Official Title of Study:

A Phase 3, Randomized, Double-blind Study of Adjuvant Immunotherapy with Nivolumab + Relatlimab Fixed-dose Combination versus Nivolumab Monotherapy after Complete Resection of Stage III-IV Melanoma

NCT Number: NCT05002569

Document Date (Date in which document was last revised): 27-Jul-2023

CLINICAL PROTOCOL CA224098

A Phase 3, Randomized, Double-blind Study of Adjuvant Immunotherapy with Nivolumab + Relatlimab Fixed-dose Combination versus Nivolumab Monotherapy after Complete Resection of Stage III-IV Melanoma

Brief Title:

Adjuvant Immunotherapy with Nivolumab + Relatlimab Fixed-dose Combination versus Nivolumab Monotherapy after Complete Resection of Stage III-IV Melanoma (**RELA**TIVITY-098)

Protocol Amendment Number: 03
Incorporates Country-Specific Requirements for Countries in the European Union (EU)

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IND: 136382

EUDRACT Number: 2021-001641-13

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Protocol Amendment 03	27-Jul-2023	Main changes include: • Updated and provided a more detailed endpoint description for [redacted] • [redacted] • [redacted] • Corrected typographical errors and included minor editorial updates in the Schedule of Activities, [redacted] and Statistical Considerations sections.
Protocol Amendment 02	22-Feb-2023	Main changes include: • Changed the trigger for [redacted] from [redacted]. • [redacted] • Population for the distant metastasis-free survival (DMFS) secondary objective was limited to randomized participants with Stage III/IVA/IVB no evidence of disease (NED) melanoma. • An additional clarification for neck magnetic resonance imaging (MRI) was provided for head and neck mucosal melanomas. • To consolidate previously published/implemented country-specific amendments with the global amendment in preparation for the European Union Clinical Trials Regulation (EU CTR) transition, certain country-specific paragraphs were delineated while others were consolidated for easier reading without changing context.

Document	Date of Issue	Summary of Change
Protocol Amendment 01	18-May-2022	Major changes include: • Addition of adolescent participants (≥ 12 years of age through < 18 years of age). [redacted] • Distant metastasis-free survival was moved from key secondary endpoint to other secondary endpoint [redacted] • Participants with a history of myocarditis, regardless of etiology, are excluded from participation in this study [redacted] • Ultrasonography was updated as a study requirement for surveillance of participants who have a sentinel lymph node biopsy but do not undergo complete lymph node dissection (CLND) and left as optional for those with CLND.
Administrative Letter 04	24-Dec-2021	[redacted]
Administrative Letter 02	12-Aug-2021	The Clinical Trial Physician of the protocol was changed.
Administrative Letter 01	28-May-2021	During finalization of the original protocol for CA224098, the IND and EUDRACT numbers were inadvertently left off both the cover page and the protocol signature page. Additionally, it was noted that the acknowledgement page had a typo in the protocol number, which was incorrectly noted as CA2224098 with a superfluous "2." This administrative letter corrects the IND/EUDRACT omission and the signature page typo.
Original Protocol	25-May-2021	Not applicable

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 03

The primary reason for this protocol amendment is to clarify and ensure consistencies in the objectives and endpoints and statistical considerations sections. Additional minor changes include corrections in the schedule of activities, [redacted] and formatting updates.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 03

Section Number & Title	Description of Change	Brief Rationale
Protocol Summary	Text has been updated to align with changes made throughout the protocol.	Alignment between Protocol Summary and body of the protocol.
Table 2-2: On Study Treatment Procedural Outline (CA224098) Table 2-3: Follow-up Assessments (CA224098) [redacted]	[redacted]	• To correct typographical errors. • To clarify the [redacted] Survival Follow-up visits.
Table 4-1: Objectives and Endpoints	• Rephrased "next-line therapies" as "next-line systemic therapies" in the secondary objective to evaluate investigator-assessed outcomes, [redacted] • [redacted]	To clarify and align with the intent of analysis.
Section 10.2.1: Recurrence-free Survival	[redacted]	• To correct a typographical error of the [redacted]

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 10.3: Analysis Sets	Clarified that the [redacted] for the analysis sets for [redacted] of recurrence-free survival (RFS), distant metastasis-free survival (DMFS), and overall survival (OS) will be provided in Table 10.4.1-2.	To streamline the definitions for the analysis data sets.
Section 10.4.1: General Considerations	[redacted]	To be consistent with the definition of RFS in Section 4.
Table 10.4.1-2: Definition of Estimands for Primary and Secondary Endpoints	[redacted] • Removed summary statistics bullet as this will be further detailed in the statistical analysis plan.	To clarify and align with the intent of analysis and clarify that details are presented in the statistical analysis plan.
[redacted]	[redacted]	To ensure accuracy and consistency of terminology.
Section 10.4.2: Primary Endpoints(s)	[redacted]	To clarify and align with the intent of analysis.
Table 10.4.2-1: Primary Endpoints Table 10.4.3-1: Secondary Efficacy Endpoints	[redacted]	To clarify and align with the intent of analysis.
Throughout	Editorial updates.	Minor; therefore, have not been summarized.

TABLE OF CONTENTS

1 PROTOCOL SUMMARY

Protocol Title: A Phase 3, Randomized, Double-blind Study of Adjuvant Immunotherapy with Nivolumab + Relatlimab Fixed-dose Combination versus Nivolumab Monotherapy after Complete Resection of Stage III-IV Melanoma

Brief Title:

Adjuvant Immunotherapy with Nivolumab + Relatlimab Fixed-dose Combination versus Nivolumab Monotherapy after Complete Resection of Stage III-IV Melanoma (**RELA**TIVITY-098)

Rationale:

Surgical resection is currently considered standard of care for Stage III-IV resectable melanoma, followed by one year of adjuvant therapy. However, there remains an unmet need to improve recurrence-free survival (RFS) while maintaining a favorable safety profile for these patients. Targeting lymphocyte activation gene 3 (LAG-3), which is involved in the immune checkpoint pathway, is a novel approach that may further overcome immune evasion mechanisms.

Study CA224098 is a Phase 3, randomized, double-blind study of nivolumab and relatlimab (nivo + rela) fixed-dose combination (FDC) compared with nivolumab monotherapy in completely resected Stage III-IV melanoma. This study will generate efficacy and safety data for the patient population with Stage IIIA (> 1 mm tumor in lymph node)/B/C/D or Stage IV (no evidence of disease [NED]) melanoma following complete resection of their lesion(s).

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To compare the efficacy, as measured by RFS, provided by nivo + rela FDC vs nivolumab monotherapy in participants with completely resected Stage III/IV NED melanoma.	• RFS time as assessed by the investigator. RFS is defined as the time between the date of randomization and the first date of documented recurrence [redacted] or death due to any cause, whichever occurs first.
Key Secondary	
• To compare the OS provided by nivo + rela FDC vs nivolumab monotherapy in participants with completely resected Stage III/IV NED melanoma.	• OS is defined as the time between the date of randomization and the date of death due to any cause.
Other Secondary	
• To assess the efficacy as measured by DMFS, provided by nivo + rela FDC vs nivolumab monotherapy in participants with completely resected Stage III/IVA/IVB NED melanoma.	• DMFS, by investigator, is defined as the time between the date of randomization and the date of first distant metastasis or date of death due to any cause, whichever occurs first.
• To assess safety and toxicity of nivo + rela FDC and nivolumab monotherapy in participants with completely resected Stage III/IV NED melanoma.	• Incidence and severity of AEs, SAEs, IMAEs, drug-related AE/SAE, other select AEs, AEs leading to discontinuation, deaths, laboratory abnormalities.

Objectives	Endpoints
• To evaluate investigator-assessed outcomes on next-line systemic therapies.	• PFS2 defined as time from randomization to second recurrence/objective disease progression on next-line systemic therapy per investigator, or death from any cause, whichever occurs first.

Abbreviations: AE, adverse event; DMFS, distant metastasis-free survival; FDC, fixed dose combination; IMAE, immune mediated adverse event; NED, no evidence of disease; nivo, nivolumab; PFS2, progression-free survival 2; rela, relatlimab; RFS, recurrence free survival; OS, overall survival; SAE, serious adverse event.

Overall Design:

This is a Phase 3, randomized, double-blind study of nivo + rela FDC compared with nivolumab monotherapy in participants (≥ 12 years of age) with completely resected Stage IIIA (> 1 mm tumor in lymph node)/B/C/D or Stage IV NED melanoma by the American Joint Committee on Cancer, version 8 (AJCC v8). Efficacy of nivo + rela FDC, as measured by RFS time (as assessed by the investigator), will be compared to nivolumab monotherapy.

