grade 5 events occurring in 2 (0.1%) participants (dyspnea and pulmonary fibrosis). At least 1 drug-related AE leading to discontinuation has been reported in 119 of 1415 (8.4%) participants. More information can be found in [redacted]

The safety profile of the combination of nivolumab 480 mg + relatlimab 160 mg FDC Q4W was confirmed in the pivotal Phase 2/3 global, multicenter Study CA224047 (n = 355), in previously untreated advanced melanoma participants (clinical data cutoff 09-Mar-2021). The study findings demonstrated a well-tolerated regimen with a manageable safety profile and without unexpected safety signals. The incidence of Grade 3-4 drug-related AEs was 18.9% in the nivolumab + relatlimab FDC group versus 9.7% in the nivolumab monotherapy group. There were 3 treatment-related deaths with nivolumab + relatlimab FDC and 2 with nivolumab monotherapy. Drug-related AEs (any grade) led to treatment discontinuation in 14.6% and 6.7% of patients in the nivolumab + relatlimab FDC and nivolumab monotherapy groups, respectively.[32] Refer to relatlimab + nivolumab FDC IB Section 5.5.2 for an updated safety analysis.[31]

Initial safety data for relatlimab SC are available from the Phase 1 Study CA224087, a multi-tumor, bioavailability study of relatlimab in combination with nivolumab. At Cycle 1 Day 1 all participants received nivolumab 480 mg IV, followed by a single dose of relatlimab SC (either 480 mg or 720 mg) co-administered with rHuPH20. After SC administration of relatlimab at Cycle 1 Day 1, all participants received nivolumab 480 mg + relatlimab 480 mg IV Q4W during

subsequent cycles. Preliminary safety data from this study were consistent with safety data seen across studies for nivolumab + relatlimab FDC IV. Further details can be found in the [redacted]

3.2.10 Nonclinical Toxicity of Recombinant Human Hyaluronidase PH20

General toxicity studies were performed in cynomolgus monkeys, and a developmental and reproductive toxicity program was performed in mice (see rHuPH20 IB[25]). [redacted]

See the rHuPH20 IB for detailed descriptions of the nonclinical pharmacology, PK, and toxicity studies of rHuPH20 and results.[25]

3.3 Benefit/Risk Assessment

[redacted] Study CA224127 has been designed to demonstrate the non-inferiority of nivolumab + relatlimab FDC SC versus nivolumab + relatlimab FDC IV. [redacted]

CA224047, a pivotal Phase 2/3 study in participants with unresectable or metastatic melanoma, demonstrated that nivolumab 480 mg + relatlimab 160 mg FDC IV Q4W has clinical benefit, with a statistically significant and clinically relevant PFS benefit of nivolumab + relatlimab FDC IV Q4W compared to nivolumab 480 mg IV Q4W (refer to Section 3.2.6).[14,33] The combination was confirmed to be well tolerated with a manageable safety profile in the 355 participants treated and there were no unexpected safety signals from this combination (refer to Section 3.2.9).[33]

[redacted]

The risks anticipated for CA224127, and proposed mitigations are summarized in Table 3.3-1. Key to mitigating these risks, Investigators and the Sponsor will utilize continuous safety assessments to determine whether additional safety measures or termination from the study are required at any time. In addition, AEs and SAEs will be reviewed on an ongoing basis by the Sponsor's Medical Monitor and Worldwide Patient Safety (WS) representatives to monitor for any safety signals or trends.

It is noteworthy to mention the benefit/risk profile in minors. Among pediatric patients with Stage IV metastatic melanoma, the median survival time is less than 1 year and 5-year overall survival is less than 12%.[42] Despite these grim statistics, these patients are poorly studied and underrepresented in clinical trials. In general, immune checkpoint inhibitors have been well tolerated in pediatric cancer patients with adverse events similar to those seen in adults.[43] Although unknown late-onset immune-related AEs are a particular concern in pediatric participants, as they have much more time to develop than in adult/elderly participants, immune-related AEs are generally more manageable than those associated with chemotherapies and radiotherapies.[44] In addition to the robust safety monitoring that is performed for all participants [redacted]. The enrollment of adolescents in CA224127 provides an opportunity to study [redacted]. The availability of this formulation could offer [redacted]. The overall benefit/risk profile is therefore perceived to be favorable in this young population and justifies enrollment of adolescents on the CA224127 trial.

[redacted]

[redacted]

Table 3.3-1: Potential Risks and Mitigation Strategy Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk[11,31,45]	Mitigation Strategy
Study Intervention(s)		
IMAEs (eg, colitis diarrhea/colitis, pneumonitis, hepatitis, nephritis, endocrinopathy, rash, neurologic)	[redacted] Nivolumab IB Sections 7.1.1, 7.1.2, 7.1.3, 7.1.4, 7.1.5, 7.1.6, 7.1.7 BMS-986213 IB Sections 5.5, 5.5.1, 5.5.2	Recommended IMAE management algorithms are included in Appendix 6 or as per institutional protocol/investigator discretion.
Potential Infusion-related Reaction and Cytokine Release	[redacted] Nivolumab IB Section 7.1.8 BMS-986213 IB Sections 1.2, 2.1. 4.4.1, 4.4.1.6, 7.1.1.3	[redacted]
Potential Injection Site Reaction	BMS-986213 IB Section 4.4.1.5 (animal studies only)	
Cardiovascular AEs (ie, myocarditis, [redacted])	[redacted] BMS-986213 IB Sections 5.5.2, 5.5.4, 7.1.1, 7.2.2	Management of myocarditis per AE Management Algorithm in Appendix 6 or as per institutional protocol/investigator discretion.
Study Procedures		
Tumor Biopsy (eg, pain, infection)	BMS-986213 IB Section 7.1.3	Per institutional protocol/investigator discretion.
Phlebotomy (eg, pain, ecchymosis, bleeding, syncope)	BMS-986213 IB Section 7.1.3	Per institutional protocol/investigator discretion.
[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)	Please refer to Section 9.1.1.1 (Methods of Measurement).	Prophylaxis and/or treatment per institutional protocol/investigator discretion.
Other (if applicable)		
Non-Clinical Safety (animal studies)	BMS-986213 IB Sections 4.2, 4.3, 4.4	Not applicable.

Abbreviations: AE, adverse event; CT, computed tomography; IB, Investigator's Brochure; [redacted]
IMAE, immune-mediated adverse event; MRI, magnetic resonance imaging; [redacted].

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Co-primary	
• To demonstrate PK non-inferiority for nivolumab + relatlimab FDC SC formulation versus nivolumab + relatlimab FDC IV formulation	• Cavgd28 of nivolumab • Cminss of nivolumab • Cavgd28 of relatlimab • Cminss of relatlimab
Secondary	
• To demonstrate the non-inferiority of ORR by BICR for nivolumab + relatlimab FDC SC formulation versus nivolumab + relatlimab FDC IV formulation	• ORR by BICR per RECIST v1.1
• To evaluate PK of nivolumab + relatlimab FDC SC formulation versus nivolumab + relatlimab FDC IV formulation	• Cmind28, Cmax1, Cmaxss, and Cavgss of nivolumab and relatlimab
• To evaluate other measures of efficacy for nivolumab + relatlimab FDC SC formulation versus nivolumab + relatlimab FDC IV formulation	• DOR, DCR and TTR, by BICR per RECIST v1.1 • ORR, DOR, DCR, and TTR by Investigator per RECIST v1.1 • PFS by BICR and Investigator per RECIST v1.1 • OS
• To assess the safety of nivolumab + relatlimab FDC SC formulation	• AEs, SAEs, AEs leading to discontinuation, IMAEs, OESIs, deaths, and laboratory abnormalities
• To characterize changes in melanoma-related symptoms and quality of life for participants treated with nivolumab + relatlimab FDC SC formulation versus nivolumab + relatlimab FDC IV formulation	• Mean changes from baseline for FACT-M (MS)
[redacted]	

Table 4-1: Objectives and Endpoints

[redacted]

Abbreviations: AE, adverse event; BICR, blinded independent committee review; Cavgd28, time-averaged serum concentration over 28 days; Cavgss, time-averaged serum concentration at steady state; Cmax1, peak serum concentration after the first dose; Cmaxss, peak serum concentration at steady state; Cmind28, trough serum concentration at Day 28; Cminss, trough serum concentration at steady state; DCR, disease control rate; DOR, duration of response; [redacted] FDC, fixed-dose combination; IG, immunoglobulin; IMAE, immune-mediated adverse event; IV, intravenous; [redacted] OESI, other event of special interest; ORR, objective response rate; OS, overall survival; [redacted] PFS, progression-free survival; PK, pharmacokinetic; RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1; [redacted] SAE, serious adverse event; SC, subcutaneous; [redacted] TTR, time to response; [redacted]

The primary estimands are the differences in time-averaged serum concentration over 28 days (Cavgd28) and trough serum concentration at steady state (Cminss) for nivolumab and relatlimab between test (nivolumab + relatlimab FDC SC Q4W) versus reference (nivolumab + relatlimab FDC IV Q4W).

Further details and the estimands framework corresponding to the co-primary and key secondary objectives are specified in Table 4-2 below.

Table 4-2: Main Estimands for the Co-Primary and Key Secondary Endpoints

Endpoint (Variable)	Population	Treatments	Intercurrent Events (IEs)	Summary Statistics
Primary Objectives				
Cavgd28 and Cminss	PK-evaluable advanced melanoma participants	Test arm (nivolumab + relatlimab FDC SC Q4W) versus reference arm (nivolumab + relatlimab FDC IV Q4W).	Intercurrent events (eg, start of subsequent surgery or subsequent radiotherapy, partial infusion/injection of BMS-986213 compound, any concomitant medications, treatment discontinuation) will be handled [redacted]. Start of subsequent systemic therapy will be handled [redacted]. Additional details will be provided in the Statistical Analysis Plan.	[redacted]
Key Secondary Objectives				
Non-inferiority of ORR by BICR for nivolumab + relatlimab FDC SC formulation versus IV formulation	Advanced melanoma all randomized participants	Test arm (nivolumab + relatlimab FDC SC Q4W) versus reference arm (nivolumab + relatlimab FDC IV Q4W).	• Start of subsequent anti-cancer therapy: [redacted]. • Randomized but not treated: Treatment policy (ie, including tumor evaluation data after IE) • Discontinued treatment: Treatment policy (ie, including tumor evaluation data after IE)	Stratified Mantel Haenszel estimate of the relative risk The difference in response rate will be computed using the Cochran-Mantel-Haenszel method of weighting,[46] which adjusts for the stratification factors.
DOR, DCR, and TTR by BICR	Advanced melanoma all randomized participants	Test arm (nivolumab + relatlimab FDC SC Q4W) versus reference arm (nivolumab + relatlimab FDC IV Q4W).	DOR: only applicable to responders • Death: Composite strategy (ie, considering death as an event) • Start of subsequent anti-cancer therapy: [redacted]	DOR: Kaplan-Meier estimation of median for each treatment arm DCR: Difference of rates TTR: Same as DOR

Table 4-2: Main Estimands for the Co-Primary and Key Secondary Endpoints

Endpoint (Variable)	Population	Treatments	Intercurrent Events (IEs)	Summary Statistics
			• Randomized but not treated: Treatment policy (ie, including progression/death after IE) • Discontinued treatment: Treatment policy (ie, including progression/death after IE) DCR: Same as ORR TTR: Same as DOR	
OS	Advanced melanoma all randomized participants	Test arm (nivolumab + relatlimab FDC SC Q4W) versus reference arm (nivolumab + relatlimab FDC IV Q4W).	• Lost to follow-up: [redacted]. • Start of subsequent anti-cancer therapy: Treatment policy (ie, including death after IE) • Randomized but not treated: Treatment policy (ie, including death after IE) • Discontinued treatment: Treatment policy (ie, including death after IE)	HR from stratified Cox proportional hazard model with CI, OS rates.
PFS	Advanced melanoma all randomized participants	Test arm (nivolumab + relatlimab FDC SC Q4W) versus reference arm (nivolumab + relatlimab FDC IV Q4W).	• Death: Composite strategy (ie, including death as PFS event) • Start of subsequent anti-cancer therapy: [redacted] • Randomized but not treated: Treatment policy (ie, including progression/death after IE as a PFS event) • Discontinued treatment: Treatment policy (ie, including PFS event after IE)	HR from Stratified Cox proportional Hazard model with CI, PFS rates

Table 4-2: Main Estimands for the Co-Primary and Key Secondary Endpoints

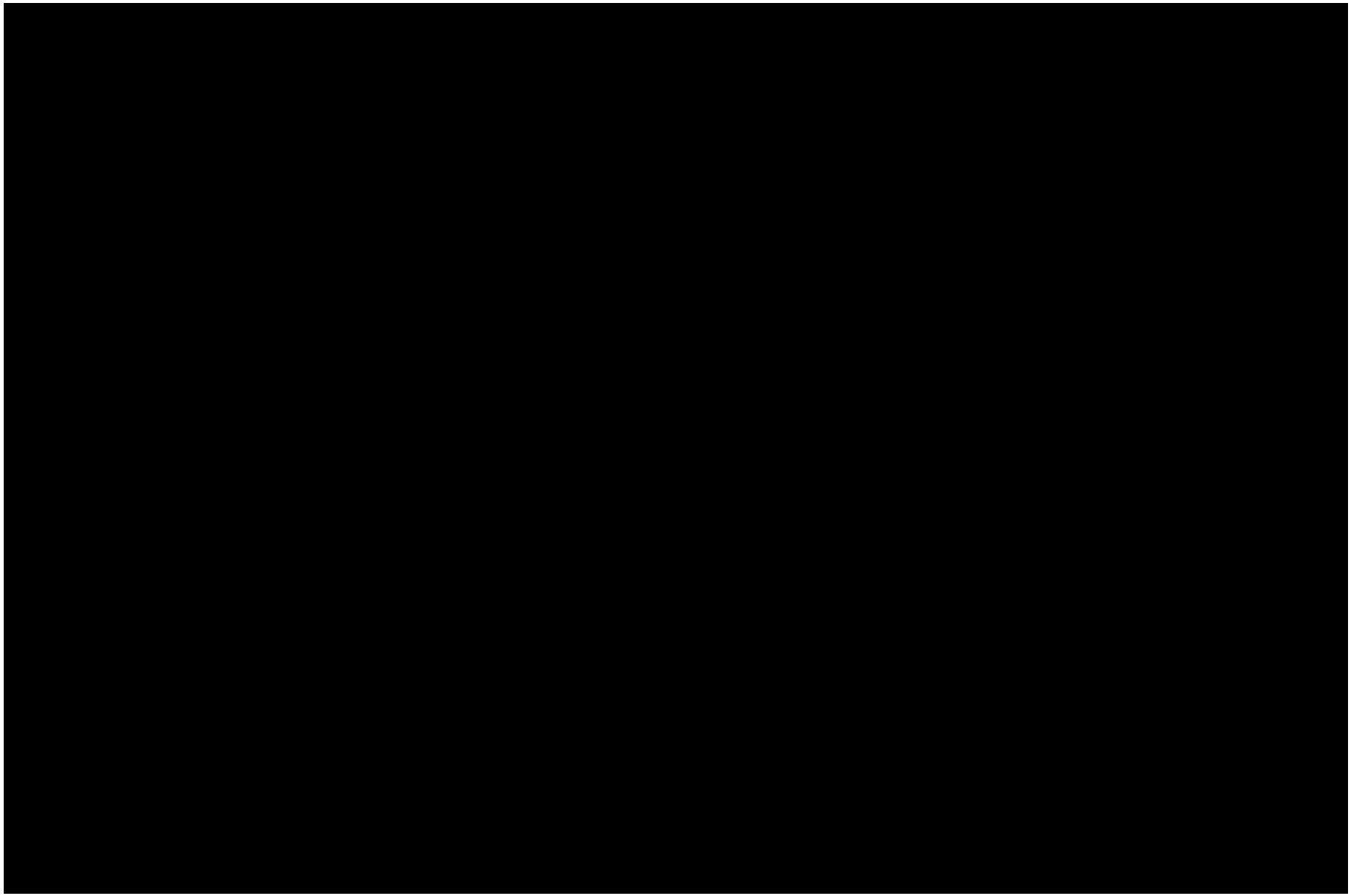
Endpoint (Variable)	Population	Treatments	Intercurrent Events (IEs)	Summary Statistics
Incidence of AEs and SAEs during the treatment/follow-up period (or incidence of AEs, SAEs, and marked abnormality/toxicities of Grade 3 or greater during the treatment period)	Advanced melanoma all treated participants	Test arm (nivolumab + relatlimab FDC SC Q4W) versus reference arm (nivolumab + relatlimab FDC IV Q4W).	• All IEs (ie, start of subsequent anti-cancer therapy) will be handled with treatment policy (ie, include AEs after IEs if AEs are within [redacted] days after last dose of study medication)	Descriptive proportion of participants with events within treatment arms.

Abbreviations: AE, adverse event; BICR, blinded independent committee review; Cavg28d, time-averaged serum concentration over 28 days; CI, confidence interval; Cminss, trough serum concentration at steady state; DCR, disease control rate; DOR, duration of response; FDC, fixed-dose combination; HR, hazard ratio; IE, intercurrent event; IV, intravenous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetic; [redacted]; Q4W, every 4 weeks; rHuPH20, recombinant human hyaluronidase PH20; SAE, serious adverse event; SC, subcutaneous; TTR, time to response.

5 STUDY DESIGN

5.1 Overall Design

CA224127 is a Phase 3, open label, randomized, PK non-inferiority study of nivolumab + relatlimab FDC SC formulation versus nivolumab + relatlimab FDC IV formulation in adult and adolescent participants with previously untreated metastatic or unresectable melanoma. Approximately [redacted] participants will be enrolled to randomize [redacted] participants. Participants will be randomized in a 1:1 ratio into 1 of 2 treatment groups [redacted]



5.1.1 Screening Period

Screening procedures will occur from the time the participant signs the informed consent form to randomization. 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 participant's 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 (Section 6.1 and Section 6.2, respectively) from the time the participant signs the informed consent form to randomization.

The screening window has been extended to accommodate potential unforeseen delays (eg, delayed results for [redacted]). All efforts should be made to randomize participants [redacted].

[redacted]

Participants will be enrolled using Interactive Response Technology (IRT). Register each participant in the IRT system to obtain a participant number. Rescreening after screen failure is allowed and requires reconsenting and a new participant number assignment. Participants who complete the Screening Period and meet the criteria for inclusion/exclusion will begin with the Treatment Period.

A formalin-fixed paraffin-embedded (FFPE) tissue block (strongly preferred) [redacted] of tumor tissue obtained from surgical specimen or biopsy (core biopsy, punch biopsy, or excisional biopsy) during screening or collected [redacted] with an associated pathology report, must be submitted to the central laboratory prior to randomization. Fine needle aspirations or other cytology samples are not acceptable. Biopsies of bone lesions that do not have a soft tissue component are not acceptable. Tissue availability needs to be determined during the screening period (refer to Section 6.1 [Inclusion Criteria], [redacted] and the Laboratory Manual for specifications and additional information).

[redacted]

[redacted]

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.

Treatment with nivolumab + relatlimab FDC SC or nivolumab + relatlimab FDC IV will be administered Q4W until unacceptable toxicity, withdrawal of consent, lost to follow up, disease progression, death, or termination of the study by the Sponsor, whichever occurs first. [redacted]

Participants will be permitted to continue study treatment beyond RECIST v1.1-defined disease progression (see Appendix 5) [redacted].

[redacted]

The incidence of AEs/SAEs will be monitored to evaluate the safety and tolerability of the nivolumab + relatlimab FDC SC formulation as compared with IV formulation. [redacted]

[redacted]

All AEs/SAEs will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (NCI-CTCAE v5.0). Patient-reported outcomes (PROs) will no longer be collected post Protocol Amendment 04. Refer to Section 9.1.2 for further details.

[redacted]

5.1.3 Follow-up Period

Safety Follow-up will begin after the Treatment Period or when the participant has discontinued study treatment for any reason (see Section 8.1).

The Safety Follow-up Period consists of [redacted] 135 days [redacted] should be collected continuously using NCI-CTCAE v5.0 during the Safety Follow-up.

Beyond the 135 days from the last dose of study intervention, participants will be followed for all drug-related AEs/SAEs until resolution, [redacted].

[redacted]

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

BMS may request that survival data be collected on all randomized participants outside of the protocol-defined window (refer to the Schedule of Activities, Table 2-3). At the time of this request, each participant will be contacted to determine their survival status unless the participant has withdrawn consent for all contacts, is deceased, or is lost to follow-up.

5.1.4 Data Monitoring Committee and Other External Committees

An independent Data Monitoring Committee (DMC) will be utilized in the study to ensure oversight of safety and provide necessary recommendations for the continued protection of participants considering the assessed benefit/risk profile. An independent statistician external to BMS will review safety data in conjunction with a DMC. The DMC will have access to periodic interim reports of safety and/or efficacy. Results may be submitted to Health Authorities if required.

The DMC charter will describe the procedures related to the committee operations in greater detail.

5.1.5 Blinded Independent Central Review

BICR will be utilized in this study for determination of BICR-assessed secondary endpoints (non-inferiority for ORR; PFS). Images will be submitted to a central imaging vendor for all randomized participants and BICR will review all available tumor assessment scans. Details of BICR responsibilities and procedures will be specified in the BICR charter.

5.2 Number of Participants

Approximately [redacted] participants will be enrolled to randomize [redacted] participants [redacted].

Participants will be randomized in a 1:1 ratio into 1 of 2 parallel treatment arms:

- nivolumab 960 mg + relatlimab 320 mg FDC + rHuPH20 24,000 units SC
- nivolumab 480 mg + relatlimab 160 mg FDC IV

[redacted]

5.3 End of Study Definition

The start of the study is defined as the first participant's first visit.

The primary completion date is defined as the date on which the last data point is collected for the study's primary endpoint. If the study has multiple primary endpoints, the primary completion date is the date on which the last data point is collected for the last primary endpoint.

End of study is defined as the last participant's last visit.

A participant is considered to have completed the study if he/she has completed the last visit or the last procedure shown in the Schedule of Activities, whichever occurs later.

[redacted]

5.4 Scientific Rationale for Study Design

The pivotal Phase 2/3 CA224047 study demonstrated that nivolumab 480 mg + relatlimab 160 mg IV FDC Q4W has established clinical benefit in participants with previously untreated metastatic or unresectable melanoma. [redacted]

[redacted]

[redacted]

5.4.9 Rationale for Enrolling Adolescent Participants ≥ 12 and < 18 Years Old

Advanced melanoma is generally regarded as a similar disease in adolescents and adults and is treated similarly. Metastatic melanoma does not commonly occur in the pediatric population from age 0 to less than 12 years.[48] The incidence reported in the US population for the age groups of 1 to 5 years, 5 to 9 years, and 10 to 14 years is 0.10, 0.16, and 0.37 per 100,000, respectively. The incidence in the US is higher in adolescents: 1.72/100,000 (15 to 19 years) (The Surveillance, Epidemiology, and End Results ([SEER] Carcinoma Statistics Review).[49] In the European Cooperative Study Group for Pediatric Rare Tumors (EXPeRT) study of melanoma incidence in Italy, Poland, Germany, and France, incidence of cutaneous melanoma was reported as 0.7 to 0.8 per million per year for ages 0 to 10 years and 10 per million per year for ages 15 to 19 years.[50] Overall, the pediatric incidence rates (5.4 per 1 million children and adolescents in the US)[51] are dramatically lower than the adult incidence and add to the difficulty of evaluating adolescent melanoma in clinical trials.

The key primary tumor characteristics, such as the site of the primary tumor, stage at diagnosis, tumor thickness, and level of invasion, are comparable between adolescent and adult melanoma patients. In an analysis of 1255 children (age younger than 20 years), the 10- to 19-year-old age group had similar baseline characteristics compared with the 20- to 24-year-old age group.[52] There are limited clinical studies evaluating treatment outcomes in pediatric and adolescent participants with melanoma. Despite the small number of participants, results of these studies showed that safety profiles and treatment effects (such as tumor shrinkage or pharmacodynamic effects of immunotherapy) in pediatric participants are comparable with adult participants.

Current treatment options for adolescent melanoma are the same as adults, as specific guidelines for treatment do not exist. In short, biology is similar and treatment options are also similar to adults. However, patients under 18 years of age have often been excluded from adult oncology trials because of safety or regulatory concerns; a practice that leads to delays in pediatric studies. Separate adult and pediatric cancer centers, distinct cooperative research groups, and oncologists specializing in different populations do not often conduct unified adult–pediatric clinical trials or drug development programs.[53]

Single-center and industry-sponsored trials often exclude advanced melanoma adolescent patients for historical or empiric reasons. A recent genomic analysis of pediatric melanoma demonstrates

that conventional melanoma in children and adolescents shares many of the genomic features that have been described in adult melanoma, including BRAF mutations. The abstract of this genomic analysis advocated for the opportunity for pediatric patients to be enrolled in pharmaceutically sponsored trials that incorporate novel agents. Many pediatric subjects who are diagnosed with melanoma get referred to and treated by medical oncologists versus pediatric oncologists, due to divergent expertise in the field.[54]

CA224127 presents an opportunity to evaluate the benefit/non-inferiority of the nivolumab and relatlimab fixed dose SC combination in an adolescent population diagnosed with previously untreated unresected/metastatic melanoma. Based on the positive benefit/risk profile of the IV nivolumab and relatlimab combination in this disease setting observed in CA224047, adolescents can be anticipated to experience this benefit in CA224127, albeit, participation on the trial will be important to study this benefit. Individual countries and sites have the option of opting out of adolescent eligibility.

5.5 Justification for Dose

5.5.1 Justification of Nivolumab + Relatlimab FDC IV Dose

The proposed dose of the FDC product is nivolumab 480 mg + relatlimab 160 mg Q4W. The dose and dosing regimen for this study were primarily based on the observed benefit/risk profile observed in metastatic melanoma participants from Study CA224047 and CA224020 PK, PD, and extensive nivolumab monotherapy clinical experience.[11,12]

Clinical efficacy and safety data from the pivotal Study CA224047 confirmed the positive benefit/risk profile of the proposed dose in adult melanoma participants. The benefit/risk of nivolumab 480 mg + relatlimab 160 mg [redacted] regimen is supported by exposure-response (E-R) efficacy and E-R safety analyses performed using data from 1L and prior-IO melanoma participants.[55]

In the Phase 1 CA224020 study, combination dose escalation up to nivolumab 480 mg + relatlimab 1440 mg [redacted] was achieved without reaching a MTD. Additionally, there are extensive PK, safety, and efficacy data available from CA224020 in previously untreated, unresectable, or metastatic melanoma participants and in participants with unresectable or metastatic melanoma who had prior treatment. The safety and efficacy of nivolumab + relatlimab FDC has been established for nivolumab 480 mg + relatlimab 160 mg FDC IV [redacted] based on registrational Study CA224047 in previously untreated metastatic or unresectable melanoma. [redacted]

5.5.1.1 Justification for 30-minute Duration of Infusion of the Nivolumab + Relatlimab FDC IV

[redacted]

[redacted]

Study CA224020 provides a robust safety experience with nivolumab + relatlimab over the broad dose range of 160 mg and 480 mg to [redacted] mg and [redacted] mg [redacted] levels, respectively. Nivolumab + relatlimab was safely administered sequentially (nivolumab was given first, followed by relatlimab within 15 to 30 minutes of completing the infusion of nivolumab) up to doses of nivolumab [redacted] mg + relatlimab [redacted] mg [redacted], which provides a similar infusion rate of ~21 mg/min as the proposed infusion of nivolumab + relatlimab FDC [redacted] in this study.[11]

[redacted]

- All infusion related reactions reported with co-administration of nivolumab 480 mg + relatlimab 480 mg infused over 60 minutes were Grade 1-2 adverse events and were manageable.[11]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5.5.3 Dose Rationale for Adolescent Participants

The nivolumab + relatlimab FDC dose in adolescent participants for this indication is supported by evidence from an adequate and well-controlled study in adults and additional data analyses that suggest that nivolumab and relatlimab exposures in pediatric patients 12 years of age or older are expected to result in similar safety and efficacy to that of adults. The PK of mABs and the course of unresectable or metastatic melanoma are sufficiently similar in adults and pediatric patients 12 years of age or older to allow extrapolation of data from adults to pediatric patients 12 years of age or older. In addition, overall exposure in adolescent participants with the SC formulation is expected to be well within the established adult safe and tolerable exposure margin. Relatlimab flat doses of 20 to 800 mg Q2W as monotherapy and up to 1440 mg Q2W in combination with nivolumab 480 mg have been studied in adults. Nivolumab + relatlimab FDC was administered as flat dosing in adults, therefore, a minimum body weight threshold in adolescents (≥ 40 kg) is defined to receive the same adult flat dose to prevent exceeding target adult exposures. Participants ≥ 12 years old who weigh ≥ 40 kg will be administered a flat dose of 480 mg nivolumab in combination with relatlimab 160 mg Q4W IV infusion (adult dosing) or 960 mg nivolumab in combination with relatlimab 320 mg Q4W SC (adult dosing).

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5.8 Clinical Pharmacology Summary

5.8.1 Nivolumab Clinical Pharmacology Summary

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 participants 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 participants with metastatic tumors; the decrease in CLss is not considered clinically relevant. Nivolumab clearance does not decrease over time in participants with completely resected melanoma, as the geometric mean population clearance is 24% lower in this participant population compared with participants 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 ($t_{1/2}$) 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: [redacted].

Renal Impairment: The effect of renal impairment on the clearance of nivolumab was evaluated by a population PK analysis in participants with mild (estimated glomerular filtration rate [eGFR] 60 to 89 mL/min/1.73 m^2), moderate (eGFR 30 to 59 mL/min/1.73 m^2), or severe (eGFR 15 to 29 mL/min/1.73 m^2) renal impairment. No clinically important differences in the clearance of nivolumab were found between participants 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 participants with HCC and in participants 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 times ULN and any AST) and in HCC patients with moderate hepatic impairment (TB greater than 1.5 to 3 times ULN and any AST). No clinically important differences in the clearance of nivolumab were found between participants with mild/moderate hepatic impairment.

Full details on the clinical pharmacology aspects of nivolumab can be found in the Investigator Brochure and product label.[45]

Full details regarding approved nivolumab dosages in their associated indications may be found in the product label. Nivolumab 480 mg Q4W IV is approved in newly diagnosed advanced melanoma, and it will be used in this study as part of the therapy.

[redacted]

[redacted]

[redacted]

[redacted]

6 STUDY POPULATION

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

6.1 Inclusion Criteria

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

1) Signed Written Informed Consent

a) Participants, or their legally acceptable representative (LAR; see Appendix 2), must have signed and dated an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved written informed consent (assent) 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) Participants must have an Eastern Cooperative Oncology Group performance status of ≤ 1 (for adults ≥ 18 years of age)/Lansky Performance Score ≥ 80% for adolescents (≥ 12 to < 18 years of age). Lansky should be converted to ECOG for reporting on the eCRF. Please refer to Appendix 7 for performance status and conversion table.

b) Participants must have histologically confirmed Stage III (unresectable) or Stage IV (metastatic) melanoma, per the AJCC staging system (8th edition; Appendix 8).

c) Participants must be treatment-naïve (ie, no prior systemic anticancer therapy for unresectable or metastatic melanoma).