Participants will be randomized 1:1 to receive treatment with one of the following:

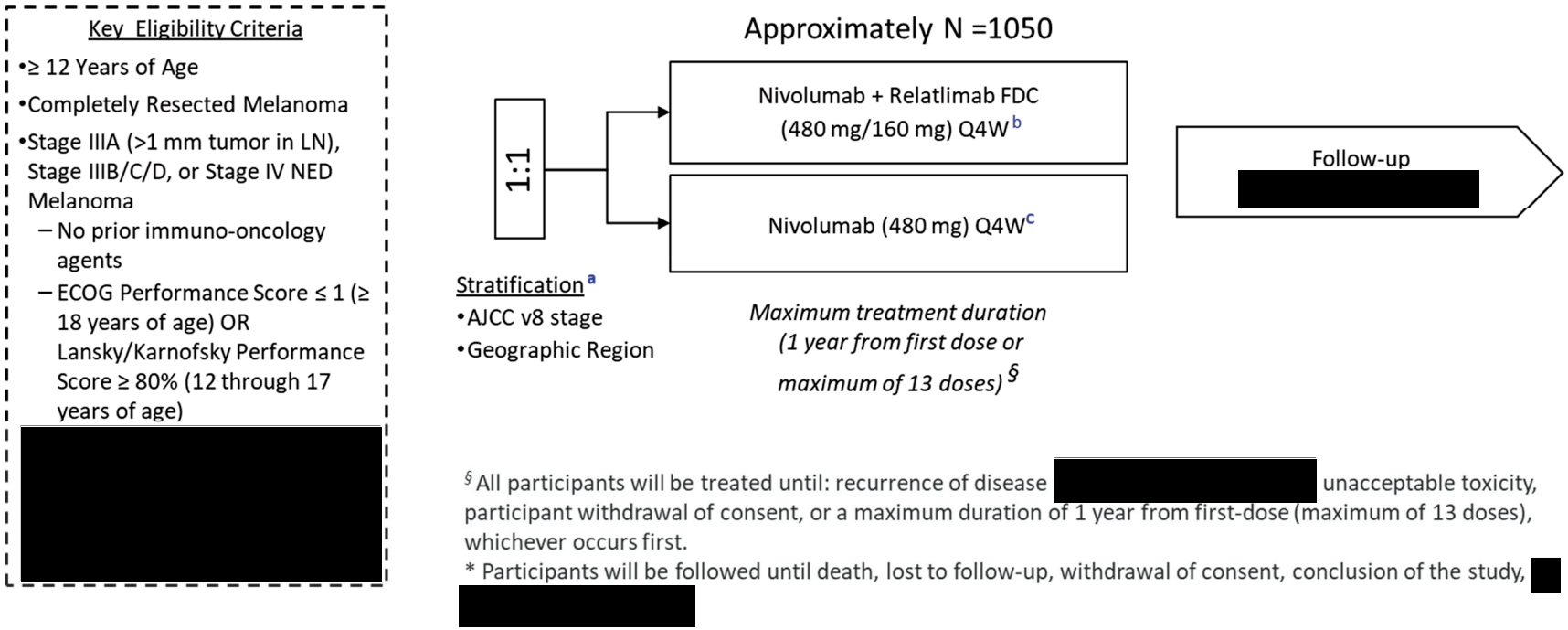
- Nivo + rela FDC dosing:
  - ≥ 18 years of age **OR** ≥ 12 years to < 18 years of age and ≥ 40 kg: nivolumab 480 mg and relatlimab 160 mg IV every 4 weeks (Q4W)
  - ≥ 12 years to < 18 years of age and < 40 kg: [redacted]
- Nivolumab dosing:
  - ≥ 18 years of age **OR** ≥ 12 years to < 18 years of age and ≥ 40 kg: nivolumab 480 mg IV Q4W
  - ≥ 12 years to < 18 years of age and < 40 kg: nivolumab 6 mg/kg IV Q4W

Participants will be stratified by AJCC v8 stage (Stage IIIA/IIIB vs IIIC vs IIID/IV [including all participants with mucosal melanoma, Stage III, Stage IVA, Stage IVB, and Stage IVC]), and geographic region (USA/Canada/Australia vs Europe vs rest of the world [ROW]). All participants will be treated until: recurrence of disease [redacted] unacceptable toxicity, participant withdrawal of consent, or a maximum of 1 year of treatment from first dose (maximum of 13 doses), whichever occurs first.

This study will consist of 3 phases: screening, treatment, and follow-up.

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

Figure 1-1: Study Design Schema



Abbreviations: AJCC v8, American Joint Committee on Cancer, version 8; ECOG, Eastern Cooperative Oncology Group; FDC, fixed dose combination; [redacted] IV, intravenous; LN, lymph node; NED, no evidence of disease; ROW, rest of the world; Q4W, every 4 weeks.

[a] Stratification:

- AJCC v8: Stages IIIA/IIIB, Stage IIIC, Stages IIID/IV (including all participants with mucosal melanoma, Stage III, Stage IVA, Stage IVB, and Stage IVC)
- Geographic Regions: USA/Canada/Australia, Europe, ROW

[b] Nivo + rela FDC dosing:

- ≥ 18 years of age **OR** ≥ 12 years to < 18 years of age and ≥ 40 kg: nivolumab 480 mg and relatlimab 160 mg IV Q4W
- ≥ 12 years to < 18 years of age and < 40 kg: [redacted]

[c] Nivolumab dosing:

- ≥ 18 years of age **OR** ≥ 12 years to < 18 years of age and ≥ 40 kg: nivolumab 480 mg IV Q4W
- ≥ 12 years to < 18 years of age and < 40 kg: nivolumab 6 mg/kg IV Q4W

Number of Participants:

Approximately 1,050 participants are expected to be randomized (1:1) to the following treatment arms:

- Nivo + rela FDC (n = 525)
- Nivolumab monotherapy (n = 525)

The randomization will be stratified by the following stratification factors:

- Geographic region (USA/Canada/Australia vs Europe vs ROW)
- AJCC v8 Stage IIIA/IIIB vs Stage IIIC vs Stage IIID/IV (including all participants with mucosal melanoma, Stage III, Stage IVA, Stage IVB, and Stage IVC)

Study Population:

Male and female participants ≥ 12 years of age with completely resected Stage IIIA (> 1 mm tumor in lymph node)/B/C/D or Stage IV NED melanoma.

Key Inclusion Criteria:

- All participants must have been diagnosed with either Stage IIIA (> 1 mm tumor in lymph node)/B/C/D or Stage IV melanoma by AJCC v8 and have histologically confirmed melanoma that is completely surgically resected (free of disease) with negative margins in order to be eligible. All melanomas, except ocular melanoma, regardless of primary site of disease, will be allowed.

  Note: Conjunctival melanoma is not considered to be ocular melanoma and is to be classified as mucosal melanoma.
- Participants are eligible if central nervous system (CNS) metastases have been resected and participants are neurologically stable.
  - Prior resected CNS metastases must be without evidence of recurrence, as determined by magnetic resonance imaging (MRI) performed at least 4 weeks after resection is complete and within 35 days prior to randomization.
  - Participants must be off immunosuppressive doses of systemic steroids (>10 mg/day prednisone or equivalent) for at least 14 days prior to study drug administration and must have returned to neurologic baseline post-operatively.
  - For CNS lesion(s), pathology report indicating that there has been complete resection of CNS lesion(s) will suffice as confirmation of negative margins.
- Complete resection must be performed [redacted] prior to randomization. Management of residual lymph nodes after positive sentinel lymph node biopsy (SLNB) (ie, completion lymph node dissection) will be as per local standards and recommendations for the individual participant.
- All participants must have disease-free status documented by a complete physical examination within 14 days prior to randomization and imaging studies within 35 days prior to

randomization. Imaging studies must include computed tomography (CT) scan of the chest, abdomen, pelvis, and all known sites of resected disease, and brain MRI.

- [redacted]
- Participants ≥ 18 years of age must have an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1. Adolescent participants between 12 and < 18 years of age must have a Lansky/Karnofsky performance score ≥ 80%.

Key Exclusion Criteria:

- History of ocular melanoma

  Note: Conjunctival melanoma is not considered to be ocular melanoma and is to be classified as mucosal melanoma
- Untreated/unresected CNS metastases or leptomeningeal metastases
- Participants with an active, known, or suspected autoimmune disease. Participants with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
- Participants with serious or uncontrolled medical disorder
- Previous severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection either suspected or confirmed within 4 weeks prior to screening. Acute symptoms must have resolved and based on investigator assessment, there are no sequelae that would place the participant at a higher risk of receiving investigational treatment.
- [redacted]
- Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) [redacted] or other immunosuppressive medications within 30 days of start of study treatment. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
- Participants with a history of myocarditis, regardless of etiology.

- [redacted]
- Treatment with any live/attenuated vaccine within 30 days of first study treatment (inactivated vaccines are permitted).
- Pregnant or breastfeeding females.
- [redacted]
- [redacted]

Intervention Groups and Duration:

As described in overall design.

Study Intervention:

Study Drug for CA224098		
Medication	**Potency**	**Investigational Product (IP)/Non-IP**
Nivo + rela FDC (Nivolumab 240 mg/ Relatlimab 80 mg)/vial	16 mg/mL	IP
Nivolumab 100 mg/vial	10 mg/mL	IP

Abbreviations: FDC, fixed dose combination; IP, investigational product; nivo, nivolumab; rela, relatlimab.

Statistical Methods

- This is a double-blind, parallel group study in which participants will be randomized 1:1 to either of the 2 treatment groups: nivo + rela FDC or nivolumab monotherapy. The randomization will be stratified by AJCC v8 stage at screening and geographic region.
- The primary objective of the study is to assess the superiority of nivo + rela FDC over nivolumab monotherapy in improving RFS in participants with completely resected Stage IIIA (> 1 mm tumor in lymph node), Stage IIIB/C/D, or Stage IV NED melanoma over a treatment duration of 1 year. RFS distributions will be compared between the 2 treatment groups (nivo + rela FDC vs nivolumab monotherapy) [redacted]

Data Monitoring Committee: Yes

A Data Monitoring Committee will be used in the study.