[redacted]

d) Participants must have measurable disease by computed tomography (CT) or magnetic resonance imaging (MRI) per RECIST v1.1 (Appendix 5).

e) [redacted]

f) Participants with known BRAF V600 mutation status, or who consent to BRAF V600 mutation testing per local institutional standards during the Screening Period with the sample collected within 3 months prior to randomization. All BRAF statuses (ie, BRAF wild-type or BRAF 600 mutation positive) are eligible.

g) A FFPE tissue block (strongly preferred) [redacted] of tumor tissue from core biopsy, punch biopsy, excisional biopsy, or surgical specimen obtained during screening or collected [redacted], with an associated pathology report, must be sent to the central laboratory prior to randomization. Fine needle aspirates or other cytology samples are not acceptable. Biopsies of bone lesions that do not have a soft tissue component are not acceptable. [redacted]

h) Participant Re-enrollment: This study permits the re-enrollment of a participant that has discontinued the study as a pre-treatment failure (ie, participant has not been randomized). If re-enrolled, the participant must re-consent.

3) Age of Participants

a) Participants must be ≥ 12 years of age. Participants who are ≥ 12 years of age and < 18 years of age (adolescents) must weigh ≥ 40 kg at the time of signing the informed consent (assent).

Except: Where local regulations and/or institutional policies do not allow for participants ≥ 12 and < 18 years of age (adolescent population) to participate. For those sites, the eligible participant population is ≥ 18 years of age.

4) Reproductive Status

[redacted]

a) Female Participants:

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

(1) Women who are not of childbearing potential (as defined in Appendix 4) are exempt from contraceptive requirements.

ii) WOCBP [redacted] must have a negative highly sensitive 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.

[redacted]

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

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

iv) 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 the duration of treatment with nivolumab and relatlimab plus 5 half-lives of study treatment for a total of [redacted] post-treatment completion and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction for the same time period.

[redacted]

6.2 Exclusion Criteria

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

1) Medical Conditions

a) Participants must not have active brain metastases or leptomeningeal metastases. [redacted]

Participants with brain disease treated with whole brain radiation are not eligible.

b) Participants must not have ocular melanoma.

c) Participants must not have an active, known, or suspected autoimmune disease. Participants may enroll with the following conditions:

   i) Type 1 diabetes mellitus.

   ii) Hypothyroidism only requiring hormone replacement therapy.

   iii) Skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment.

   iv) Conditions not expected to recur in the absence of an external trigger.

d) Participants must not have a history of myocarditis, regardless of etiology.

e) Participants must not have a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within [redacted] 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.

f) Participants must not have a concurrent malignancy (present during screening) requiring treatment or history of prior malignancy active within 2 years prior to randomization (ie, participants with a history of prior malignancy are eligible if treatment was completed at least 2 years before randomization and the participant has no evidence of disease). Participants with history of prior early stage basal/squamous cell skin cancer or non-invasive or in situ cancers that have undergone definitive treatment at any time are also eligible.

g) Participants must not have known human immunodeficiency virus (HIV) positive with an acquired immunodeficiency syndrome (AIDS) defining opportunistic infection within the last year, or a current CD4 count <350 cells/μL. Participants with HIV are eligible if:

   i) they have received antiretroviral therapy (ART) for at least [redacted] prior to randomization as clinically indicated.

   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.

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

h) Participants must not have any serious or uncontrolled medical disorder that, in the opinion of the investigator in consultation with the BMS Medical Monitor, may increase the risk associated with study participation or study treatment administration, impair the ability of the participant to receive protocol therapy, or interfere with the interpretation of study results.

i) Participants must not have previous SARS-CoV-2 infection either suspected or confirmed within [redacted] prior to screening. [redacted]

j) Participant has not recovered adequately from toxicity and/or complications from surgery prior to starting study treatment.

2) Reproductive Status (Refer to Section 6.1 Inclusion Criterion 4) a) for further information)

a) Female participants who are breastfeeding.

b) Female participants who are pregnant.

3) Prior/Concomitant Therapy

a) [redacted]

b) Participant must not have had prior treatment with relatlimab or any other LAG-3 targeted agents.

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

d) Treatment with complementary medications (eg, herbal supplements or traditional Chinese medicines) to treat the disease under study within 2 weeks prior to first study treatment. [redacted]

e) Prior radiation therapy within 2 weeks prior to first study treatment. Participants must have recovered (ie, Grade ≤1 or at baseline) from radiation-related toxicities prior to first study treatment.

f) Treatment with any live / attenuated vaccine [redacted]

g) Participants currently in other interventional trials, including those for coronavirus disease 2019 (COVID-19), may not participate in BMS clinical trials until the protocol-specific washout period is achieved. If a study participant has received an investigational COVID-19 vaccine or other investigational product designed to treat or prevent COVID-19 prior to screening, enrollment must be delayed until the biologic impact of the vaccine or investigational product is stabilized, as determined by discussion between the investigator and the Medical Monitor.

[redacted]

[redacted]

5) Allergies and Adverse Drug Reaction

a) Participants must not have a history of allergy or hypersensitivity to study intervention components.

6) Other Exclusion Criteria

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

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

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

[redacted]

6.4 Lifestyle Restrictions

Not applicable. No restrictions are required.

6.5 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but who are not subsequently randomized 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 adverse events (SAEs) that occurred following consent.

6.5.1 Retesting During Screening or Lead-in Period

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.

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

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

Laboratory parameters and/or assessments that are included in Table 2-1, Screening Procedural Outline, may be repeated in an effort to find all possible well-qualified participants. Consultation with the Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

[redacted]

[redacted]

7 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

Study intervention includes 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.

In this protocol, the IPs are the following:

- nivolumab 960 mg + relatlimab 320 mg FDC + 24,000 units rHuPH20 SC
- nivolumab 480 mg + relatlimab 160 mg FDC IV

[redacted]

There are no non-IPs used in this study.

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

7.1 Study Interventions Administered

Both drugs used in this open-label study qualify as IPs, and the description, storage information, dose, and timing are summarized in Table 7.1-1 below. Study treatment will be dispensed at the study visits as listed in Schedule of Activities (Section 2).

Table 7.1-1: Study Interventions

Arm Name	Nivolumab + Relatlimab FDC IV	Nivolumab + Relatlimab FDC SC
Intervention Name	BMS-986213 (relatlimab [redacted] mg/nivolumab [redacted] mg)	Nivolumab, relatlimab, rHuPH20 injection
Type	Drug	Drug
Dose Formulation	Solution for infusion	Solution for injection
Unit Dose Strength(s)	4 mg/mL, 12 mg/mL	[redacted] mg, [redacted] mg, [redacted] Units/mL
Dosage Level(s)	Relatlimab 160 mg Nivolumab 480 mg Once every 4 weeks	Nivolumab 960 mg Relatlimab 320 mg rHuPH20 24,000 Units Once every 4 weeks
Route of Administration	IV infusion	SC injection
Use	Experimental	Experimental
IP/Non-IP/AxMP Blinded or Open-label Use	IP Open label	IP Open label
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labeling	Study intervention will be provided in a kit comprised of 2 vials. Each vial and kit will be labeled as required per country requirement.	Study intervention will be provided in a vial. Each vial will be labeled as required per country requirement.
Current/Former Name(s) or Alias(es)	BMS-986213	BMS-986213

Abbreviations: AxMP, Auxiliary Medicinal Product; FDC, fixed-dose combination; IP, Investigational Product; IV, intravenous; rHuPH20, recombinant human hyaluronidase; SC, subcutaneous.

[redacted]

7.1.1 Relatlimab Combined with Nivolumab Administration

Study treatment will be dispensed by interactive response technology (IRT) at the study visits as listed in Section 2 (Schedule of Activities). The selection and timing of dose for each participant is provided in Table 7.1-1. The selection, timing, and other parameters regarding dose administration for participants are further described as follows:

Participants will receive nivolumab + relatlimab FDC (SC or IV) on Day 1 of every 4-week cycle ± 3 days. [redacted]

[redacted]

[redacted]

Subcutaneous Administration

The dose of nivolumab + relatlimab FDC SC should be administered subcutaneously [redacted]

[redacted]

Instructions for storage, preparation, and administration of nivolumab + relatlimab FDC SC are provided in the Pharmacy Manual.

Intravenous Administration (comparator arm)

[redacted]

Nivolumab + relatlimab FDC IV is to be administered as an IV infusion [redacted]

[redacted]

[redacted]

For details on prepared drug storage, preparation, and administration, please refer to the IBs and/or Pharmacy Manual.

7.2 Assignment to Study Intervention

Before the study is initiated at an investigative site, each site user will receive login information and directions on how to access an IRT. Specific instructions for using IRT will be provided to the investigational site in a separate document.

During the screening visit, after the participant's informed consent has been obtained and initial eligibility is established, the participant must be enrolled into the study by using IRT to obtain a 5-digit participant number that will be unique across all sites. Every participant who signs the informed consent form must be assigned a participant number in IRT. 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:

- Year of birth
- Gender

All enrolled participants will be assigned sequential participant numbers starting with [redacted] (eg, [redacted]). The patient identification number (PID) will ultimately comprise the site number and participant number. For example, the first participant screened (ie, enrolled) at site number 1 will have a PID of [redacted].

Once it is determined that the participant meets the eligibility criteria following the screening visit, the investigative site will login to the IRT to randomize the participant into 1 of 2 parallel treatment arms in 1:1 ratio.

[redacted] The site will record the treatment assignment on the applicable Case Report Form (CRF). Refer to the IRT manual for further detail of the randomization procedures.

Study treatment will be dispensed prior to each treatment visit, per the Schedule of Activities (Section 2).

7.3 Blinding

This is a randomized open-label study. It has been determined that blinding is not feasible since the specific treatments in each arm have a different route of administration. Therefore, 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. The site will record the treatment assignment on the applicable CRF, if required.

7.4 Dosage Modification

No dose modifications for either treatment are permitted.

7.4.1 Dose Delay Criteria for Nivolumab and Relatlimab

Dose delay criteria apply for all drug-related AEs graded using NCI-CTCAE v5.0 (regardless of whether the event is attributed to nivolumab, relatlimab, or rHuPH20).

Delay administration of nivolumab + relatlimab FDC SC or nivolumab + relatlimab FDC IV if any of the delay criteria in Table 7.4.1-1 are met.

Delay nivolumab + relatlimab FDC SC or nivolumab + relatlimab FDC IV dosing for any AE, laboratory abnormality, or intercurrent illness that in the judgment of the Investigator, warrants delaying the dose of study medication.

Dose must be delayed for nivolumab + relatlimab FDC SC or nivolumab + relatlimab FDC IV for SARS-CoV-2 infection either confirmed or suspected.

[redacted]

Table 7.4.1-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Nivolumab + Relatlimab FDC

Drug-Related Adverse Event (AE) per CTCAE V5.0	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	
[redacted]	[redacted]	[redacted]	[redacted]
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.

Table 7.4.1-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Nivolumab + Relatlimab FDC

Drug-Related Adverse Event (AE) per CTCAE V5.0	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
	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, 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.
	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 intervention.
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 intervention.
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.

Table 7.4.1-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Nivolumab + Relatlimab FDC

Drug-Related Adverse Event (AE) per CTCAE V5.0	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
	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 intervention.
Hyperthyroidism or Hypothyroidism	Grade 2 or 3	Delay dose	Dosing may resume if endocrinopathy resolves to be asymptomatic, or is adequately controlled with only 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 intervention.
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	

Table 7.4.1-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Nivolumab + Relatlimab FDC

Drug-Related Adverse Event (AE) per CTCAE V5.0	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
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	
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	

Table 7.4.1-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Nivolumab + Relatlimab FDC

Drug-Related Adverse Event (AE) per CTCAE V5.0	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Cardiovascular			
[redacted]	[redacted]	[redacted]	[redacted]
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 intervention.
	Grade 3 or 4 uveitis	Permanently discontinue	
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	

Table 7.4.1-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Nivolumab + Relatlimab FDC

Drug-Related Adverse Event (AE) per CTCAE V5.0	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
	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 intervention: • 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
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	[redacted]

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE v5.0, Common Terminology Criteria for Adverse Events version 5.0; DRESS, drug reaction with eosinophilia and systemic symptoms; FDC, fixed-dose combination; GBS, Guillain-Barre syndrome; MG, myasthenia gravis; SJS, Stevens-Johnson syndrome; T. Bili, total bilirubin; TEN, toxic epidermal necrolysis; ULN, upper limit of normal.

[redacted]

[redacted]

[redacted]

[redacted]

7.5 Preparation/Handling/Storage/Accountability

The IP/Non-IMP/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/IMP/Non-IMP/AxMP is only dispensed to study participants. The IP/IMP/Non-IMP/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 the Sponsor. If concerns regarding the quality or appearance of the study intervention arise, the study intervention should not be dispensed, and the Sponsor should be contacted immediately.

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

IP/IMP/Non-IMP/AxMP documentation (whether supplied by the Sponsor 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.
- Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply, prepare, or administer study intervention.
- All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
- 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 the 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 Study Intervention Compliance

Study intervention compliance will be monitored by drug accountability as well as the participant's medical record and electronic Case Report Form (eCRF). Drug accountability should be reviewed by the study site staff at each visit to confirm treatment compliance. The source data will be verified by the BMS Unblinded Site Monitor through regularly scheduled monitoring visits.

7.7 Concomitant Therapy

Concomitant medications are recorded at baseline and throughout the treatment phase of the study in the appropriate section of the CRF. All medications (prescriptions and over-the-counter medications) continued at the start of the study or started during the study and different from the study treatment must be documented in the concomitant therapy section of the CRF.

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-986213 is unknown.

[redacted]

[redacted]

[redacted]

7.7.2 Other Restrictions and Precautions

Participants are prohibited from joining another interventional clinical trial that includes systemic treatment with another investigational agent (investigational medicinal product) 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 are appropriate. Specific to magnetic resonance imaging (MRI), participants with severe renal insufficiency [redacted] 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.

[redacted]

[redacted]

[redacted]

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

At the end of the study, the Sponsor will continue to provide Sponsor-supplied study intervention to participants [redacted] The Sponsor reserves the right to terminate access to Sponsor-supplied study intervention if any of the following occur: a) the study is terminated due to safety concerns; b) the development of nivolumab + relatlimab FDC subcutaneous formulation is terminated for other reasons, including, but not limited to, lack of efficacy and/or not meeting the study objectives; c) the participant can obtain medication from a government-sponsored or other health program. In all cases, BMS will follow local regulations.

8 DISCONTINUATION CRITERIA

If a participant receiving nivolumab + relatlimab FDC SC or IV meets criteria for discontinuation per Table 7.4.1-1, they must discontinue nivolumab + relatlimab FDC SC or IV and be taken off the treatment phase of the study.

Discontinuation of specific sites or of the study as a whole is detailed in Appendix 2.

8.1 Discontinuation of Study Intervention

Participants MUST discontinue IP/IMP (and Non-IMP/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 test result 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 the Sponsor
- 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.)

- In the case of pregnancy, the investigator must immediately, within 24 hours of awareness of the pregnancy, notify the Sponsor Medical Monitor or designee of this event. In most cases, the study treatment will be permanently discontinued in an appropriate manner. Refer to Section 9.2.5: Pregnancy.
- Disease progression in the absence of clinical benefit as determined by the investigator.
- Noncompliance of the participant with protocol-mandated procedures based on the judgment and agreement of both the investigator and Sponsor.

[redacted]

Refer to the Section 2: 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: Schedule of Activities. 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.

[redacted]

[redacted]

[redacted]

8.1.3 Post-study Intervention Study Follow-up

In this study, PFS and OS are 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 [redacted]) for collection of outcome [redacted] as required and in line with Section 5: Study Design until death or the conclusion of the study.

BMS may request that survival data be collected on randomized participants outside of the protocol defined window (Table 2-3). 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.

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 **3** documented phone calls, faxes, or emails, as well as lack of response by participant to **1** registered mail letter. All attempts should be documented in the participant's medical records.
- 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, such as public health registries and databases, 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.
- If it is determined that the participant has died, the site will use permissible local methods to obtain date and cause of death.

9 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the Schedule of Activities (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 (Section 2), 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 (Section 2).
- Safety/laboratory/analyte results that could unblind the study will not be reported to blinded sponsor personnel prior to primary database lock except as noted in Section 7.3.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed regional and/or institutional guidelines. Priority will be given to safety laboratory assessments and PK.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- 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 intervention-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.

9.1 Efficacy Assessments

9.1.1 Imaging Assessment for the Study

Images will be submitted to a central imaging vendor for BICR during the study as specified in the Study Imaging Manual. Prior to scanning the first participant, sites should be qualified 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.

Collect any additional imaging that may demonstrate tumor response or progression (including scans performed at unscheduled timepoints and/or at an outside institution) for RECIST v1.1 tumor assessment and submit to the imaging vendor. X-rays and bone scans that clearly demonstrate interval progression of disease, for example most commonly as unequivocal lesions that are unmistakably new since the prior CT/MRI, should be submitted to the central imaging vendor.

9.1.1.1 Methods of Measurement

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

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

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

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

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

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

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

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

9.1.1.2 Imaging and Clinical Assessment

Tumor assessments should continue per protocol-defined imaging schedule irrespective of whether the dosing is delayed or discontinued. Changes in tumor measurements and tumor responses will be assessed by the same investigator or designee using RECIST v1.1 criteria. Investigators will report the number and size of new lesions that appear while on study. The timepoint of tumor assessments will be reported on the eCRF based on the investigator's assessment using RECIST v1.1 criteria (see Appendix 5 for specifics of RECIST v1.1 criteria to be used in this study). Any unscheduled scans, including bone that shows disease progression, will be reported in eCRF on the tumor assessment folder. Assessments of PR and complete response (CR) must be confirmed at least 4 weeks (28 days) after initial response. Subsequent documentation of a CR may provide confirmation of a previously identified CR even with an intervening non-evaluable (NE) or PR (eg, CR NE CR or CR PR CR [confirmation of CR with intervening timepoint PR is only applicable when the response for the non-target lesion is "NE" due to one of the non-target lesions unevaluable/not done and target lesion is CR, making the overall response at that timepoint PR. In all other scenarios when the response is PR after CR makes the disease progressive]). Subsequent documentation of a PR may provide confirmation of a previously identified PR even with an intervening NE or stable disease (SD) (eg, PR NE PR or PR SD PR). However, only 1 intervening time point will be allowed between PRs/CRs for confirmation. A best overall response (BOR) of SD requires a minimum of 49 days for a participant to be on a study from the date of randomization to the date of the first imaging assessment.

9.1.2 Clinical Outcome Assessments for the Study

Clinical outcome assessment data will be collected using electronic data collection methods at designated times. When possible, participants should complete the PRO measures prior to any other assessments or study procedures when they are being administered during study visits. [redacted] **Post protocol amendment 04, clinical outcome assessment data will no longer be collected.**

9.1.2.1 FACT-M

The FACT-M questionnaire will be used to assess the effects of disease symptoms on functioning and well-being. As a generic cancer-related core, the FACT-M includes the 27-item FACT General (FACT-G) to assess physical well-being (PWB; 7 items), social/family well-being (SWB; 7 items), emotional well-being (EWB; 6 items), and functional well-being (FWB; 7 items). In addition, the FACT-M includes a 16-item disease-specific Melanoma Subscale (MS). Each FACT-M item is rated on a 5-point scale ranging from 0 (not at all) to 4 (very much). Scores for the PWB, FWB, SWB, and EWB subscales can be combined to produce a FACT-G total score, which provides an overall indicant of generic quality of life, while the FACT-G and MS scores can be combined to

produce a total score for the FACT-M, which provides a composite measure of general and targeted quality of life.

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, a surrogate, or the participant's legally acceptable representative).

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.

Refer to Appendix 3 for SAE reporting.

Use CTCAE v5.0 definitions and grading for safety reporting of all AE and SAEs on the case report form.

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

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs must be collected from the time of signing the consent, including those thought to be associated with protocol-specified procedures, until 135 days following discontinuation of dosing.

For participants randomized to treatment and never treated with study intervention, collect SAEs for [redacted] days from the date of randomization. All AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection must be collected from the date of the participant's written consent until 135 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).

- All SAEs will be recorded and reported to Sponsor or designee, promptly and not to exceed 24 hours of awareness of the event, 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.

9.2.2 Method of Detecting AEs and SAEs

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

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

9.2.3 Follow-up of AEs and SAEs

- 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 will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up (as defined in Section 8.3: Lost to Follow-up).

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

Additionally, all 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.

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 suspected, unexpected serious adverse reaction (SUSAR) 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

This section is applicable to WOCBP [redacted].

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

In all cases, the study intervention will be discontinued in an appropriate manner.

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.

After a pregnancy is confirmed, study treatment must be discontinued, and the participant followed. If, for whatever reason, the pregnancy has ended, as confirmed by negative serum pregnancy test, treatment may be resumed (at least 3 weeks and not greater than 6 weeks after the pregnancy has ended), following approvals of participant, sponsor, and IRB/EC, as applicable.

9.2.6 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the Adverse Events – Non serious and Serious Events CRF page. 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 requires the participant to have study intervention discontinued or interrupted
- Any laboratory test result abnormality that requires the participant to receive specific corrective therapy

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

9.2.7 Potential Drug-induced Liver Injury

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential drug-induced liver injury (DILI) event. All occurrences of potential DILIs meeting the defined criteria must be reported as SAEs (see Section 9.2: Adverse Events and Appendix 3: ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING for reporting details).

A potential DILI is defined as follows:

- Aminotransferase (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]) elevation > 3× upper limit of normal (ULN)

  AND

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

  AND

- No other immediately apparent possible causes of aminotransferase 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, [redacted] radiological imaging, 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).

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

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

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

9.4 Safety

Planned time points for all safety assessments are listed in Section 2: Schedule of Activities.

9.4.1 Physical Examinations

Refer to Schedule of Activities (Section 2).

[redacted]

[redacted]

9.4.2 Vital Signs

Refer to Schedule of Activities (Section 2).

[redacted]

9.4.4 Clinical Safety Laboratory Assessments

Laboratory assessments are listed in Table 9.4.4-1.

- Investigators must document their review of each laboratory safety report.
- All clinical safety laboratory assessments will be performed locally per the Schedule of Activities.

Table 9.4.4-1: Clinical Laboratory Assessments

Hematology	
Hemoglobin	
Hematocrit	
Total leukocyte count, including differential	
Platelet count	
Chemistry	
Aspartate aminotransferase Alanine aminotransferase Total bilirubin Alkaline phosphatase Gamma-glutamyl transferase only when alkaline phosphatase is ≥ Grade 2 Creatinine Blood urea nitrogen or serum urea Glucose Lactate dehydrogenase Uric acid	Albumin Sodium Potassium Chloride Calcium Phosphorus Thyroid-stimulating hormone (TSH), free T3 and free T4 - screening TSH, with reflexive fT3 and fT4 if TSH is abnormal - on treatment Creatine phosphokinase Creatinine clearance (CrCl) - if used, at screening only
[redacted]	

Table 9.4.4-1: Clinical Laboratory Assessments

Urinalysis
Protein
Glucose
Blood
Leukocyte esterase
Specific gravity
pH
[redacted]
[redacted]
Other Analyses
Pregnancy test (WOCBP[redacted]: minimum sensitivity 25 IU/L or equivalent units of hCG; at screening, within 24 hours prior to first dose and then every [redacted] [± 1 week] irrespective of dosing schedule).
Follicle stimulating hormone - screening only for women only, only required to confirm menopause in women < age 55

NOTE: Collection of total T3 may be allowed if collection of free T3 is not feasible.

Abbreviations: [redacted] fT3, free triiodothyronine; fT4, free thyroxine; [redacted] hCG, human chorionic gonadotropin; [redacted] HIV, human immunodeficiency virus; [redacted] T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone; WOCBP, women of childbearing potential.

9.4.5 Imaging/Other Safety Assessments

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.

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

[redacted]

9.7 [redacted]

[redacted]

9.7.3 [redacted]

[redacted]

[redacted]

9.7.3.5 Tumor Samples

Tumor biopsy specimens will be obtained from consenting participants prior to treatment [redacted]. Pre-treatment tumor samples are required for all participants. An FFPE tissue block (strongly preferred) [redacted] of tumor tissue from core biopsy, punch biopsy, excisional biopsy, or surgical specimen obtained during screening or collected [redacted] with an associated pathology report, must be sent to the central laboratory prior to randomization. Fine needle aspirations or other cytology samples are not acceptable. Biopsies of bone lesions that do not have a soft tissue component are not acceptable. [redacted]

9.7.3.6 Tumor Sample Collection

The Investigator, in consultation with the radiology staff, must determine the degree of risk associated with the procedure and find it acceptable. Biopsies may be done with local anesthesia or conscious sedation. Institutional guidelines for the safe performance of biopsies should be followed. Excisional biopsies may be performed to obtain tumor biopsy samples. Invasive procedures that require general anesthesia should not be performed to obtain a biopsy specimen; however, if a surgical procedure is performed for a clinical indication, excess tumor tissue may be used for research purposes with the consent of the participant. Detailed instructions of the obtaining, processing, labeling, handling, storing, and shipping of specimens will be provided in a separate Laboratory Manual.

[redacted]

[redacted]

9.8 Optional Future Research

This protocol will include residual sample storage for optional future research.

Samples kept for future research will be stored at the Sponsor-designated storage facility.

[redacted]

Samples will be stored in a coded fashion, and no researcher will have access to the key. The key will be 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 laboratory procedure manual.

9.9 Other Assessments

Not applicable.

9.10 Health Economics OR Medical Resource Utilization and Health Economics

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

10 STATISTICAL CONSIDERATIONS

10.1 Statistical Hypotheses

The aim of the study is to demonstrate PK non-inferiority of nivolumab + relatlimab FDC SC compared with nivolumab + relatlimab FDC IV. [redacted]

[redacted]

10.2 Sample Size Determination

[redacted]

[redacted]

[redacted]

[redacted]

Approximately [redacted] participants will be enrolled in the study to ensure at least [redacted] participants are randomly assigned to each arm.

[redacted]

10.3 Analysis Sets

For the purposes of analysis, the following populations are defined in Table 10.3-1 below.

Table 10.3-1: Populations for Analysis

Population	Description
All Enrolled	All participants who signed an ICF and are registered into the IRT. This is the primary dataset for disposition.
All Randomized	All participants who are randomized to any treatment group in the study. This is the primary dataset for analyses of demography, protocol deviations, baseline characteristics, efficacy, and outcome research.
All Per Protocol	All participants who are compliant with study criteria such as absence of relevant protocol deviations. The per-protocol analysis set will be used for supplementary analyses of ORR in the context of the non-inferiority design.
All Treated	All participants who receive at least 1 dose of nivolumab + relatlimab FDC either SC or IV. This is the primary dataset for dosing and safety analyses.
PK-evaluable	All treated participants with at least 1 post-treatment concentration-time data point available for nivolumab and relatlimab.

[redacted]

Abbreviations: FDC, fixed-dose combination; ICF, informed consent form; IRT, Interactive Response Technology; IV, intravenous; ORR, objective response rate; PK, pharmacokinetic; SC, subcutaneous.

10.4 Statistical Analyses

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

[redacted]

10.4.1 General Considerations

The primary and secondary estimands are described in Table 4-2.

[redacted]

10.4.2 Primary Endpoint(s)

The PK co-primary endpoints (Cavgd28 and Cminss for nivolumab and relatlimab) and secondary endpoints (Cmax1, Cmaxss, and Cavgss for both drugs) after the first dose of study treatment and steady state will be derived from all PK-evaluable participants using PPK analysis. [redacted]

[redacted]

[redacted]

Table 10.4.2-1: Endpoints

Primary Endpoint	Description	Timeframe
Pharmacokinetics – Cavgd28 of nivolumab	Time-averaged serum concentration over 28 days	First 28 days of treatment
Pharmacokinetics – Cavgd28 of relatlimab	Time-averaged serum concentration over 28 days	First 28 days of treatment
Pharmacokinetics – Cminss of nivolumab	Trough serum concentration at steady state	17 weeks after the start of treatment
Pharmacokinetics – Cminss of relatlimab	Trough serum concentration at steady state	17 weeks after the start of treatment

10.4.3 Secondary Endpoint(s)

ORR non-inferiority will be tested using BICR evaluation as per RECIST v1.1, unless noted otherwise. Similar approach will be used for other efficacy endpoints such as disease control rate (DCR), time to response (TTR), DOR, and PFS. Analyses in this section will be tabulated for all randomized participants by treatment group as randomized, unless otherwise specified. Unless stated otherwise, whenever a stratified analysis is specified, the stratification factors (recorded at randomization as per IRT) described in Section 10.4.1 will be used.

[redacted]

The number and percentage of subjects in each category of BOR per BICR CR, PR, SD, progressive disease, or unable to determine) will be presented by treatment group. Estimates of response rate, along with its exact 2-sided 95% CI by Clopper and Pearson will be presented, by treatment group. A 2-sided 95% CI for difference of response rate between the treatment groups will also be computed.

[redacted]

10.4.5 Other Safety Analyses

Unless specified otherwise, safety analyses will be performed on all treated participants. The assessment of safety will be based on frequency of deaths, AEs, SAEs, AEs leading to discontinuation of study intervention, select AEs, IMAEs, and abnormalities in specific clinical laboratory assessments. AEs from first dose date (of any study medication) to [redacted] or 135 days after last dose date will be summarized by treatment group for each population. AEs will be coded using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA). AEs and laboratory values will be graded for severity according to the NCI-CTCAE v5.0.

[redacted]

[redacted]

11 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
%CV	coefficient of variation
1L	first line
[redacted]	
AE	adverse event
AIDS	acquired immunodeficiency syndrome
AJCC	American Joint Committee on Cancer
ALT	alanine aminotransferase
[redacted]	
ART	antiretroviral therapy
AST	aspartate aminotransferase
[redacted]	
AxMP	Auxiliary [Medicinal] Product
BICR	blinded independent central review
BMS	Bristol-Myers Squibb Company
BOR	best overall response
C	cycle
Cavg	average observed concentration
Cavgd28	time-averaged serum concentration over 28 days
Cavgss	average observed concentration at steady state
CD	cluster of differentiation
CHO	Chinese hamster ovary
CI	confidence interval
CL	clearance
CLss	steady-state clearance
Cmax	maximum observed concentration
Cmax1	peak serum concentration after the first dose
Cmaxss	maximum observed concentration at steady state
Cmin	minimum observed concentration
Cmind28	trough serum concentration at Day 28

Term	Definition
Cminss	trough serum concentration at steady state
cN	clinical nodes
[redacted]	
COA	clinical outcomes assessments
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
[redacted]	
CR	complete response
CRC	colorectal cancer
CrCl	creatinine clearance
CRF	case report form
CSR	clinical study report
CT	computed tomography
CTCAE v5.0	Common Terminology Criteria for Adverse Events version 5.0
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
[redacted]	
cTNM	clinical tumor, nodes, metastasis
[redacted]	
D	day
DCR	disease control rate
DIL	Dear Investigator Letter
DILI	drug-induced liver injury
DLTs	dose-limiting toxicities
DMC	Data Monitoring Committee
[redacted]	
DOR	duration of response
DRAE	drug-related adverse event
DRESS	drug reaction with eosinophilia and systemic symptoms
[redacted]	

Term	Definition
[redacted]	
eCOA	electronic clinical outcomes assessment
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
eGFR	estimated glomerular filtration rate
[redacted]	
E-R	exposure-response
EU	European Union
EWB	emotional well-being
FACT-G	Functional Assessment of Cancer Therapy - General
FACT-M	Functional Assessment of Cancer Therapy - Melanoma
FACT-MS	Functional Assessment of Cancer Therapy - Melanoma subscale
FDA	Food and Drug Administration
FDC	fixed-dose combination
FGL-1	fibrinogen-like protein 1 (FGL-1),
FFPE	formalin-fixed paraffin-embedded
[redacted]	
FSH	follicle-stimulating hormone
fT3	free triiodothyronine
fT4	free thyroxine
FWB	functional well-being
GBS	Guillain-Barre syndrome
[redacted]	
HCC	hepatocellular carcinoma
hCG	human gonadotropin
HCP	healthcare provider
[redacted]	