Other Committee: Yes

A Study Steering Committee will be used in the study.

Brief Summary:

The purpose of this study is to assess the efficacy, measured as RFS, of nivo + rela FDC compared with nivolumab monotherapy, in the setting of adjuvant treatment of Stage III-IV melanoma after complete resection. Study details are as follows.

Study drug will be given for a maximum of 1 year from first dose (maximum of 13 doses), [redacted]

While study drug is being administered, study visits will be every 4 weeks (for a maximum of 1 year). Once study intervention is completed or discontinued early, the first follow-up visit will be 30 days from the date of the last dose. The second follow-up visit is 135 days following last dose of study intervention. Long-term follow up visits will be every 12 weeks subsequently (in clinic or by telephone) [redacted] The trial will end once this follow-up has concluded. [redacted]

2 SCHEDULE OF ACTIVITIES

Table 2-1: Screening Procedural Outline (CA224098)

Procedure	Screening	Notes: [a] All windows are based on calendar days.
Eligibility Assessments		
Informed Consent	X	Must be obtained prior to performing any screening procedures. See Section 6.1. For adolescent participants (≥ 12 years to < 18 years), please refer to Informed Consent Process in Appendix 2. Where local regulations do not allow for participants < 18 years of age (adolescent population) to participate, the eligible participant population is ≥ 18 years of age (refer to Appendix 9). Study allows for re-enrollment of a participant that has discontinued the study as a pre-treatment failure. If re-enrolled, the participant must be re-consented and assigned a new participant number from IRT.
Enroll in IRT	X	Register in IRT system to obtain participant number.
Inclusion/Exclusion Criteria	X	Assessed at screening and must be confirmed prior to randomization.
Medical History	X	All medical history relevant to the disease under study. [redacted]
Tumor Sample Submission	X	[redacted]

Table 2-1: Screening Procedural Outline (CA224098)

Procedure	Screening	Notes: [a] All windows are based on calendar days.
Review of Pathology Report	X	Diagnosis must be stated in a pathology report confirming negative margins that has been finalized prior to randomization. A deidentified copy of the report must be provided to the central lab.
Body Imaging	X	Contrast-enhanced CT of the chest, abdomen, pelvis, and all suspected sites of disease, within 35 days prior to randomization. See Section 9.1.2 for further details and exceptions. Please refer to Appendix 9 for Germany-specific imaging language.
Brain Imaging	X	MRI of the brain (with and without contrast) is required for ALL participants during screening to rule out brain metastases, within 35 days prior to randomization. CT of the brain (with and without contrast) can be performed if MRI is contraindicated. See Section 9.1.2 for further details.
Ultrasound of Region(s) relevant to the Participant's Tumor Resection	X	Ultrasound of region(s) relevant to the participant's tumor resection must be performed for surveillance of participants who have a positive SNLB who do not undergo immediate CLND. Ultrasound is optional for participants who have undergone CLND relevant to the tumor resection. All suspicious lesion(s) should undergo proper evaluation. If disease is detected, all lesions must be removed and NED must be confirmed within 35 days prior to randomization. Ultrasounds should not be submitted to the imaging vendor.
Safety Assessments		
Complete Physical Examination, Measurements, Vital signs	X	Complete physical exam including height, weight, blood pressure, heart rate, and temperature. Must be collected within 14 days prior to randomization.
Performance Status	X	Within 14 days prior to randomization. ECOG Performance Status (≥ 18 years old) OR Lansky/Karnofsky Performance Score for adolescents (12 to < 18 years old) (Appendix 6).
Assessment of Signs and Symptoms	X	Within 14 days prior to randomization.
Concomitant Medications	X	Within 14 days prior to randomization. Confirm no live vaccine use within 30 days prior to first study treatment.

Table 2-1: Screening Procedural Outline (CA224098)

Procedure	Screening	Notes: [a] All windows are based on calendar days.
SAE Assessment	X	SAEs collected from time of consent. All AEs (SAEs or non-serious AEs) associated with SARS-CoV-2 infection collected from time of consent.
12-Lead ECG	X	12-lead ECGs should be recorded after the participant has been supine for at least 5 minutes. Must be performed within 14 days prior to randomization. ECG abnormalities should be reviewed and addressed, if needed, prior to randomization.
Laboratory Tests		
Clinical Laboratory Assessments	X	Laboratory tests must be performed within 14 days prior to randomization. Viral testing to be completed within 35 days prior to randomization. For HIV: testing at sites where locally mandated (see Appendix 9). Refer to Section 9.4.4 for list of laboratory tests to conduct.
Pregnancy Test (WOCBP)	X	Serum or urine pregnancy test (minimum sensitivity equivalent units 25 IU/L or equivalent units of HCG) to be done within 35 days prior to randomization.
FSH	X	Females under the age of 55 years must have a serum FSH level > 40 mIU/mL to confirm menopause. If not confirmed, protocol pregnancy testing requirements must be followed.
[redacted]		
[redacted] **Assessments**		
[redacted]	[redacted]	

Abbreviations: AE, adverse event; [redacted] CLND, complete lymph node dissection; [redacted] eCRF, electronic case report form; CT, computed tomography; ECG(s), electrocardiogram(s); ECOG, Eastern Cooperative Oncology Group; [redacted] FSH, follicle-stimulating hormone; HCG, human chorionic gonadotropin; HIV, human immunodeficiency virus; IRT, interactive response technology; MRI,

magnetic resonance imaging; NED, no evidence of disease; [redacted] SAE(s), serious adverse event(s); SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SNLB, sentinel lymph node biopsy; [redacted] ULN, upper limit of normal; WOCBP, women of child-bearing potential.

[a] 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.

Table 2-2: On Study Treatment Procedural Outline (CA224098)

Procedure	C1D1[a] (Cycle Duration = 4 weeks)	C2D1 and D1 of Each Subsequent Cycle (± 3 days)	Notes:[b]
Study Treatment			
Randomize	X		
IRT Drug Assignment	X		Participant must receive the first dose of study medication within 3 days from randomization.
Dispense Study Treatment	X	X	First drug to be administered within 3 calendar days following randomization, subsequent doses can be administered within 3 days before or after scheduled date if necessary (every 28 days ± 3 days). Treatment will continue until recurrence, unacceptable toxicity, withdrawal of consent, or after a maximum duration of 1 year from first-dose (maximum of 13 doses), whichever occurs first. See treatment details in Section 7.1.1.
Safety Assessment			
Targeted Physical Examination, Measurements, and Vital Signs[c]	X*	X	Weight, blood pressure, heart rate, and temperature within 3 days prior to dosing. *Targeted physical exam not required on C1D1 if a full physical exam was completed within 3 days of first dose.
Performance Status[c]	X	X	ECOG Performance Status (≥ 18 years old) OR Lansky/Karnofsky Performance Score for adolescents (12 to < 18 years old). See Appendix 6.
AE and SAE Assessment	Continuously		Record at each visit. All AEs (SAEs or non-serious AEs), including those associated with SARS-CoV-2 infection, must be collected continuously during the treatment period.
Concomitant Medications	Continuously		Record at each visit.

[redacted]

Table 2-2: On Study Treatment Procedural Outline (CA224098)

Procedure	C1D1[a] (Cycle Duration = 4 weeks)	C2D1 and D1 of Each Subsequent Cycle (± 3 days)	Notes:[b]
Laboratory Tests			
Pregnancy Test (WOCBP)	X*	X^	Serum or urine (minimum sensitivity equivalent units 25 IU/L or equivalent units of HCG); a negative pregnancy test should be documented within 1 day prior to administration of first dose of study treatment. [redacted] *Pregnancy test not required to be repeated on C1D1 if completed within 24 hours of first dose (during screening). ^For subsequent cycles, a negative pregnancy test should be documented within 3 days prior to dosing.
Clinical Laboratory Assessments[c]	X	X	Laboratory testing should be performed within 3 days prior to each dose. For the first treatment visit, labs need not be repeated if they were performed within 3 days and the results are available and have been reviewed for eligibility. Refer to Section 9.4.4 for the list of laboratory tests to be conducted.
[redacted]			

Table 2-2: On Study Treatment Procedural Outline (CA224098)

Procedure	C1D1[a] (Cycle Duration = 4 weeks)	C2D1 and D1 of Each Subsequent Cycle (± 3 days)	Notes:[b]
Efficacy Surveillance			
Body Imaging	See Notes		Contrast-enhanced CT of the chest, abdomen, pelvis, and all other suspected sites of disease should occur every 12 weeks (± 7 days) from randomization for the first 2 years and every 26 weeks (± 14 days) beyond the Week 108 imaging time point thereafter until investigator assessed [redacted] In case of suspected lesions in the extremities, contrast-enhanced MRI can be substituted for contrast-enhanced CT. For head and neck mucosal melanomas, contrast-enhanced MRI of the head and neck is required at every time point for nodal surveillance. Please refer to Appendix 9 for Germany-specific imaging language.
Brain Imaging	See Notes		Participants with a history of brain metastasis or symptoms should have a surveillance MRI (without and with contrast) approximately every 12 weeks ± 7 days from randomization for the first 2 years and every 26 weeks (± 14 days) beyond the Week 108 imaging time point thereafter until investigator assessed [redacted] or sooner if clinically indicated. Participants without history of brain metastases should have MRI if clinically indicated. See Section 9.1.2 for further details.