Term	Definition
[redacted]	
HIV	human immunodeficiency virus
HR	hazard ratio
[redacted]	
HuMAb	human monoclonal antibody
IB	Investigator's Brochure
IC50	half maximal inhibitory concentration
ICF	informed consent form
IE	intercurrent event
IEC	Independent Ethics Committee
[redacted]	
Ig	immunoglobulin
IgG4	immunoglobulin G4
[redacted]	
IL-2	interleukin 2
IMAE	immune-mediate adverse events
[redacted]	
IO	immuno-oncology
IP/IMP	investigational [Medicinal] Product
IRB	Institutional Review board
IRT	Interactive Response Technology
IV	intravenous
Kd	dissociation constant
LAG-3	lymphocyte activation gene 3
LAR	legally acceptable representative
[redacted]	
M	metastasis
[redacted]	
MCH	major histocompatibility complex
MedDRA	Medical Dictionary for Regulatory Activities
MG	myasthenia gravis

Term	Definition
[redacted]	
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
[redacted]	
NCI CTCAE v5.0	National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0
NE	non-evaluable
[redacted]	
NK	natural killer
NR	not reached
NSCLC	non-small cell lung cancer
OESI	other event of special interest
ORR	objective response rate
OS	overall survival
[redacted]	
PD-1	programmed death-1
PD-L1	programmed death-ligand 1
PD-L2	programmed death-ligand 2
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic
[redacted]	
PPK	population PK
PR	Partial Response
PRO	patient-reported outcome
pTNM	pathological tumor, nodes, metastasis
PWB	physical well-being
Q2W	every 2 weeks
Q4W	every 4 weeks
RCC	renal cell carcinoma
RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
rHuPH20	recombinant human hyaluronidase PH20
[redacted]	

Term	Definition
[redacted]	
RR	relative risk
[redacted]	
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
[redacted]	
SC	subcutaneous
SCCHN	squamous cell cancer of the head and neck
SCLC	small cell lung cancer
SD	stable disease
SJS	Stevens-Johnson syndrome
SmPC	Summary of Product Characteristics
SLN	sentinel lymph node
SNP	single nucleotide polymorphism
SUSAR	suspected, unexpected serious adverse reaction
SWB	social/family well-being
T. Bili/TB	total bilirubin
t1/2	half life
T3	triiodothyronine
T4	thyroxine
[redacted]	
TEN	toxic epidermal necrolysis
TIL	tumor-infiltrating lymphocyte
Tmax1	time to Cmax1
[redacted]	
TSH	thyroid-stimulating hormone
[redacted]	
TTR	time to response
ULN	upper limit of normal
US	United States

Term	Definition
USPI	United States Package Insert
WOCBP	women of childbearing potential
WWPS	Worldwide Patient Safety

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

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

REGULATORY AND ETHICAL CONSIDERATIONS

This study will be conducted in accordance with:

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

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

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

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

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

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

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

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

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

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

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

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

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

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

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

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

FINANCIAL DISCLOSURE

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

RECRUITMENT AND INFORMED CONSENT PROCEDURES

Potential participants may be identified by the recruiting investigational team (called “site”) within the affiliated clinic/hospital, and/or group practice, through their own chart/database review, using the inclusion/exclusion criteria defined by the protocol. Potential participants may also be referred

to the site by medical doctors from surrounding hospitals/practices or directly contact one of the investigative 'sites' following study and site identification through a public registry, such as clinicaltrials.gov or euclinicaltrials.eu. The investigator has access to the participant's medical file, so, the medical data will remain confidential without the Sponsor having access to them. Recruitment material will also be utilized as an additional tool to recruit participants per local regulations and requirements.

The principal investigator or sub-investigator, or a qualified designee of the investigator's research team will approach potential participants to discuss the option of participating in the clinical trial and the consent process. Informed consent will be obtained by the principal investigator or a qualified delegate on the principal investigator's research team from each participant prior to enrolment into the study. The participant will be provided the opportunity to read the information sheet and consent form and have all their questions and concerns addressed before giving consent in writing.

INFORMED CONSENT PROCESS

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

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

The investigator or his/her representative must:

- Obtain IRB/IEC written approval/favorable opinion of the written ICF and any other information to be provided to the participant prior to the beginning of the study and after any revisions are completed for new information.
- Provide a copy of the ICF and written information about the study in the language in which the participant is proficient prior to clinical study participation. The language must be nontechnical and easily understood.
- Explain the nature of the study to the participant or his/her legally acceptable representative and answer all questions regarding the study.
- Inform the participant that his/her participation is voluntary. The participant or his/her legally acceptable representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR Part 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 the participant or his/her legally acceptable representative to inquire about the details of the study.
- Obtain an ICF signed and personally dated by the participant or his/her legally acceptable representative and by the person who conducted the informed consent discussion.

- Include a statement in the participant's medical record that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Re-consent the participant to the most current version of the ICF(s) during his/her participation.
- Revise the ICF whenever important new information becomes available that is relevant to the participant's consent. The investigator, or a person designated by the investigator, should fully inform the participant or his/her legally acceptable representative of all pertinent aspects of the study and of any new information relevant to the participant's willingness to continue participation in the study. This communication should be documented.

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

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

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

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

For minors, according to local legislation, one or both parents or a legally acceptable representative must be informed of the study procedures and must sign the ICF approved for the study prior to clinical study participation.

Minors who are judged to be of an age of reason must also give their written consent.

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

CLINICAL TRIALS ON MINORS

1. A clinical trial on minors may be conducted only where all of the following conditions are met:
    a. The informed consent of their legally designated representative has been obtained.
    b. The minors have received the information in a way adapted to their age and mental maturity and from investigators or members of the investigating team who are trained or experienced in working with children.
    c. The explicit wish of a minor who is capable of forming an opinion and assessing the information to refuse participation in, or to withdraw from, the clinical trial at any time, is respected by the investigator.
    d. No incentives or financial inducements are given to the participant or his or her legally designated representative except for compensation for expenses and loss of earnings directly related to the participation in the clinical trial.

e. The clinical trial is intended to investigate treatments for a medical condition that only occurs in minors, or the clinical trial is essential with respect to minors to validate data obtained in clinical trials on persons able to give informed consent or by other research methods.

f. The clinical trial either relates directly to a medical condition from which the minor concerned suffers or is of such a nature that it can only be carried out in minors.

g. There are scientific grounds for expecting that participation in the clinical trial will produce:

i. A direct benefit for the minor concerned outweighing the risks and burdens involved; or

ii. Some benefit for the population represented by the minor concerned and such a clinical trial will pose only minimal risk to, and will impose minimal burden on, the minor concerned in comparison with the standard treatment of the minor's condition.

2. The minor shall take part in the informed consent procedure in a way adapted to his or her age and mental maturity.
3. If during a clinical trial the minor reaches the age of legal competence to give informed consent, his or her express informed consent shall be obtained before that participant can continue to participate in the clinical trial.

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:

5) Responsibilities of IT Personnel
6) Securing the BMS Digital Infrastructure
7) Identity and Access Management
8) External Partner Connections
9) Cyber Threat Detection and Response
10) Internal Cyber Incident Investigation

SOURCE DOCUMENTS

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

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

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

The investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original, and attributable, whether the data are handwritten on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic

devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical records/electronic health records, adverse event (AE) tracking/reporting, protocol-required assessments, and/or drug accountability records.

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

STUDY INTERVENTION RECORDS

Records for study intervention (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 the following: • 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 • non-study 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, per the Delegation of Authority Form
Sourced by site and not supplied by BMS or its vendors (examples include Investigational Product sourced from the site's stock	The investigator or designee accepts responsibility for documenting traceability and study intervention integrity in accordance with requirements applicable under law and the standard operating procedures/standards of the sourcing pharmacy

If	Then
or commercial supply or a specialty pharmacy)	

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

CASE REPORT FORMS

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

For sites using the Sponsor or designee electronic data capture (EDC) tool, eCRFs will be prepared for all data collection fields except for fields specific to serious adverse events (SAEs) and pregnancy, which will be reported on the electronic SAE form and Pregnancy Surveillance Form, respectively. If the electronic SAE form is not available, a paper SAE form can be used.

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

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

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

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

MONITORING

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

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site, they will review study records and directly compare them

with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable.

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

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

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

RECORDS RETENTION

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

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

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

Records collected throughout the trial will be stored in the BMS clinical data management system for a duration of the life of product plus 25 years.

RETURN OF STUDY INTERVENTION

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

If	Then
Study interventions supplied by BMS (including its vendors)	Any unused study interventions supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor, unless study intervention containers must be immediately destroyed as required for safety or to meet local regulations (eg, cytotoxic or biologic agents). Partially used study interventions and/or empty containers may be destroyed after proper reconciliation and documentation. However, unused Investigational Medicinal

If	Then
	product must be reconciled by the site monitor/clinical research associate prior to destruction. If study interventions will be returned, the return will be arranged by the responsible study monitor.
Study interventions sourced by site, not supplied by BMS (or its vendors; eg, study interventions sourced from the site's stock or commercial supply or a specialty pharmacy)	It is the investigator's or designee's responsibility to dispose of all containers according to the institutional guidelines and procedures.

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

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

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

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

STUDY AND SITE CLOSURE

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

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

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

For study termination:

- Discontinuation of further study intervention development

For site termination:

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

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

DISSEMINATION OF CLINICAL STUDY DATA

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

In the European Union (EU), the summary of results and summary for laypersons will be submitted within 6 months 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 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 period set forth in the CTAg.

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

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

1) Substantial intellectual contribution to the conception or design of the work; or the acquisition of data (ie, evaluable participants with quality data), analysis, or interpretation of data for the work (eg, problem solving, advice, evaluation, insights, and conclusion)
2) Drafting the work or revising it critically for important intellectual content
3) Final approval of the version to be published
4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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

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

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

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

ADVERSE EVENTS

Adverse Event Definition:
An adverse event (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition occurring in a clinical investigation participant after signing of informed consent, whether or not considered related to the study intervention.
An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory test result), symptom, or disease temporally associated with the study intervention.
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 sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Note that abnormal laboratory test results or other safety assessment findings 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 the condition 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 the 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 that hypothetically might have caused death if it were more severe).
Requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below). NOTE: The following hospitalizations are not considered SAEs in BMS clinical studies: • A visit to the emergency department or other hospital department < 24 hours that does not result in admission (unless considered an important medical or life-threatening event). • Elective surgery that was planned prior to signing consent. • Admissions 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 enrollment in 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 results 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 department or at home for allergic bronchospasm and blood dyscrasias or convulsions that do not result in hospitalization. Potential drug-induced liver injury (DILI) is also considered an important medical event. (See Section 9.2.7: Potential Drug-induced Liver Injury of the protocol for the definition of a potential DILI.)

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

EVALUATING AES AND SAES

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the Investigator's Brochure and/or product information for marketed products, in his/her assessment.
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

- **Assessment of Intensity**

Use National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI CTCAE v5.0) definitions and grading for safety reporting of all AE and SAEs.

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 intervention or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or the designee) using the same procedure used for transmitting the initial SAE report.

All AEs/SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

- SAEs, whether related or not related to study intervention, and pregnancies must be reported to BMS (or the designee) promptly and not to exceed 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 the designee).
    - In this case, the paper form is transmitted via email or confirmed fax 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 fax transmission.

SAE Email Address: worldwide.safety@BMS.com

SAE Fax 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 Women of Childbearing Potential (WOCBP) 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: Inclusion Criteria of the protocol. Only the contraception methods as described in Section 6.1: Inclusion Criteria of the protocol are acceptable for this study.

DEFINITIONS

Women 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:

[redacted]

- Pre-menopausal 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.

- Post-menopausal female
  - A post-menopausal state is defined as 12 months of amenorrhea in a woman over the age of 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 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 judgment 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 time point at which the study intervention (Investigational Medicinal Product [IP/IMP] and other study interventions ie, Non-IMP/AxMP required for study) or any active major metabolites have decreased to a concentration that is no longer considered 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 study intervention to pass which corresponds to [redacted] after the last dose.

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 in which 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 in which 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 in which hormonal contraception is permitted by the study protocol.)[b] • Intrauterine device.

• Intrauterine system (IUS). (This method of contraception can only be used by WOCBP participants in studies in which hormonal contraception is permitted by the study protocol.)[b,c] • Bilateral tubal occlusion.
• Vasectomized partner. Having a vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
• Sexual abstinence. *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. 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 of the protocol. • 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, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactation 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 intervention, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the Investigational Medicinal Product 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 Section 6.1: Inclusion Criteria [redacted] of the protocol. [c] IUSs are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness. For information specific to this study regarding permissibility of hormonal contraception, refer to Section 6.1: Inclusion Criteria [redacted] 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 in which hormonal contraception is prohibited.)
Unacceptable Methods of Contraception
• Periodic abstinence (calendar, symptothermal, post-ovulation 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: Pregnancy of the protocol and Appendix 3.

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

1 EVALUATION OF LESIONS

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

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

1.1 Measurable

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

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

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

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

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

1.2 Non-Measurable

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

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

1.3 Special Considerations Regarding Lesion Measurability

1.3.1 Bone lesions

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

1.4 Baseline Documentation Of 'Target' And 'Non-Target' Lesions

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

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

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

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

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

2 RESPONSE CRITERIA

2.1 Evaluation of Target Lesions

- **Complete Response (CR):** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

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

2.1.1 Special Notes on the Assessment of Target Lesions

2.1.1.1 Lymph nodes

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

2.1.1.2 Target lesions that become 'too small to measure'

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

2.1.1.3 Lesions That Split or Coalesce on Treatment

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

2.2 Evaluation of Non-Target Lesions

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

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

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

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

2.2.1.1 When the Patient Also Has Measurable Disease

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

2.2.1.2 When the Patient Has Only Non-measurable Disease

This circumstance arises in some trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include, an increase in lymphangitic disease from localized to widespread, or may be

described as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

2.2.2 New Lesions

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

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

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

1) Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
2) No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

2.3 Response Assessment

2.3.1 Evaluation of Best Overall Response

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

2.3.2 Time Point Response

At each protocol specified time point, a response assessment occurs. Table 10.4.6-1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline. When patients have non-measurable (therefore non-target) disease only, Table 10.4.6-2 is to be used.

Table 10.4.6-1: Time Point Response

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

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

Table 10.4.6-2: Time Point Response: Patients with Non-target Disease Only

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

CR = complete response, PD = progressive disease and NE = inevaluable

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

2.3.3 Best Overall Response

Best response determination of complete or partial response requires confirmation: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point of ≥ 4 weeks (28 days) later. In this circumstance, the best overall response can be interpreted as in Table 10.4.6-3. When SD is believed to be best response, it must meet the protocol specified minimum time from the date of first treatment or randomization date.

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

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

Table 10.4.6-3: Best Overall Response (Confirmation of CR and PR Required)

Overall Response First Time Point	Overall Response Subsequent Time Point	Best Overall Response
CR	CR	CR
CR	PR	SD, PD OR PR[e]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE
CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable		

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed

when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

2.3.4 Confirmation Scans

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

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

REFERENCES

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

APPENDIX 6 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.