Table 2-2: On Study Treatment Procedural Outline (CA224098)

Procedure	C1D1[a] (Cycle Duration = 4 weeks)	C2D1 and D1 of Each Subsequent Cycle (± 3 days)	Notes:[b]
Ultrasound of Region(s) relevant to the Participant's Tumor Resection	See Notes		For participants without CLND, active surveillance using ultrasound of region(s) relevant to the participant's tumor resection must occur every 12 weeks (± 7 days) from randomization for the first 2 years and every 26 weeks (± 14 days) beyond the Week 108 imaging time point thereafter until disease recurrence. Ultrasound is not required for head and neck mucosal participants. Ultrasound is optional for participants who have undergone CLND relevant to the tumor resection. Ultrasounds should not be submitted to the imaging vendor.

[redacted]

Table 2-2: On Study Treatment Procedural Outline (CA224098)

Procedure	C1D1[a] (Cycle Duration = 4 weeks)	C2D1 and D1 of Each Subsequent Cycle (± 3 days)	Notes:[b]
[redacted]			

Abbreviations: AE, adverse event; C, cycle; CLND, complete lymph node dissection; [redacted] D, day; eCOA, electronic clinical outcome assessments; ECOG, Eastern Cooperative Oncology Group; [redacted] HCG, human chorionic gonadotropin; IMAE, immune-mediated adverse event; IRT, interactive response technology; MRI, magnetic resonance imaging; [redacted] SAE, serious adverse event; [redacted] WOCBP, women of child-bearing potential.

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

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

[c] Screening assessments performed within 3 days of first dose are not required to be repeated at C1D1.

Table 2-3: Follow-up Assessments (CA224098)

Procedure	Follow-Up Visits 1 & 2[a]	Long-term Follow-up[b]	Notes:[c]
Safety Assessment			
Targeted Physical Examination, Vital Signs, and Performance Status	X		Include weight, blood pressure, heart rate, temperature, performance status.
AE and SAE Assessment	X* (see notes)	X* (see notes)	Record at each visit. All SAEs and non-serious AEs should be collected continuously during the treatment period and for a minimum of 135 days following discontinuation of study treatment. *Beyond 135 days from the last dose of study therapy, participants will be followed for drug-related AEs/SAEs until resolution, return to baseline, or event(s) is deemed irreversible, or until the participant is lost to follow-up, or withdraws study consent. For all confirmed or suspected SARS-CoV-2 infections, participants will be followed for all SAEs, non-serious AEs of special interest (as defined in Section 9.2.3), and all AEs (SAEs and non-serious AEs) 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. Please refer to Section 9.2, and Appendix 3 for further details regarding the collection and follow-up of AEs.
Concomitant Medications	X (see notes)	X (see notes)	All medications with a start date within 135 days of the last dose date of study drug are considered concomitant.
Laboratory Tests			
Pregnancy Test (WOCBP)	X		Serum or urine (minimum sensitivity equivalent units 25 IU/L or equivalent units of HCG). [redacted]

Table 2-3: Follow-up Assessments (CA224098)

Procedure	Follow-Up Visits 1 & 2[a]	Long-term Follow-up[b]	Notes:[c]
Clinical Laboratory Assessments	X (see notes)		To be performed at Follow-up Visit 1, repeat at Follow-up Visit 2 if study treatment-related toxicity persists. Refer to Section 9.4.4, Clinical Safety Laboratory Assessments for the list of laboratory tests. 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 drug related toxicities resolve, return to baseline, or are deemed irreversible.
Efficacy Surveillance			
Survival Status[b]	X	X (See Notes)	During Long-term Follow-up, participant survival status is assessed every 12 weeks (± 14 days) by either a clinic visit or telephone contact, and must include documentation of subsequent therapy. Participants will be followed until death, loss to follow-up, withdrawal of consent, conclusion of the study, [redacted]
Body Imaging	See Notes		Contrast-enhanced CT of the chest, abdomen, pelvis, and suspected sites of disease should occur every 12 weeks (± 7 days) for the first 2 years from randomization and every 26 weeks (± 14 days) beyond the Week 108 imaging time point until investigator assessed [redacted] In cases of suspected lesions of the extremities, contrast-enhanced MRI may be substituted for contrast-enhanced CT. For head and neck mucosal melanomas, contrast-enhanced MRI of head and neck is required at every time point for nodal surveillance. Please refer to Appendix 9 for Germany-specific imaging language.

Table 2-3: Follow-up Assessments (CA224098)

Procedure	Follow-Up Visits 1 & 2[a]	Long-term Follow-up[b]	Notes:[c]
Brain Imaging	See Notes		Participants with a history of brain metastasis or symptoms should have surveillance MRIs (without and with contrast) per standard of care (approximately every 12 weeks ± 7 days from randomization for the first 2 years and every 26 weeks (± 14 days) beyond the Week 108 imaging time point thereafter until disease recurrence) [redacted] or sooner if clinically indicated. See Section 9.1.2 for further details.
Ultrasound of Region(s) Relevant to the Participant's Tumor Resection	See Notes		For participants without CLND, active surveillance using ultrasound of region(s) relevant to the participant's tumor resection must occur every 12 weeks (± 7 days) from randomization for the first 2 years and every 26 weeks (± 14 days) beyond the Week 108 imaging time point thereafter until disease recurrence. Ultrasound is not required for head and neck mucosal participants. Ultrasound is optional for participants who have undergone CLND relevant to the tumor resection. Ultrasounds should not be submitted to the imaging vendor.

[redacted]

Table 2-3: Follow-up Assessments (CA224098)

Procedure	Follow-Up Visits 1 & 2[a]	Long-term Follow-up[b]	Notes:[c]
[redacted]			

Table 2-3: Follow-up Assessments (CA224098)

Procedure	Follow-Up Visits 1 & 2[a]	Long-term Follow-up[b]	Notes:[c]
[redacted]			

Abbreviations: AE(s), adverse event(s); BMS, Bristol-Myers Squibb; CLND, complete lymph node dissection; CT, computed tomography; [redacted] U, follow-up; HCG, human chorionic gonadotropin; MRI, magnetic resonance imaging; [redacted] SAE, serious adverse event; [redacted] WOCBP, women of child-bearing potential.

[a] Participants must be followed for at least 135 days after last dose of study treatment. Follow-Up Visit 1 should occur 30 days from the last dose (± 7 days) or can be performed on the date of discontinuation if that date is greater than 30 days after last dose. Follow-up Visit 2 occurs approximately 135 days (± 7 days) from last dose of study medication if date of discontinuation is < 135 days after last dose. If date of discontinuation is ≥ 135 days after the last dose and the timing of Follow-up 2 overlaps with Follow-up 1, then only one follow-up visit (Follow-up 1) needs to be completed. Follow-up visits must be conducted in person.

[b] Long-Term Follow-up visits to occur [redacted] (± 14 days) from the last Follow-up visit completed. If Follow-up visit is not completed, then Survival visit should be based off the off-treatment date. Visit may be conducted in clinic or by telephone. BMS may request that survival data be collected on all treated participants outside of [redacted]. 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.

[c] 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 regulation.

3 INTRODUCTION

Study CA224098 is a Phase 3, randomized, double-blind study of nivolumab + relatlimab (nivo + rela) fixed dose combination (FDC) compared with nivolumab monotherapy in completely resected Stage III-IV melanoma. This study will generate efficacy and safety data for the patient population with Stage IIIA (> 1 mm tumor in lymph node)/B/C/D or Stage IV (no evidence of disease [NED]) melanoma following complete resection of their lesion(s). The study will allow for direct comparison of the clinical benefits, as measured by the primary endpoint of recurrence free survival (RFS), provided by nivo + rela FDC compared with nivolumab monotherapy administered over a treatment duration of 12 months.

Melanoma may modulate and evade the host immune response through a number of mechanisms, including down regulation of tumor-specific antigen expression and presentation, secretion of anti-inflammatory cytokines, and upregulation of inhibitory ligands. Immune checkpoint blockade has recently demonstrated clinical efficacy in several cancer types, including melanoma, hepatocellular carcinoma (HCC), gastric cancer, non-small cell lung cancer (NSCLC), and hematologic malignancies.[1,2,3]

Nivolumab is a fully human, immunoglobulin G4 (IgG4 [kappa]) isotype monoclonal antibody that binds the programmed death-ligand 1 (PD-1) receptor on activated immune cells and disrupts engagement of the receptor with its ligands PD-L1 (B7-H1/CD274) and programmed death-ligand 2 (PD-L2) (B7-DC/CD273), thereby abrogating inhibitory signals and augmenting the host anti-tumor response. In early clinical trials, nivolumab has demonstrated activity in several tumor types, including melanoma, renal cell cancer (RCC), and NSCLC.[4] Furthermore, adjuvant nivolumab after complete resection of Stage III-IV melanoma has become a standard of care.

Relatlimab is a fully human lymphocyte activation gene 3 (LAG-3) specific antibody that was isolated following immunization of transgenic mice expressing human immunoglobulin (Ig) genes. Relatlimab binds to LAG-3 receptors expressed on T-cells with high affinity and prevents binding of this receptor to cells bearing its ligands, such as major histocompatibility complex (MHC) Class II[5] which is the peptide antigen presentation molecule recognized by cluster of differentiation 4 (CD4)+ T cells and fibrinogen-like protein 1 (FGL-1)[6], which is upregulated in a variety of human solid tumors. Relatlimab binding inhibits the negative regulatory function of LAG-3 mediated through its interaction with ligands in vitro; and elevated plasma levels of FGL-1 are correlated with poor prognosis.[6] FGL-1 was shown to be capable of delivering an inhibitory signal into T cells upon binding to the LAG-3 receptor and has been implicated as having a suppressive effect on anti-tumor immunity that is dependent on LAG-3.[7] Preclinical evidence suggests that the FGL-1-LAG-3 pathway may be a previously unknown immune evasion mechanism limiting responses to current cancer immunotherapies, including PD-1 pathway blockade.[6] By blocking the inhibitory LAG-3 signaling pathway, relatlimab enhances the anti-tumor immune response and, thus, has the potential to inhibit the growth of multiple malignancies when administered in combination with other therapeutic immuno-oncology (IO) agents. Dual

checkpoint inhibition with nivolumab and relatlimab results in enhanced T-cell effector function that is greater than the effects of either antibody alone in murine syngeneic tumor models.[8]

3.1 Study Rationale

Surgical resection followed by 1 year of adjuvant therapy is currently considered standard of care for Stage III-IV resectable melanoma. However, there remains an unmet need to improve RFS while maintaining favorable safety profile for these patients. The clinical benefit observed with nivo + rela FDC in patients with untreated metastatic or unresectable melanoma in the CA224047 Phase 2/3 study supports the rationale of evaluating nivo + rela FDC in patients with resectable melanoma.

Targeting LAG-3, which is involved in the immune checkpoint pathway, is a novel approach that may further overcome immune evasion mechanisms. LAG-3 (CD223) is a checkpoint receptor and expressed on several immune cell types including activated CD4+ and CD8+ T cells, memory T cells, regulatory lymphocytes, and natural killer cells.[5] Activation of the LAG-3 pathway occurs when LAG-3 interacts with its ligands, such as MHC Class II or other emerging ligands (eg, FGL-1), which triggers inhibitory activity that reduces the function of effector T cells.[5,6]

LAG-3 is often expressed on chronically exhausted T-cells and is frequently co-expressed with PD-1 on tolerized tumor infiltrating lymphocytes (TILs) across many tumor types.[9,10,11] Increased expression of LAG-3 on TILs, especially in the context of PD-1 expression, further promotes T cell exhaustion, leading to an impaired ability to attack tumor cells and an increased potential for tumor growth.[5,12] Preclinical studies indicate that inhibition of the LAG-3 pathway may restore effector function of T cells, promoting proinflammatory cytokine signaling, and ultimately, an anti-tumor response. The combination of LAG-3 and PD-1 inhibition demonstrated enhanced anti-tumor activity by targeting independent pathways with distinct functions.[5]

Relatlimab is a blocking antibody specific to the LAG-3 receptor. Relatlimab is being investigated in different indications and lines of therapies in combination with nivolumab. In the CA224020 Phase 1/2a study, the combination of nivolumab and relatlimab demonstrated tolerability, and preliminary clinical activity in advanced melanoma participants that had been previously treated with anti-PD-1/PD-L1 therapy.[8,13,14] In the CA224047 Phase 2/3 study, nivo + rela FDC demonstrated clinical benefit measured by progression-free survival (PFS) in patients with previously untreated metastatic or unresectable melanoma. PFS at 24 months was 38.5% for the nivo + rela FDC group versus 29% for the nivolumab monotherapy group.[15]

3.1.1 Research Hypothesis

Treatment with systemically administered nivo + rela FDC when compared with nivolumab will result in improved RFS in participants with completely resected Stage III-IV melanoma.

3.2 Background

Melanoma accounts for less than 5% of all skin cancers; however, it causes the greatest number of skin cancer–related deaths worldwide.[16] In 2020, it is estimated that there will be 100,350 new cases of melanoma and 6,850 deaths due to melanoma.[17]

Early melanoma detection followed by surgical excision is usually curative. In contrast, advanced melanoma frequently metastasizes to the lung, brain, or liver, and usually has poor prognosis.

The 5-year melanoma-specific survival (MSS) rate according to Stage III subgroups ranges from 93% in patients with Stage IIIA disease (1-3 clinically occult, tumor-involved sentinel lymph nodes [N1a or N2a] and T1a, T1b, or T2a primaries) to 32% for those with Stage IIID disease (patients with a thick and ulcerated primary [T4b] and either ≥ 4 tumor-involved regional nodes [N3a or N3b] or ≥ 2 tumor-involved nodes and evidence of microsatellite, satellite, or in-transit metastases [N3c]). Stage IIIB and Stage IIIC had 5-year MSS rates of 83% and 69%, respectively. For patients with > 1 mm of tumor burden in the lymph node, the 5-year MSS is 72% as compared to those with tumor burden in the lymph node of ≤ 1 mm with 5-year MSS of 91%.[18,19]

Cancer immunotherapies and B-RAF proto-oncogene (BRAF)/mitogen-activated protein kinase (MEK) inhibitors have played a role in the Stage III/IV adjuvant setting; however opportunities exist to continue enhancing clinical outcomes.

A potential mechanism of resistance to anti-PD-1 therapies is the presence of alternative checkpoint receptors that may be upregulated and further impede the function of effector T cells within the tumor microenvironment. Thus, targeting such additional checkpoint pathways may provide a therapeutic means to delay recurrence in melanoma patients who may rely on such checkpoint pathways to suppress the anti-tumor immune response. LAG-3 is one such checkpoint and is a potential cancer immunotherapeutic target due to its negative regulatory role on T cells.

The disease course for melanoma has fundamentally changed with the introduction of immunotherapies targeting the cytotoxic T lymphocyte associated antigen 4 (CTLA-4) and PD-1 checkpoints as well as BRAF and MEK inhibitors. Such agents have dramatically improved outcome for patients with metastatic melanoma; however, their role in the adjuvant setting continues to be evaluated. Studies have demonstrated that these agents enhance survival in the adjuvant setting albeit with waning durability in the long term. Therefore, novel immunotherapy combinations could address this long-term unmet need.

RFS rates at 1 year for adjuvant checkpoint inhibitor use range from 60.8% with ipilimumab (IPI) to 70.5% with nivolumab and 75.4% with pembrolizumab, yet there is a decline to 45% to 58% at 3 years, irrespective of which checkpoint inhibitor was used.[20,21,22] Similarly, adjuvant therapy with BRAF and MEK inhibitor combinations yield 3- and 4-year RFS rates of 58% and 54%, respectively compared to RFS rates of 88% at 1 year and 67% at 2 years with combination Dabrafenib/Trametinib treatment.[23,24]

Additional data from key studies are provided in Table 3.2-1.

Table 3.2-1: Data Comparison of Adjuvant Trials

Patient Population	**CM238 Completely resected Stage IIIB/C or IV melanoma**[20]		**COMBI-AD Completely resected, BRAF v600 E/K-positive Stage IIIA/B/C Melanoma**[24]		**KN054 Completely resected Stage IIIA/B/C Melanoma**[22]		**CM915 Completely resected Stage IIIB/C/D or IV Melanoma**[25]	
Treatment	Nivo	Ipi	Dab/ Tram	Placebo	Pembro	Placebo	Nivo/Ipi	Nivo
N	453	453	438	432	514	505	920	924
RFS HR	0.65 (97.56% CI 0.51-0.83), P < 0.0001		0.47 (95% CI 0.39-0.58), P < 0.001		0.57 (98.4% CI 0.43-0.74), P < 0.001		0.92 (97.295% CI, 0.77–1.09); P = 0.269	
1-year RFS rate (%)	71	61	88	56	75	61	N/A	N/A
18-months RFS rate (%)	66	53	N/A	N/A	71.4	53.2	N/A	N/A
2-years RFS rate (%)	N/A	N/A	N/A	N/A	N/A	N/A	64.6%	63.2%
3-years OS rate (%)	N/A	N/A	86	77	N/A	N/A	N/A	N/A
Grade 3-5 TRAEs (%)	14	46	31	5	15	3	33	13
DC rate due to AEs (%)	10	43	26	3	14	2	34	12

Abbreviations: AE, adverse event; BRAF, B-RAF proto-oncogene; CI, confidence interval; Dab, dabrafenib; DC, discontinuation; HR, hazard ratio; Ipi, ipilimumab; IV, intravenous; N/A, not applicable; Nivo, nivolumab; OS, overall survival; Pembro, pembrolizumab; RFS, recurrence-free survival; TRAE, treatment-related adverse events; Tram, trametinib.

The safety profiles of therapies in the adjuvant setting remains an important consideration. For instance, in the COMBI-AD trial, 26% of patients had adverse events (AEs) leading to treatment discontinuation, 38% had AEs leading to a dose reduction, and 66% had AEs leading to a dose interruption.[24] It is important to closely monitor for Grade 3 and 4 toxicities, such as colitis, rash, pneumonitis, endocrinopathies, and hepatitis with immune checkpoint inhibitors. Additional safety information is provided in Table 3.2-1.

Targeting LAG-3 should present a valuable mechanism to improve RFS.

3.2.1 Nivolumab Combined with Relatlimab Preclinical Activity

LAG-3 has been shown to be expressed in TILs of several tumor types, including melanoma, HCC, 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.[7,8] 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 *Lag-3*$^{-/-}$*Pdcd1*$^{-/-}$ double knockout mice revealed a cooperative requirement for LAG-3 and PD-1 in maintaining immune homeostasis.