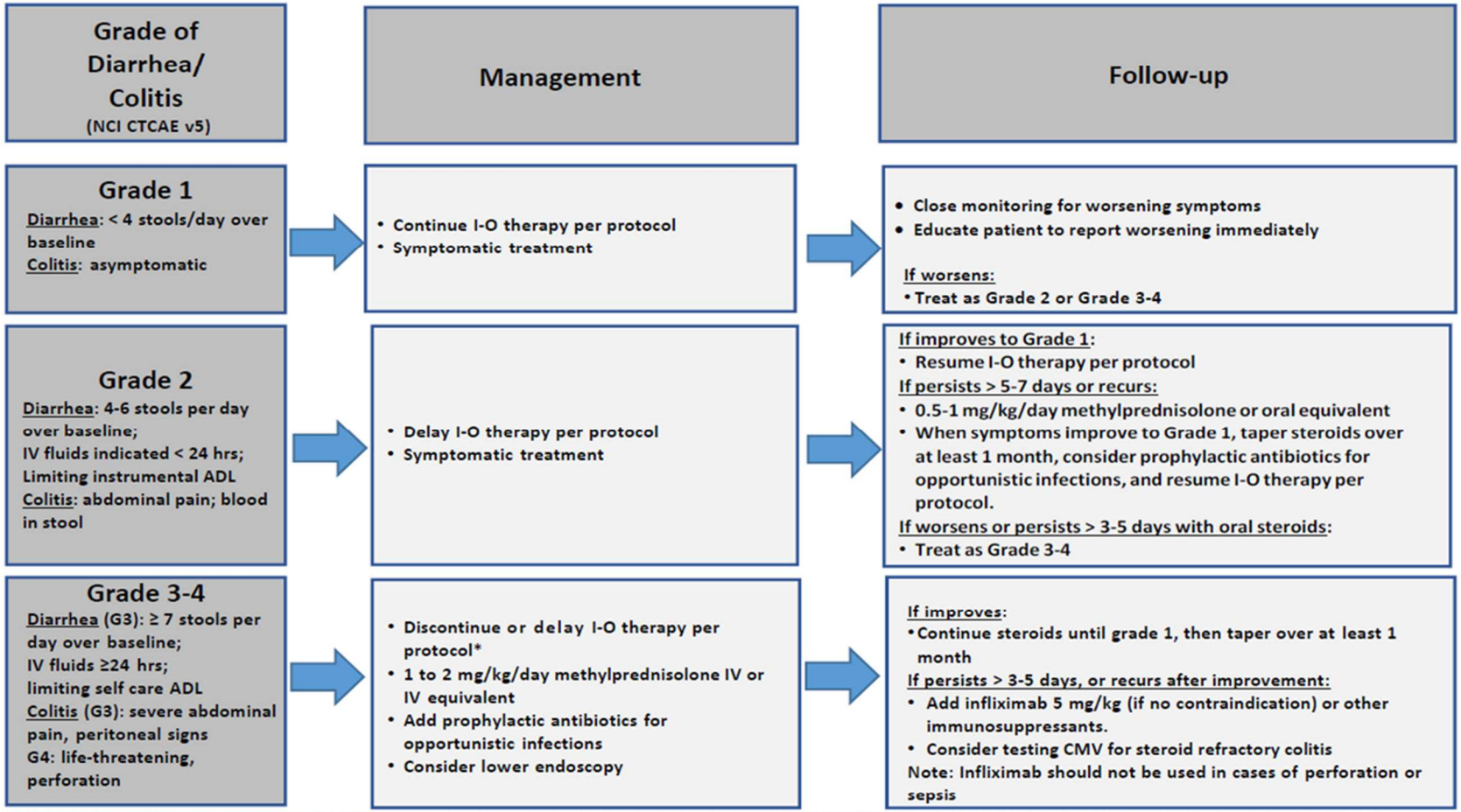
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the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



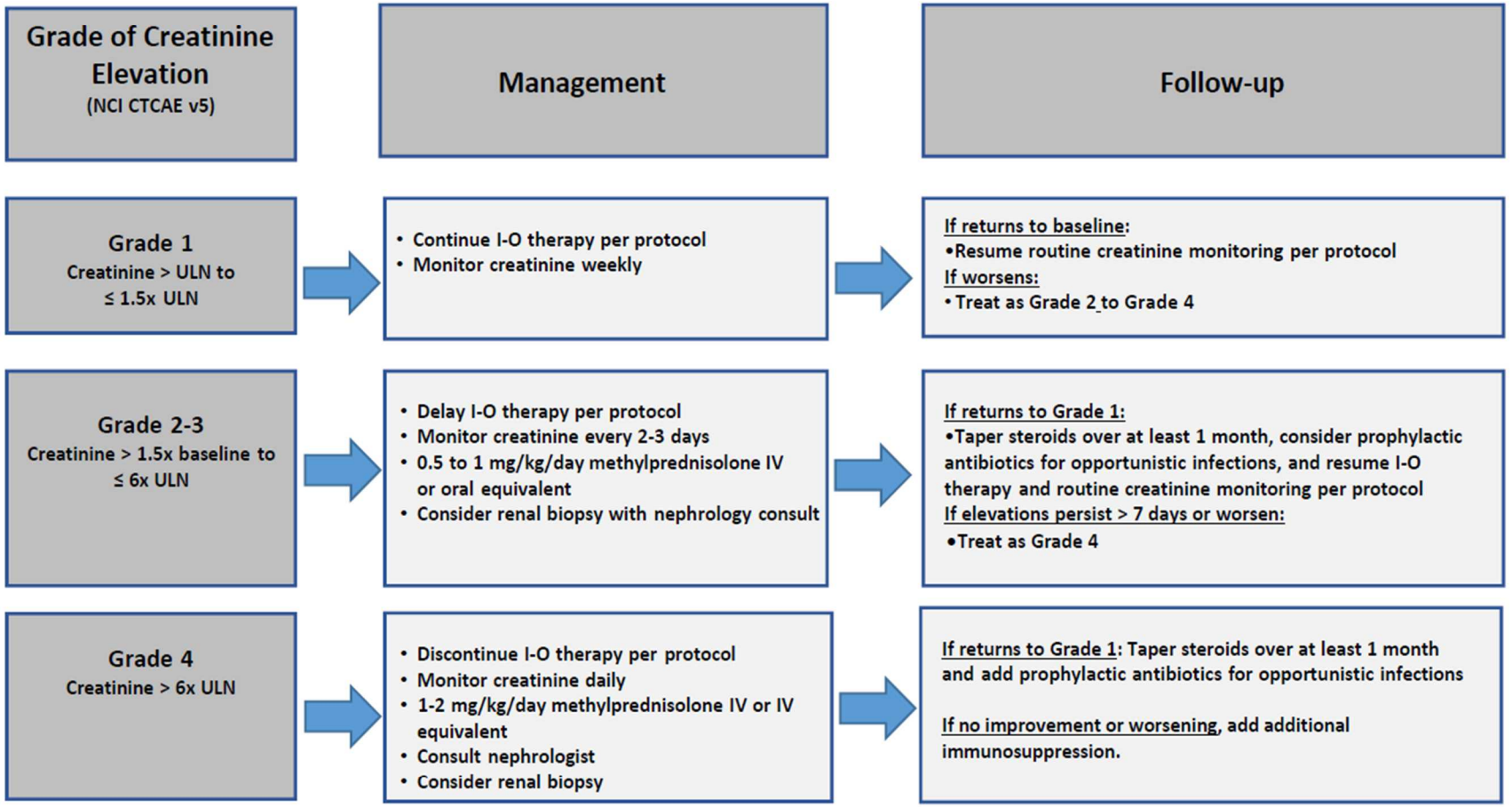
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

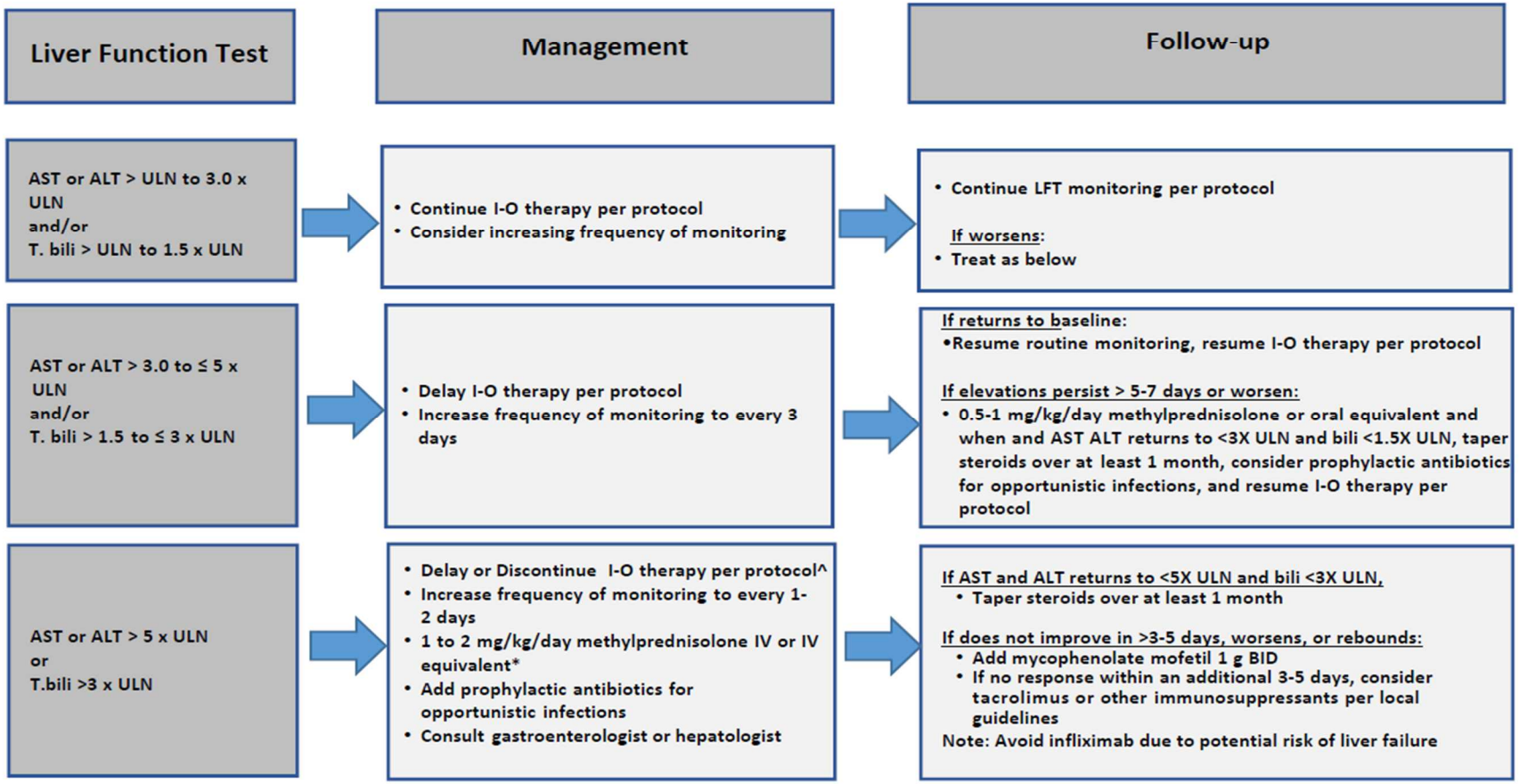
Grade of Pneumonitis (NCI CTCAE v5)	Management	Follow-up
Grade 1 Radiographic changes only	• Consider delay of I-O therapy • Monitor for symptoms every 2-3 days • Consider Pulmonary and ID consults	• Re-image at least every 3 weeks If worsens: • Treat as Grade 2 or 3-4
Grade 2 Mild to moderate new symptoms	• Delay I-O therapy per protocol • Pulmonary and ID consults • Monitor symptoms daily, consider hospitalization • 1 mg/kg/day methyl prednisolone IV or oral equivalent • Consider bronchoscopy, lung biopsy	If improves to Grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recur: • 0.5-1 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to Grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as Grade 3-4
Grade 3-4 Severe new symptoms; New/worsening hypoxia; Life-threatening	• Discontinue I-O therapy per protocol • Hospitalize • Pulmonary and ID consults • 2-4 mg/kg/day methyl prednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider bronchoscopy, lung biopsy	If improves to baseline: • Taper steroids over at least 6 weeks If not improving after 48 hours or worsening: • Add additional immunosuppression

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.

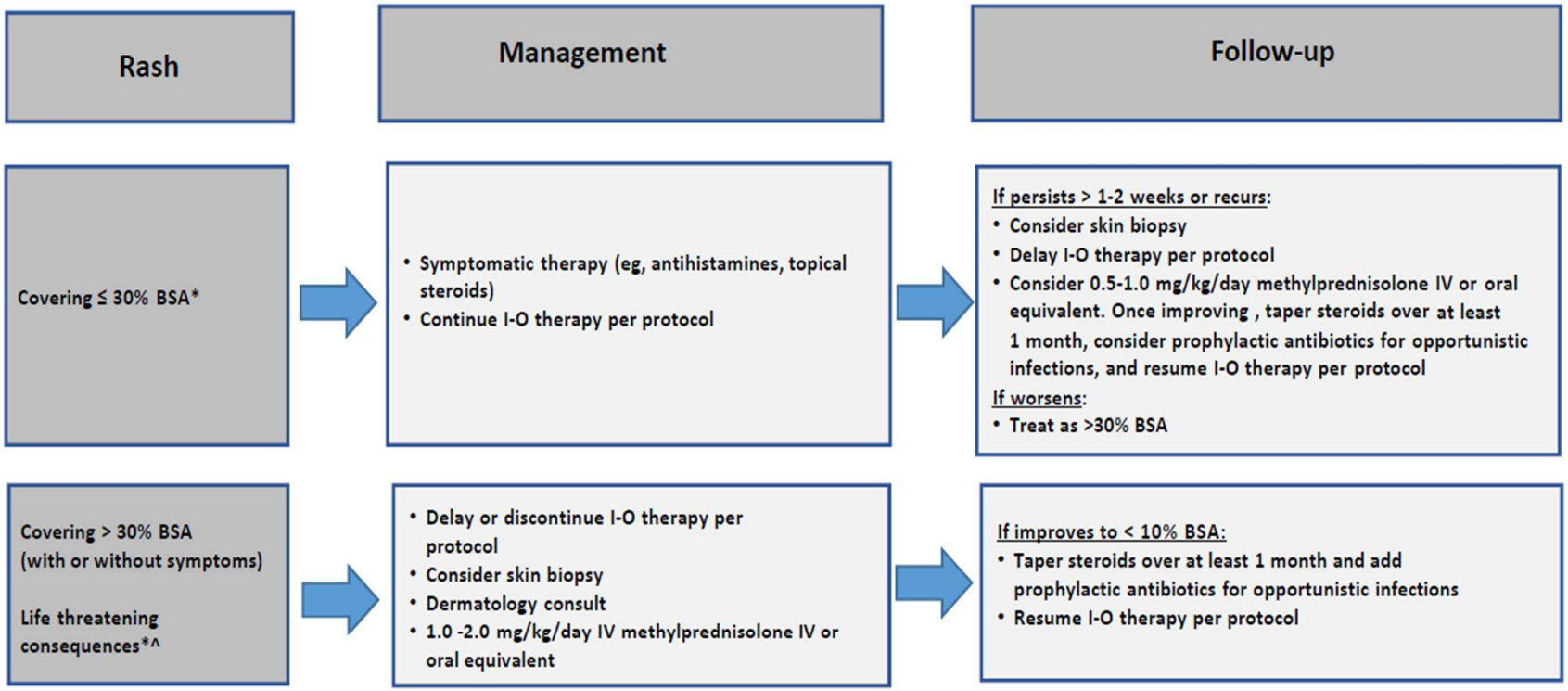
Endocrinopathy	Management	Follow-up
Asymptomatic TSH abnormality or Hyperglycemia requiring no medical intervention	• Continue I-O therapy per protocol • If TSH < 0.5 x LLN, or TSH > 2 x ULN, or consistently out of range in 2 subsequent measurements: ○ include fT4 at subsequent cycles as clinically indicated; ○ 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.