[redacted]

3.2.2 Nivolumab Combined with Relatlimab 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.[8]

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]

Additionally, in Parts D1, D2, [redacted] 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 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 (ORR) of 11.8% (22/186 response evaluable) and a meaningful number of complete responses (8) and durability of these responses. [redacted]

CA224047, a global, double-blind, randomized, Phase 2/3 study comparing a fixed-dose combination (FDC) of nivolumab 480 mg + relatlimab 160 mg 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 PFS by BICR with nivo + rela FDC (3:1) compared to nivolumab monotherapy in all randomized subjects (N = 714) (PFS hazard ratio = 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 nivo + rela FDC 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 nivo + rela FDC (3:1) and nivo monotherapy, respectively. The PFS benefit of nivo + rela FDC (3:1) was consistent across key prespecified subgroups.[30,31] 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.[30,31]

Due to the statistical non significance of the secondary endpoint of OS, ORR was not formally tested per the statistical testing hierarchy; however, clinically meaningful numerical differences were observed with the nivolumab + relatlimab FDC arm over nivolumab monotherapy (43.1% vs 32.6%).[32]

3.2.3 Nivolumab Clinical Activity

Nivolumab has demonstrated durable responses exceeding 6 months as monotherapy in several tumor types, including NSCLC, melanoma, RCC, classical Hodgkin's lymphoma (cHL), SCLC, gastric cancer, SCCHN, urothelial cancer, 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 USPI and SmPC.

3.2.4 Relatlimab Mechanism of Action

Relatlimab is a fully human antibody specific for human LAG-3 that was isolated from immunized transgenic mice expressing human Ig genes.[8] 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 [redacted]

3.2.5 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 PD-1 CD279 cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes. Binding of PD-1 to its ligands, PD-L1 and PD-L2, results in the down-regulation of lymphocyte activation. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens. Nivolumab is expressed in Chinese hamster ovary (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).

3.2.6 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, [redacted] tested in every 2 week (Q2W) and Q4W dosing intervals. [redacted] Part C included expansion cohorts with multiple tumor types and Parts D [redacted] included advanced melanoma participants (1L and progressed on prior-PD-1 therapy). [redacted]

[redacted]

[redacted]

Troponin is a highly sensitive non-specific indicator of myocardial injury. Troponin is not typically monitored during treatment with immune checkpoint inhibitors due to uncertain value in preventing immune-related cardiac morbidity. [redacted] While myocarditis is a recognized risk with immune checkpoint inhibitors, routine troponin monitoring during treatment has not been recommended by clinical guidelines due to lack of demonstrated value in preventing morbidity or mortality. [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.[31] Refer to relatlimab + nivolumab FDC IB Section 5.5.2 for an updated safety analysis based on the clinical data cutoff date of 30-Jun-2021.[30]

3.3 Benefit/Risk Assessment

As described in Section 3.2.2, clinical activity was seen with the combination of nivolumab + relatlimab in multiple tumor types, including treatment naive and previously heavily treated tumors including previous anti-PD-1 therapy, in the CA224020 study.[8] The clinical efficacy of the combination was further confirmed in study CA224047, a global, double-blind Phase 2/3 randomized controlled trial that demonstrated a statistically significant and clinically meaningful PFS benefit of nivolumab + relatlimab FDC Q4W compared to nivolumab 480 mg Q4W,[31] as well as clinically meaningful improvement in OS and ORR, although the OS result was not statistically significant and ORR could not be formally tested.[32]

The combination of nivolumab and relatlimab has shown well-defined toxicity profiles based on a safety database comprised of participants treated with either relatlimab monotherapy or as a combination across multiple tumor types. [redacted] The most frequent drug-related AEs included fatigue, decreased appetite, pruritus, diarrhea, rash, rash maculo-papular, anemia, arthralgia, increased lipase, nausea, dry mouth, asthenia, hypothyroidism, hyperthyroidism, cough, pyrexia, increased alanine aminotransferase, and increased aspartate aminotransferase.[8] Immune-mediated AEs (IMAEs) seen with nivolumab in combination with relatlimab appear consistent with those seen with other immunotherapy agents, and can potentially include pneumonitis, colitis, hepatitis, nephritis, endocrinopathy, neurologic, and skin AEs. In combination with nivolumab, the frequency, severity, and reversibility of IMAEs appear consistent with the mechanisms of action of either drug. The majority of all drug-related AEs and IMAEs were reversible or manageable by withholding study intervention administration, providing standard medical care, and/or following IMAE management algorithms (see Appendix 5). Most immune-mediated study intervention-related endocrinopathies will require life-long management by hormone replacement therapies. The overall safety profile of nivolumab + relatlimab across these studies remains unchanged and manageable with established management guidelines (including myocarditis cases). [redacted]

Furthermore, nivolumab 480 mg + relatlimab 160 mg FDC (3:1) administered Q4W was confirmed to be well tolerated with a manageable safety profile in 355 1L advanced melanoma participants treated in the CA224047 study. There were no unexpected safety signals from this combination.[31] [redacted]

Safety results to date indicate that sequential, co-administration, and the FDC of nivolumab + relatlimab administration have similar manageable safety profiles that are consistent with the

mechanisms of action of each agent, nivolumab and relatlimab. No new types of clinically important events have been identified.[8,30]

Given the safety profile of relatlimab as monotherapy and combination therapy observed to-date,[8] and the positive benefit-risk of the pivotal Phase 2/3 study of nivo + rela FDC (3:1) demonstrated in participants with previously untreated metastatic or unresectable advanced melanoma,[31] and the significant unmet medical need in adjuvant treatment for Stage III-IV resectable melanoma population, the continuing evaluation of nivo + rela FDC is justified for the patient population in this protocol.

Investigators and the Sponsor will utilize continuous safety assessments to determine whether additional safety measures or termination from the study is required at any time. In addition, AEs and SAEs will be reviewed on an ongoing basis by the Sponsor's Medical Monitor/designee and Worldwide Patient Safety (WS) representatives to monitor for any safety signals or trends. As relatlimab is an experimental agent, it is possible that unforeseen, unknown, or unanticipated reactions may occur; however, data shows that nivo + rela is safe and tolerable at 480 mg nivolumab + 160 mg relatlimab Q4W using FDC product in other studies.

3.3.1 Risk Assessment

Table 3.3.1-1: Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Interventions		
Immune-mediated AEs (eg, colitis diarrhea/colitis, pneumonitis, hepatitis, nephritis, endocrinopathy, rash, neurologic, AEs)	FDC (BMS-986213) IB	Recommended IMAE management algorithms are included in Appendix 5 or as per institutional protocol/investigator discretion
Potential Infusion Related Reaction	FDC (BMS-986213) IB	Recommended management algorithms are included in Appendix 5 or as per institutional protocol/ investigator discretion
Dermatologic AEs	Nivolumab IB	Recommended management algorithms are included Appendix 5 or as per institutional protocol/ investigator discretion
Cardiovascular AEs (ie, myocarditis, troponin elevation)	FDC (BMS-986213) IB	Management of Myocarditis per AE Management Algorithm in Appendix 5 or as per institutional protocol/ investigator discretion.
Hemorrhage AE (eg, epistaxis, gingival bleeding, GI blood loss)	Relatlimab IB	Monitor clinical signs/symptoms/ CBC and coagulation parameters. Management as per institutional protocol/investigator
Opportunistic Infections due to Immunosuppression	FDC (BMS-986213) IB	Monitor signs/symptoms, may require additional laboratory tests. Management as per institutional protocol/investigator
Potential developmental toxicity	FDC (BMS-986213) IB	Exclusion criteria, pregnancy testing, contraception per protocol, as per Section 6.1, 4) and Appendix 4.
Study Procedures		
Tumor Biopsy (eg, pain, infection)	Not applicable	Per institutional protocol/ investigator discretion.
Phlebotomy (eg, pain, ecchymosis, bleeding, syncope)	Not applicable	Per institutional protocol/ investigator discretion.
MRI	Not applicable	Management per institutional protocol/investigator discretion.
CT	Not applicable	Management per institutional protocol/investigator discretion.
Ultrasound	Not applicable	Management per institutional protocol/investigator discretion.

Table 3.3.1-1: Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Other (if applicable)		
Allergy to contrast agent (eg, reaction to anaphylaxis)	Not applicable	Prophylaxis and/or treatment per institutional protocol/ investigator discretion

Abbreviations: AE, adverse event; CBC, complete blood count; CT, computed tomography; FDC, fixed dose combination; GI, gastrointestinal; IB, investigator brochure; IMAE, immune-mediated adverse events; MRI, magnetic resonance imaging.

3.3.2 Benefit Assessment

This study investigates if the adjuvant use of systemic therapy of nivo + rela FDC will improve recurrence free survival (RFS) for Stage III-IV completely resected melanoma participants with no evidence of disease. Currently, nivolumab monotherapy is an approved treatment for adjuvant melanoma patients in many countries. While nivo + rela FDC provided PFS benefit for the treatment of untreated metastatic or unresectable melanoma, it is not yet approved for any indication.

Despite the availability of effective adjuvant therapies, there is an unmet need to provide safe and effective adjuvant systemic therapy that offers additional clinical benefit in RFS in this patient population. It is unknown if nivo + rela FDC will improve RFS compared to nivolumab monotherapy. Although benefits are hypothesized, actual clinical benefits to patients with Stage III or Stage IV resectable melanoma have not been established yet. Participation in this study may help offer new therapies for advanced resectable melanoma patients and establish the clinical benefits of the combination therapy.

Participants enrolled in this study will be randomized to either the nivo + rela FDC or nivolumab monotherapy. Participants will have an equal chance of being randomized to the nivo + rela FDC therapy or the standard of care nivolumab monotherapy.

3.3.3 Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risk to participants in this study, the potential risks identified in association with nivo + rela FDC are justified by the anticipated benefits that may be afforded to participants with resectable melanoma.

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

If such evaluation suggests that the risk/benefit profile of the study has become unfavorable to participants, the Sponsor will pause enrollment and/or treatment until further evaluation of data,

and interaction with the appropriate Health Authority(ies) can take place on potential actions. Such actions may include (but are not limited to) study continuation, substantial amendment, or termination of the study.

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Primary	
• To compare the efficacy, as measured by RFS, provided by nivo + rela FDC vs nivolumab monotherapy in participants with completely resected Stage III/IV NED melanoma.	• RFS time as assessed by the investigator. RFS is defined as the time between the date of randomization and the first date of documented recurrence [redacted] or death due to any cause, whichever occurs first.
Key Secondary	
• To compare the OS provided by nivo + rela FDC vs nivolumab monotherapy in participants with completely resected Stage III/IV NED melanoma.	• OS is defined as the time between the date of randomization and the date of death due to any cause.
Other Secondary	
• To assess the efficacy, as measured by DMFS, provided by nivo + rela FDC vs nivolumab monotherapy in participants with completely resected Stage III/IVA/IVB NED melanoma.	• DMFS, by investigator, is defined as the time between the date of randomization and the date of first distant metastasis or date of death due to any cause, whichever occurs first.
• To assess safety and toxicity of nivo + rela FDC vs nivolumab monotherapy in participants with completely resected Stage III/IV NED melanoma.	• Incidence and severity of AE, SAEs, AEs leading to DC, IMAEs, drug-related AEs, deaths, laboratory abnormalities, and other select AEs.
• To evaluate investigator-assessed outcomes on next-line systemic therapies.	• PFS2 defined as time from randomization to second recurrence/objective disease progression on next-line systemic therapy per investigator, or death from any cause, whichever occurs first.
Exploratory	
[redacted]	

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
[redacted]	[redacted]

Abbreviations: AE(s), adverse event(s); [redacted] DC, discontinuation; DMFS, distant metastasis-free survival; [redacted] FDC, fixed dose combination; [redacted] NED, no evidence of disease; nivo, nivolumab; [redacted] PFS2, progression-free survival 2; [redacted] RFS, recurrence-free survival; OS, overall survival; rela, relatlimab; SAE, serious adverse event; [redacted]

a [redacted]

5 STUDY DESIGN

5.1 Overall Design

This is a Phase 3, randomized, double-blind study of nivo + rela FDC compared with nivolumab monotherapy in participants (≥ 12 years of age) with completely resected Stage IIIA (> 1 mm tumor in lymph node)/B/C/D or Stage IV NED melanoma by American Joint Committee on Cancer version 8 (AJCC v8). Efficacy of nivo + rela FDC, as measured by RFS time (as assessed by the investigator), will be compared to nivolumab monotherapy.

Participants will be randomized 1:1 to receive treatment with one of the following:

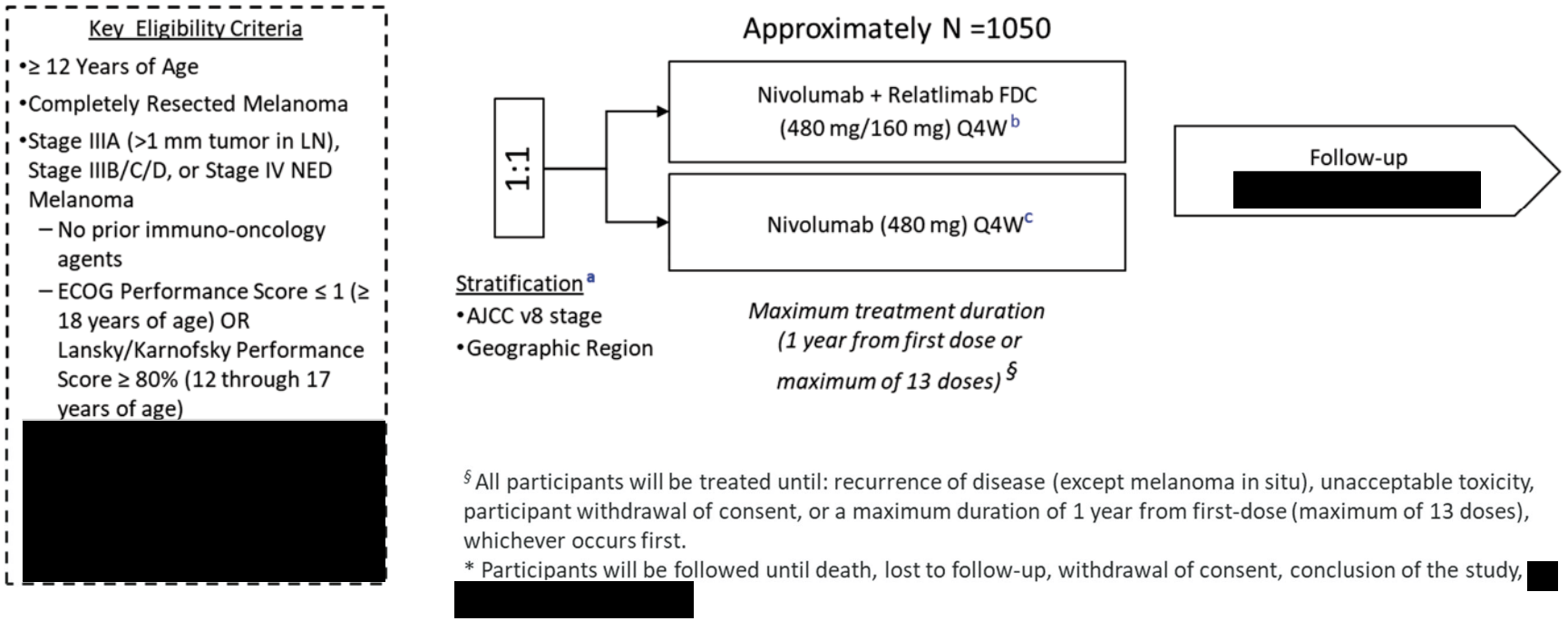
- Nivo + rela FDC dosing:
  - ≥ 18 years of age **OR** ≥ 12 years to < 18 years of age and ≥ 40 kg: nivolumab 480 mg and relatlimab 160 mg IV every 4 weeks (Q4W)
  - ≥ 12 years to < 18 years of age and < 40 kg: [redacted]
- Nivolumab dosing:
  - ≥ 18 years of age **OR** ≥ 12 years to < 18 years of age and ≥ 40 kg: nivolumab 480 mg IV Q4W
  - ≥ 12 years to < 18 years of age and < 40 kg: nivolumab 6 mg/kg IV Q4W

Participants will be stratified by AJCC v8 stage (Appendix 7) and geographic region. All participants will be treated until: recurrence of disease [redacted], unacceptable toxicity, participant withdrawal of consent, or a maximum of 1 year of treatment from first dose (maximum of 13 doses), whichever occurs first.

This study will consist of 3 phases: screening, treatment, and follow-up. For a complete list of study required procedures, please refer to Section 2.

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

Figure 5.1-1: Study Design Schema



Abbreviations: AJCC v8, American Joint Committee on Cancer version 8; ECOG, Eastern Cooperative Oncology Group; FDC, fixed dose combination; [redacted] IV, intravenous; LN, lymph node; NED, no evidence of disease; ROW, rest of the world; Q4W, every 4 weeks

[a] Stratification:

- AJCC v8: Stages IIIA/IIIB, Stage IIIC, Stages IIID/IV (including all participants with mucosal melanoma, Stage III, Stage IVA, Stage IVB, and Stage IVC)
- Geographic Regions: USA/Canada/Australia, Europe, ROW

[b] Nivo + rela FDC dosing:

- ≥ 18 years of age **OR** ≥ 12 years to < 18 years of age and ≥ 40 kg: nivolumab 480 mg and relatlimab 160 mg IV Q4W.
- ≥ 12 years to < 18 years of age and < 40 kg: [redacted]

[c] Nivolumab dosing:

- ≥ 18 years of age **OR** ≥ 12 years to < 18 years of age and ≥ 40 kg: nivolumab 480 mg IV Q4W.
- ≥ 12 years to < 18 years of age and < 40 kg: nivolumab 6 mg/kg IV Q4W.

5.1.1 Data Monitoring Committee and Other Committees

When required, adjudicated events will be submitted to the Data Monitoring Committee (DMC) and Health Authorities for review on a specified timeframe in accordance with the adjudication documentation.

A DMC will be established to provide oversight of safety and efficacy considerations and to provide advice to the Sponsor regarding actions the committee deems necessary for the continued protection of participants enrolled in the study. The DMC will be charged with assessing such actions in light of an acceptable benefit/risk profile for nivo + rela FDC. The DMC will act in an advisory capacity to BMS and will monitor participant safety and evaluate the available efficacy data for the study. The oncology therapeutic area of BMS has primary responsibility for design and conduct of the study.