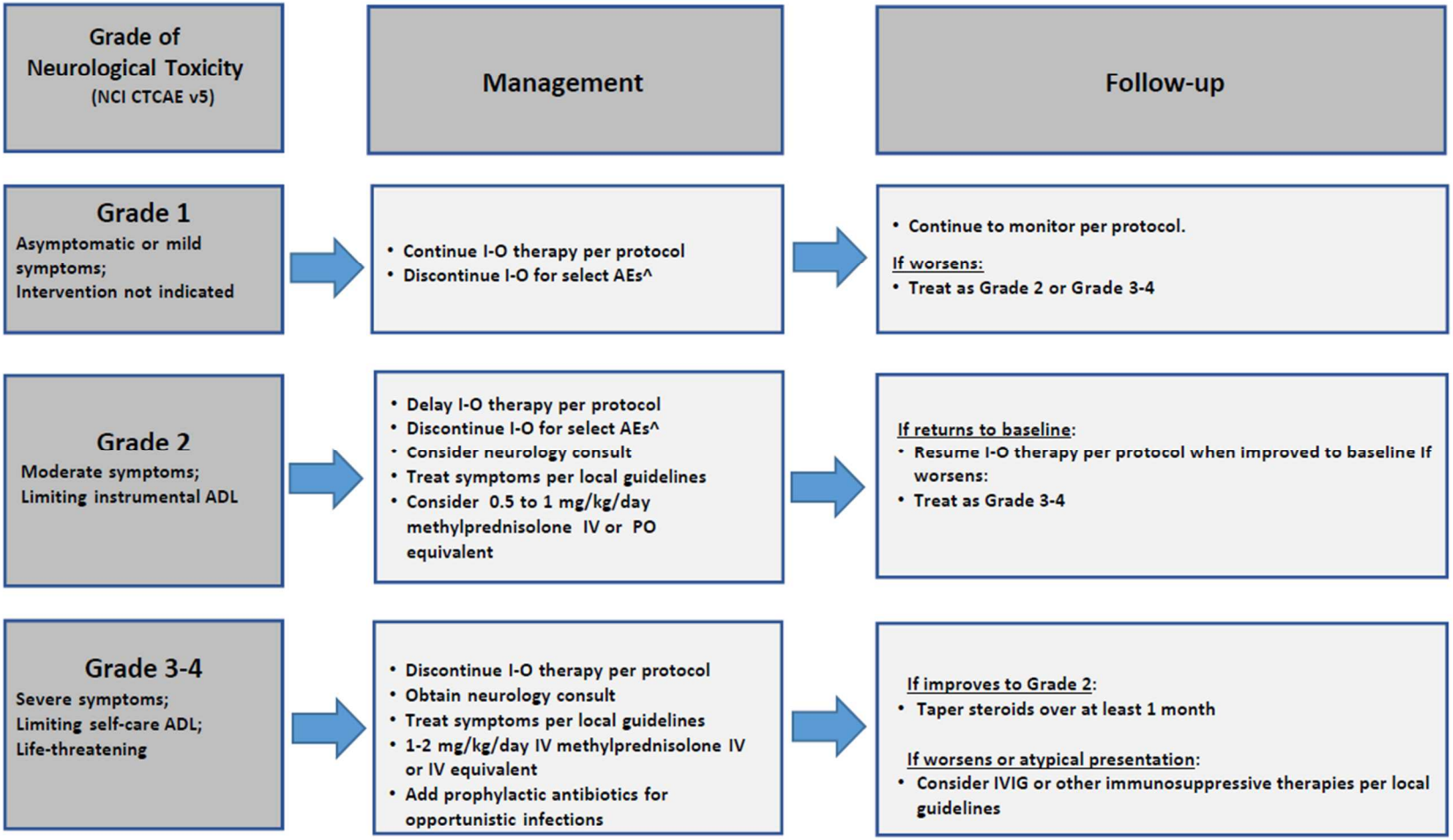
*Refer to NCI CTCAE v5 for term-specific grading criteria.

^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

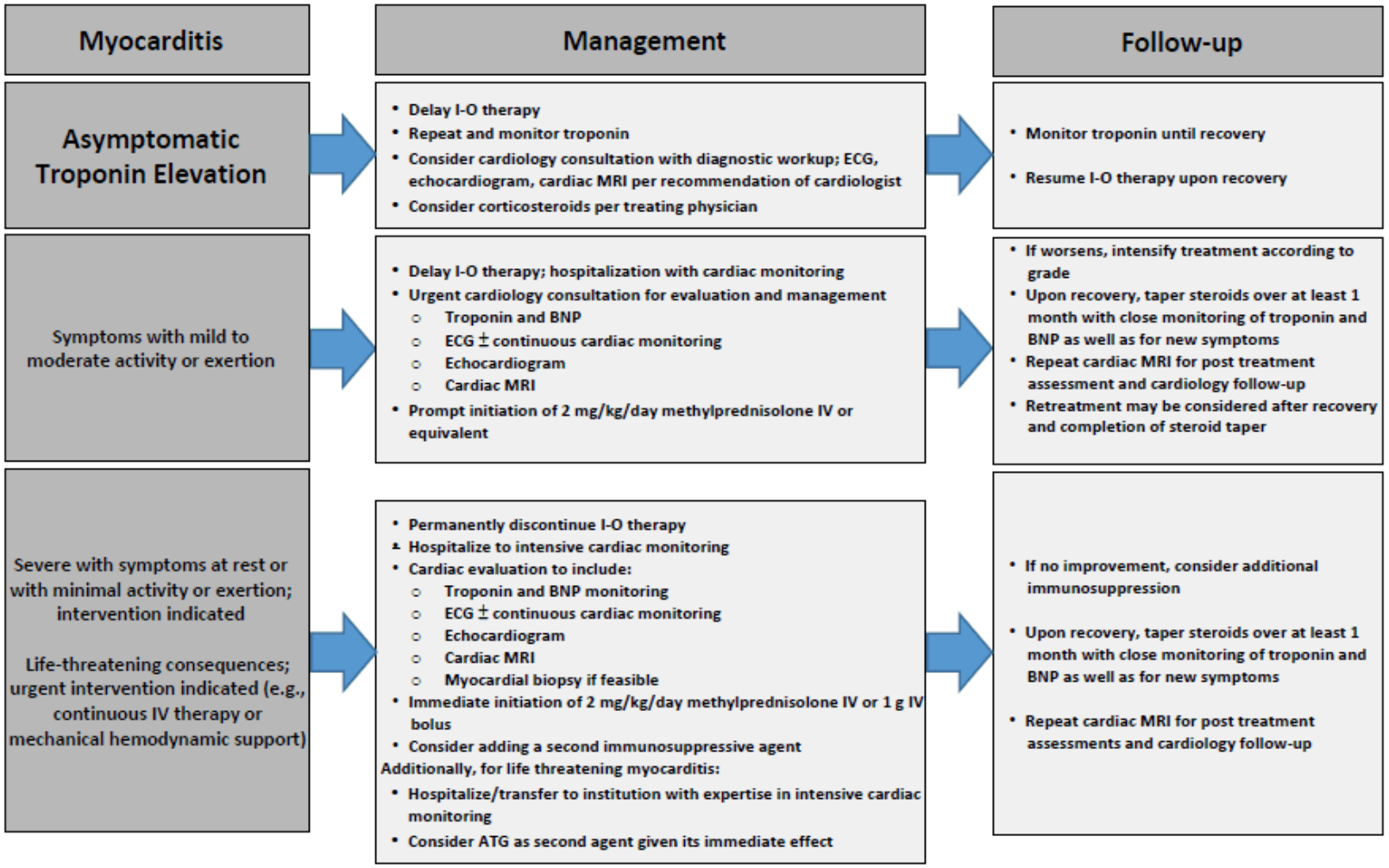
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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



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

APPENDIX 7 ECOG PERFORMANCE STATUS AND LANSKY PERFORMANCE STATUS SCALES AND CONVERSION FORM

ECOG (≥ 18 years)[a]		Lansky (≥ 12 to < 18 years)	
Score	**Description**	**Score**	**Description**
0	Fully active, able to carry on all pre-disease performance without restriction	100	Fully active, normal
		90	Minor restrictions in physically strenuous activity
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work	80	Active, but tires more quickly
		70	Substantial restriction of, and less time spent, in play activity
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours	60	Out of bed, but minimal active play; keeps busy with quiet activities
		50	Gets dressed, but inactive much of day; no active play, able to participate in quiet play
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours	40	Mostly in bed; participates in some quiet activities
		30	In bed; needs assistance even for quiet play
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair	20	Often sleeping; play limited to passive activities
		10	No play; does not get out of bed
5	Dead	0	Unresponsive

[a] 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 8 AJCC MELANOMA STAGING (CANCER STAGING MANUAL 8TH EDITION)

[From AJCC Cancer Staging Manual, 8th Edition. Amin MB, Edge S, Greene F, Byrd DR, Brookland RK, Washington MK, et al. editors. Springer International Publishing. 2017 (pages 577 & 578)]

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 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 (eg, 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 (ie, 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 (ie, 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 (ie, 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

Abbreviations: cN, clinical nodes; SLN, sentinel lymph node.

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	Distant metastasis to non-CNS visceral sites with or without M1a or M1b sites of disease	Not recorded or unspecified
M1c(0)		Not elevated
M1c(1)		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.		

Abbreviations: CNS, central nervous system; LDH, lactate dehydrogenase.

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.

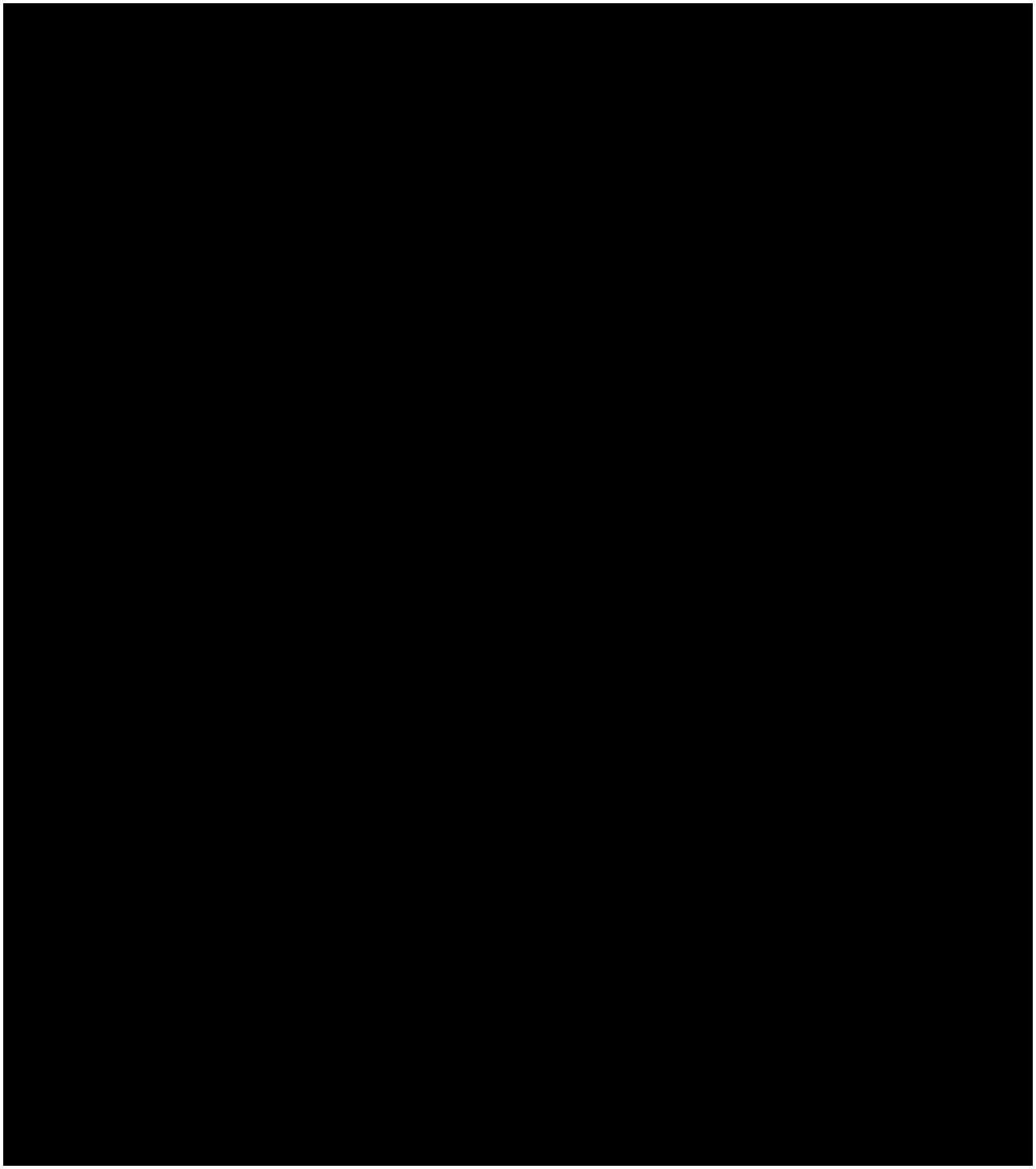
When T is...	And N is...	And M is...	The clinical stage is...
Tis	N0	M0	0
T1a	N0	M0	IA
T1b	N0	M0	IB
T2a	N0	M0	IB
T2b	N0	M0	IIA
T3a	N0	M0	IIA
T3b	N0	M0	IIB
T4a	N0	M0	IIB
T4b	N0	M0	IIC
Any T, Tis	≥N1	M0	III
Any T	Any N	M1	IV

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
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.			



APPENDIX 10 COUNTRY SPECIFIC REQUIREMENTS/DIFFERENCES

Original Language	Country-specific Language or Differences
Criteria for exclusion of HIV-positive participants in **Argentina, Germany, Mexico, and any other countries** where exclusion of HIV-positive participants is locally mandated. Section 6.2 Exclusion Criteria, criterion 1) g)	Exclusion Criterion 1) g): "Participants must not have 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: • they have received antiretroviral therapy (ART) for at least [redacted] prior to randomization as clinically indicated while enrolled on study. • they continue on ART as clinically indicated while enrolled on study. • CD4 counts and viral load are monitored per standard of care by a local health care provider. **NOTE: Testing for HIV must be performed at sites where mandated locally. HIV positive participants must be excluded where mandated locally (Refer to Appendix 10)"** to be replaced with **"Positive test for HIV."**
Section 2 Flow Chart/Time and Events Schedule, Table 2-1: Screening Assessments - Laboratory Tests	Add "HIV" to the list of laboratory tests.
Germany Table 2-2 On-treatment Procedural Outline (CA224127) [redacted] Section 6:1 Inclusion Criteria, Appendix 2: Study Governance Considerations	[redacted] Provision for consent by a legally acceptable representatives (LAR) is prohibited in Germany. Minors will not be enrolled in Germany.
Sweden	Minors will not be enrolled in Sweden.
USA Section 2-1 Screening Procedural Outline (CA224127) None. [redacted] Section 10.4 Statistical Analyses	Added a row, Demography and Participant Characteristics. [redacted] Added the following text:

Original Language	Country-specific Language or Differences
None.	"A description of the participant population will be included in the CSR, including subgroups of age, gender, gender identity, race, and other study-specific populations and demographic characteristics. A description of participant disposition will also be included in the CSR."

APPENDIX 11 PROTOCOL AMENDMENT SUMMARY OF CHANGE HISTORY

Overall Rationale for Protocol Amendment 03, 05-Mar-2024

This protocol has been amended to add more flexibility by eliminating the [redacted]-day screening window (time from signing consent to randomization) while preserving the timeframe for critical assessments related to safety and/or efficacy (eg, safety and tumor imaging assessments).

To accommodate participants for whom sufficient tumor tissue may not be available (ie, [redacted] enabling stratification and other key analysis requirements. [redacted]

[redacted]

In addition, this amendment clarifies that the calculation of response rate difference will be performed using the Cochran-Mantel-Haenszel method adjusting for stratification factors. The secondary PK endpoint of time to peak serum concentration after the first dose (Tmax1) was removed throughout the protocol, as this is not determined as part of the [redacted].

Other changes include the addition of country-specific requirements for Mexico in Appendix 10 and updates to Appendix 8 to include the definition of distant metastasis (M) and regional lymph node (N) and the American Joint Committee on Cancer (AJCC) prognostic stage groups.

Minor changes were made to the adverse event (AE) language in Section 9.2.1.

This protocol amendment applies to all the participants in the study.

Additional changes are described in the table below.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	Updated the contact information of the clinical scientist.	Administrative change.
Section 1: Protocol Summary	Updated to reflect changes made in the body of the protocol.	To align with protocol updates.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-1: Screening Procedural Outline (CA224127) Section 5.1.1: Screening Period Section 6.1: Inclusion Criteria Section 9.7.3.5: Tumor Samples	The tumor sample submission requirements were updated: • [redacted] • A FFPE tissue block or slides of tumor tissue from a surgical specimen or biopsy can now be obtained during screening or collected [redacted].	• To provide flexibility for sites and reduce barriers to trial participation. • [redacted]
Table 2-1: Screening Procedural Outline (CA224127) Table 2-2: On-treatment Procedural Outline (CA224127) Table 2-3: Follow-up Assessments (CA224127)	Clarified that all AEs and SAEs must be collected from the time of signing the informed consent form.	To align with the changes made to Section 9.2.1: Time Period and Frequency for Collecting AE and SAE Information.
Table 2-1: Screening Procedural Outline (CA224127)	[redacted]	
Table 2-1: Screening Procedural Outline (CA224127) Table 9.4.4-1: Clinical Laboratory Assessments		
Table 4-1: Objectives and Endpoints [redacted] Section 10.4.2: Primary Endpoint(s)	The secondary endpoint of Tmax1 was removed.	It is not estimated as part of [redacted].

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 10.4.3: Secondary Endpoint(s)		
Table 4-2: Main Estimands for the Co-Primary and Key Secondary Endpoints Section 10.4.3: Secondary Endpoint(s)	[redacted] • In the key secondary objectives, clarified that the difference in response rate will be computed using the Cochran-Mantel-Haenszel method of weighting.	[redacted] • To provide clarification on the methodology for calculating the difference in response rates.
Section 5.1.1: Screening Period	Updated the screening window by eliminating the [redacted]-day timeframe. The screening window was revised to "from the time the participant signs the informed consent form to randomization."	To provide sites with additional flexibility and minimize repeating study assessments due to potential unforeseen delays.
Section 9.2.1: Time Period and Frequency for Collecting AE and SAE Information	Removed conflicting language related to the collection of AEs.	Correction.
Appendix 2: Study Governance Considerations	Removed the requirement to adhere to the European Union (EU) Directive 2001/20/EC.	To align with new EU regulations.
Appendix 8: AJCC Melanoma Staging (Cancer Staging Manual 8th Edition)	Added the definition of distant metastasis (M) and regional lymph node (N) and the AJCC on Cancer prognostic stage groups.	Inadvertently not included in previous versions of the protocol.
Appendix 10: Country Specific Requirements/Differences	Removed Romania and added Mexico to the list of countries where specific criteria for the exclusion of human immunodeficiency virus (HIV) -positive participants apply.	Romania is not one of the countries participating in the CA224127 trial. The exclusion of HIV-positive participants is locally mandated in Mexico.
All	Formatting and typographical corrections.	Minor; therefore, have not been summarized.

Overall Rationale for Protocol Amendment 02, 16-Jun-2023

The overall rationale for this protocol amendment is to address country-specific requirements (Germany and Sweden) and provide clarification to ensure consistency and participant safety.

[redacted] this protocol is being amended during the initial phase of the study with 4 participants randomized as of 12-Jun-2023.

The amendment includes some key changes such as modification [redacted]

[redacted]
insertion of an eligibility criterion excluding participants who have not recovered adequately from toxicity and/or complications from surgery prior to starting study treatment [redacted]

[redacted]

These revisions have been made in the Protocol Summary as well and are not summarized in the table below.

Minor editorial, formatting, and typographical corrections have been made and therefore have not been summarized.

This protocol amendment applies to all participants in the study.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-1: Screening Procedural Outline (CA224127) Table 2-2: On-treatment Procedural Outline (CA224127) Table 2-3: Follow-up Assessments (CA224127) Section 6.1: Inclusion Criteria Table 9.4.4-1: Clinical Laboratory Assessments	[redacted]	
Table 2-1: Screening Procedural Outline (CA224127) Table 2-2: On-treatment Procedural Outline (CA224127) Table 2-3: Follow-up Assessments (CA224127)		

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-1: Screening Procedural Outline (CA224127) Abbreviations Table 9.4.4-1: Clinical Laboratory Assessments	[redacted]	[redacted]
Table 2-2: On-treatment Procedural Outline (CA224127) Abbreviations Table 9.4.4-1: Clinical Laboratory Assessments		
Table 2-2: On-treatment Procedural Outline (CA224127)	The following statement was added in the Body and Brain Imaging rows: [redacted]	To clarify [redacted]

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Table 2-3: Follow-up Assessments (CA224127)	Revised frequency of clinical laboratory assessments from "To be performed at [redacted], repeat at [redacted] if study treatment-related toxicity persists" to "To be performed at [redacted]".	Included [redacted] to ensure early detection of new late onset immune-related adverse events (AEs), after the last dose of study treatment.
Table 2-3: Follow-up Assessments (CA224127) Footnote b Table 4-2: Main Estimands for the Co-Primary and Key Secondary Endpoints under column "Population" Section 5.1.3: Follow-up Period Section 5.1.5: Blinded Independent Central Review	Text was revised from "all treated participants" to "all randomized participants."	To align with the population specified in the Table 10.3-1 for the intention-to-treat (ITT) analysis.
Section 3.3: Benefit/Risk Assessment	[redacted] Added an overall benefit/risk analysis for including the adolescent population in the trial.	[redacted] Language inserted [redacted] since it was inadvertently not included in the previous protocol versions.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 3.2.9: Nivolumab Combined with Relatlimab Clinical Safety	Removed the following text: "based on the clinical data cutoff date of 30-Jun-2021".	The clinical cutoff date in the revised IB for Nivolumab + Relatlimab FDC has been updated based on the current safety data and is no longer as of 30-Jun-2021.
[redacted]		
Table 4-2: Main Estimands for the Co-Primary and Key Secondary Endpoints, under the column "Intercurrent Events".	[redacted] The sentence "Pharmacometric Analysis Plan will provide details on how to handle all IEs (eg, infusion reaction)" has been revised to "Additional details will be provided in the Statistical Analysis Plan."	[redacted] to provide clarification on how intercurrent events will be handled for primary pharmacokinetic (PK) endpoints.
	[redacted] Also, "responders" has been replaced with "tumor evaluation data" for the participants "Randomized but not treated" and "Discontinued treatment" for key secondary efficacy endpoint "ORR".	Updated [redacted] to censor the response such as ORR and PFS of the participants who have been on the subsequent therapy to prevent objective response rate (ORR), duration of response (DOR), disease control rate (DCR), time to response (TTR), and progression-free survival (PFS) from being influenced by therapies other than the study treatment.
	Deleted "progression" for secondary efficacy endpoint "OS".	This was included inadvertently in previous protocol versions.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted] Section 6.1: Inclusion Criteria	Revised the criteria to add "(for adults ≥ 18 years of age)" after "Participants must have an Eastern Cooperative Oncology Group performance status of ≤ 1." [redacted]	To specify the criteria applies to age ≥ 18 for ECOG to be consistent with Appendix 7 as it provides information on ECOG/Lansky Performance Score criteria for eligibility for age ≥ 18 years (ECOG) and ≥ 12 to < 18 years (Lansky).
Section 5.2: Number of Participants [redacted]	The following language was removed: "...which allows a non-evaluable rate of approximately 40%". [redacted]	[redacted]
[redacted]		
Section 5.4.9: Rationale for Enrolling Adolescent Participants ≥ 12 and < 18 Years Old	New section added.	Included [redacted] to provide justification for the inclusion of minors in the study.
[redacted]		
Section 6.1: Inclusion Criteria Appendix 10: Country-specific Requirements/Differences	The following language was added to Inclusion Criterion #3a: "Except: Where local regulations and/or institutional policies do not allow	Updated [redacted] to provide an exception to the countries where local regulations

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
	for participants ≥ 12 and < 18 years of age (adolescent population) to participate. For those sites, the eligible participant population is ≥ 18 years of age."	and/or institutional policies do not allow adolescent participants.
	Added a row for Sweden in Appendix 10 to indicate minors will not be enrolled in Sweden.	To exempt Sweden from enrolling adolescent participants.
Section 6.2: Exclusion Criteria	Added Exclusion Criterion #1j: "Participant has not recovered adequately from toxicity and/or complications from surgery prior to starting study treatment".	Updated [redacted] to ensure the safety of participants.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 02

Section Number & Title	Description of Change	Brief Rationale
Section 7.1.1: Relatlimab Combined with Nivolumab Administration (Subcutaneous Administration)	Added the following language: [redacted]	[redacted]
[redacted]		
Section 9.2.5: Pregnancy	The sentence "This section is not applicable for WNOCBP" has been updated to "This section is applicable to WOCBP [redacted].	[redacted]
[redacted]		
Section 10.4.3: Secondary Endpoint(s)	Removed the following language: [redacted]	[redacted]

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Appendix 2: Study Governance Considerations	Added section titled "Recruitment and Informed Consent Procedures".	Updated [redacted] to provide a clear description of the general procedures for recruitment and informed consent.
	Added section titled "Clinical Trials on Minors".	Clarification on the study's informed consent procedure regarding the inclusion of minors, per CTR Article 32.
	Added the following to the "Records Retention" section: "Records collected throughout the trial will be stored in the BMS' Clinical Data Management System for a duration of the Life of Product plus 25 years".	Clarification on where data collected in the study will be stored during the study and required archival period.
	Deleted the following from the "Informed Consent Process" section: "Participants who are unable to give their written informed consent (eg, due to stroke or participants with severe dementia) may only be enrolled in the study with the consent of a legally acceptable representative. The participant must also be informed about the nature of the study to the extent compatible with his or her understanding, and should this participant become capable, he or she should personally sign and date the ICF as soon as possible. The explicit wish of a participant who is unable to give his or her written consent, but who is capable of forming an opinion and assessing information to refuse participation in, or to be withdrawn from, the clinical study at any time, should be considered by the investigator".	Updated [redacted] to clarify that incapacitated participants will not be enrolled in the study.
	Deleted the following from the "Informed Consent Process" section: "The explicit wish of a minor, who is capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the clinical study at any time, should be considered by the investigator".	This sentence is deleted under "Informed Consent Process" since this is covered by bullet #1c of the "Clinical Trials on Minors".

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
	Deleted the following from the "Informed Consent Process" section: "Minors who reach the age of majority (legal adulthood) during the clinical study must give their written consent."	This sentence is deleted under "Informed Consent Process" since this is covered by bullet #3 of the "Clinical Trials on Minors".
Appendix 4: Women of Childbearing Potential Definitions and Methods of Contraception End of Relevant Systemic Exposure	Added language to the definition of End of Relevant Systemic Exposure specifying that 5 half-lives correspond to [redacted] after the last dose.	Specified 5 half-lives of study treatment for a total of [redacted] post-treatment completion in Appendix 4 for consistency with the body of the protocol and the Informed Consent Form.
Appendix 10: Country Specific Requirements/Differences	Clarified that provision of consent by a legally acceptable representative (LAR) is prohibited in Germany. Minors will not be enrolled in Germany.	Updated [redacted] to provide clarification that only participants who were able to provide consent personally are to be included in Germany. Revised [redacted]

Overall Rationale for the Protocol Amendment 01, 17-Jun-2022

[redacted] In addition, minor clarifications and editorial updates have been made throughout the protocol.

Revisions apply to all the participants, unless mentioned otherwise.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-1: Screening Procedural Outline (CA224127) Section 10.4.1: General Considerations	[redacted]	[redacted]

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-1: Screening Procedural Outline (CA224127) Appendix 9: Country Specific Requirements/Differences	Added a row, Demography and Participant Characteristics.	To align with the US Food and Drug Administration (FDA) Guidance for Industry and Food and Drug Administration Staff Collection of Race and Ethnicity Data in Clinical Trials, October 2016.
Table 2-2: On-treatment Procedural Outline (CA224127)	[redacted]	[redacted]
Table 2-2: On-treatment Procedural Outline (CA224127)	Added the following text corresponding to the row Body Imaging: "Relative to date of randomization."	To avoid scheduling errors. Text referring to a reference point (randomization) was added to ensure that body imaging would be conducted at consistent intervals in both study arms.
[redacted]		
Section 1: Protocol Summary Section 3: Introduction Section 4: Objectives and Endpoints Table 4-2: Main Estimands for the Co-Primary and Key Secondary Endpoints	Modified the existing text in Section 3 and added it to Section 1. "Throughout the protocol, the coformulation of nivolumab 960 mg + relatlimab 320 mg FDC (BMS-986213) and rHuPH20 24,000 units will be referred to as nivolumab + relatlimab FDC SC, and the IV formulation of nivolumab 480 mg + relatlimab 160 mg FDC (BMS-986213) will be referred to as nivolumab + relatlimab FDC IV."	To clarify the nomenclature for study interventions.
Section 3.1: Study Rationale Section 3.3: Benefit/Risk Assessment Section 3.2.9: Relatlimab Combined with Nivolumab Clinical Safety [redacted]	Order of the text was revised from relatlimab + nivolumab to nivolumab + relatlimab and associated information where applicable.	For consistency in presentation of nomenclature for study interventions.
Section 3.2.6: Relatlimab Combined with Nivolumab Clinical Activity	Added the following text to the existing sentence: "for IV administration in adult and pediatric patients 12 years of age or older with unresectable or metastatic melanoma."	Updated the text based on the literature information for OPDUALAG™.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
[redacted] Appendix 9: Country Specific Requirements/Differences	Added the following text along with the supporting FDA reference in a new subsection: "In accordance with the FDA guidance, data will be collected from participants such as race, ethnicity, sexual orientation, and gender/gender they identify with. Participation in the main study is not contingent upon providing responses to race, ethnicity, sexual orientation, or gender identity questions." "This data may be combined with data from other BMS studies to conduct subsequent research on how the disease or treatment impacts certain populations."	To align with the FDA Guidance for Industry and Food and Drug Administration Staff Collection of Race and Ethnicity Data in Clinical Trials, October 2016.
Section 1: Protocol Summary Table 2-1: Screening Procedural Outline (CA224127) Section 5.1.1 Screening Period Section 6.1: Inclusion Criterion 2 g) Section 9.7.3.5: Tumor Samples	[redacted]	[redacted]
Section 7.2: Assignment to Study Intervention	Added the following text next to region: [redacted]	For consistency.
Section 8.1: Discontinuation of Study Intervention Section 9.2.5: Pregnancy	Removed the following text: (eg, dose tapering if necessary for participant safety).	Clarified that dose tapering is not applicable to this study.
Table 9.4.4-1: Clinical Laboratory Assessments	Added the following text to Pregnancy test under Other Analyses:	To clarify and make it consistent with Pregnancy Test row in Table 2-2.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
	"24 hours prior to first dose and then every [redacted] (± 1 week) irrespective of dosing schedule" Removed the following text in the Pregnancy test row under Other Analyses: "predose, discharge"	
[redacted]		
Section 10.4: Statistical Analyses Appendix 9: Country Specific Requirements/Differences	Added the following text: "A description of the participant population will be included in the CSR, including subgroups of age, gender, gender identity, race, and other study-specific populations and demographic characteristics (For USA only. See Appendix 9 for further information). A description of participant disposition will also be included in the CSR."	To align with the FDA Guidance for Industry and Food and Drug Administration Staff Collection of Race and Ethnicity Data in Clinical Trials, October 2016.
Section 1: Summary Table 2-2: On-treatment Procedural Outline (CA224127) Appendix 9: Country Specific Requirements/Differences	[redacted]	
All	Minor formatting and typographical corrections	Minor, therefore, have not been summarized.

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