Details of the DMC responsibilities and procedures will be outlined in the DMC charter.

A Study Steering Committee (SSC), consisting of Investigators and personnel members representing the Sponsor of the study, will be established to obtain scientific guidance and advice for the protocol and conduct of the study. Details of the SSC responsibilities and procedures will be specified in the SSC charter.

5.2 Number of Participants

Approximately 1,050 participants are expected to be randomized to the following treatment arms:

- Nivo + rela FDC (n = 525)
- Nivolumab monotherapy (n = 525)

See Section 10.2 for sample size determination.

The randomization will be stratified by the following stratification factors:

- Geographic region (USA/Canada/Australia vs Europe vs ROW)
- American Joint Committee on Cancer (AJCC v8) Stage IIIA/IIIB vs Stage IIIC vs Stage IIID/IV (including all participants with mucosal melanoma, Stage III, Stage IVA, Stage IVB, and Stage IVC - see Appendix 8)

5.3 End of Study Definition

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

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

A participant is considered to have completed the study if he/she has died, is lost to follow-up, has withdrawn consent, the study has concluded, the last visit completed, or has been [redacted]

5.4 Scientific Rationale for Study Design

5.4.1 Participant Input Into Study Design

BMS may approach advocacy groups and other organizations to discuss key details of the study. Those suggestions may be implemented into the study design, at the determination of the sponsor.

5.4.2 Rationale for Use of Nivolumab + Relatlimab Fixed Dose Combination

The rationale for combining a LAG-3 inhibitor and an anti-PD-1/PD-L1 agent is based on the potential role of LAG-3 in T-cell exhaustion and anti-PD-1 resistance.[10] Relatlimab binds to LAG-3 receptors with high affinity and blocks its interaction with ligands such as major histocompatibility complex (MHC) Class II on antigen presenting cells. Nivolumab binds to PD-1 receptors with high affinity and blocks its interaction with its ligands, PD-L1 and PD-L2. LAG-3 and PD-1 are immune-checkpoint receptors that act synergistically on effector T cells, leading to the development of T-cell dysfunction and impaired cytotoxic function. Combined nivolumab and relatlimab mediated inhibition enables T-cell activation and restores effector function of T cells, that is greater than the effects of either antibody alone, leading to the initiation of an improved immune response and promoting tumor cell death.

The central hypothesis is that dual LAG-3 and PD-1 checkpoint blockade has the potential to offer superior efficacy compared with single agent anti-PD-1 therapy in the immunotherapy-naive treatment setting, as well as to provide meaningful efficacy to patients who experienced disease progression during anti-PD-1 therapy. The mechanism of action for both agents and preclinical data support the potential for producing clinical benefit. See Section 3.2 for more details on the mechanism of action and preclinical data of relatlimab and nivolumab. Preliminary data from a Phase 1/2a study of nivolumab (anti-PD-1) and relatlimab (anti-LAG-3) in combination showed promising clinical activity in participants with previously treated recurrent or metastatic melanoma, with a safety profile similar to nivolumab monotherapy. In the CA224047 Phase 2/3 study, nivo + rela FDC demonstrated clinical benefit measured by PFS in patients with previously untreated metastatic or unresectable melanoma. The FDC was well-tolerated and there were no new safety signals reported.

The FDC product contains nivolumab and relatlimab in protein-mass ratio 1:3 in a single vial. The FDC will be administered via intravenous (IV) infusion over approximately 30 minutes. Key advantages of a FDC are as follows:

- Patients benefit from reduced infusion time and less time in the clinic and/or doctor's office
- Increased ease of administration

- Pharmacists require less time in preparation of the intravenous solution to be administered to the patient
- Reduces potential error for medication preparation and administration

5.4.3 Rationale for Choice of Comparator

In the adjuvant Stage III/IV resected melanoma setting, nivolumab is an established standard of care that is recognized in guidelines globally with positive recommendation ratings. In CheckMate-238, nivolumab demonstrated clinical benefit with an acceptable safety profile in the patient populations (Stage IIIA with > 1 mm tumor in lymph node was not included) that are being evaluated in this study.

CheckMate-238 randomly assigned patients with resected Stage IIIB, IIIC, or IV disease to receive nivolumab vs ipilimumab. Patients' diseases were categorized by the AJCC v7, and all patients underwent resection and lymph node dissection. The 12-month RFS was 70.5% in the nivolumab group vs 60.8% in the ipilimumab group. At 24 months, RFS was 62.6% in the nivolumab group vs 50.2% in the ipilimumab arm. This benefit was found regardless of stage, PD-L1 status, or BRAF status. Treatment was better tolerated in the nivolumab group, with 14.4% of patients experiencing Grade 3 or 4 toxicity compared with 45.9% in the ipilimumab group. On the basis of the results of CheckMate 238, the use of ipilimumab is no longer recommended in the adjuvant setting given the superiority of nivolumab coupled with less toxicity.[20]

Based on the available data and given the fact that nivolumab is approved for adjuvant treatment of patients with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection, nivolumab is deemed an appropriate clinical comparator.

5.4.4 Rationale for Choice of Primary Endpoint

Recurrence free survival (RFS) is a validated clinical endpoint and is defined as the time from randomization until first recurrence (loco-regional or distant metastasis) or death due to any cause, whichever was observed first. Treatment options that are clinically active are increasingly available to patients with resected Stage III/IV adjuvant melanoma. These options have demonstrated a RFS improvement and have subsequently been granted regulatory approvals.

Overall survival (OS) is often used as the primary endpoint in oncology clinical trials. However, OS, although clinically meaningful, has the disadvantages of requiring extended follow-up and of being confounded by subsequent lines of treatment. An endpoint that is reached more rapidly could potentially expedite decisions on efficacy.

Based on the available data, a RFS improvement compared with an established standard of care would demonstrate a potentially new combination in the resected Stage III/IV adjuvant melanoma setting.

5.4.4.1 Rationale for Choice of Stratification Factors

In order to minimize the potential for imbalances across treatment arms, there will be 2 stratification factors utilized in this trial: AJCC v8 - Melanoma Stage IIIA/IIIB vs Stage IIIC vs

Stage IIID/IV (including all participants with mucosal melanoma, Stage III, Stage IVA, Stage IVB, and Stage IVC) and geographic region (USA/Canada/Australia vs Europe vs ROW).

Prognostic implications of AJCC v8 staging are well established. There is a continued need to move beyond histopathologic and clinical criteria for risk stratification.

Geographic region (USA/Canada/Australia vs Europe vs ROW): Differences in patient populations and clinical practice patterns in the different regions are well known and can impact outcomes. Region has been included as a stratification factor to control for potential differences in patient populations and different approaches to clinical practice in the different regions. ROW will include Central America, Latin America, and China.

5.4.5 Rationale for Blinding

The study will be double-blinded in order to:

- Minimize bias including bias arising from differences in thresholds for classification of recurrence between the arms which could subsequently affect treatment duration between the arms and have an impact on the primary endpoint of RFS
- Curtail bias in reporting, classification, and management of adverse events

As participants who progress will not require knowledge of which treatment arm they were assigned to for selection of subsequent therapies, blinding will be maintained even after disease progression. The Sponsor's central protocol team (including but not limited to clinical, statistics, and data management) will remain blinded to treatment assignment throughout the duration of the study until the primary endpoint of RFS has been reached or the decision is made to stop the study.

5.4.6 Rationale for Evaluation of [redacted]

Immune checkpoint signaling through immune inhibitory pathways such as the PD-1 axis to its ligand (PD-L1) and/or LAG-3 interaction with its ligands significantly dampens anti-tumor immune responses in different tumor types, including melanoma, NSCLC, and HCC. Unfortunately, not all patients respond to immune checkpoint blockade. Therefore, there is a continued medical need for a better understanding of factors [redacted] that predict benefit and recurrence free survival (RFS).

Data from CA224020 demonstrated that participants with LAG-3 expression are more likely to respond to treatment with nivo + rela FDC in those with advanced melanoma with prior anti-PD-1/PD-L1 treatment.[13,14] In the CA224047 study of patients with previously untreated metastatic or unresectable melanoma, longer PFS was observed in participants with LAG-3 expression treated with either nivolumab monotherapy or nivo + rela FDC. [redacted]

[redacted]

5.4.7 Rationale for Inclusion of Adolescent Participants

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.[34] 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 SEER Carcinoma Statistics Review).[35] 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.[36] Overall, the pediatric incidence rates (5.4 per 1 million children and adolescents in the US)[37] 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.[38] 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 as adults. The FDA approval in Mar-2022 of Opdualag™ for the treatment of adult and adolescent patients (12 years and older and weighing at least 40 kg) with unresectable or metastatic melanoma provides further justification for the inclusion of this population to cover an unmet need in future studies.

5.4.8 Rationale for Ultrasound in Disease Surveillance

Ultrasound is one of several imaging modalities (ie, CT scan, chest x-ray) and non-imaging modalities (ie, physical exam, blood tests) that have been applied in the follow-up of melanoma patients, all of which have had varying levels of effectiveness for detection of recurrence.[39] In a meta-analyses of 74 studies spanning 10,528 melanoma patients, ultrasonography was noted to have the greatest sensitivity, specificity, and diagnostic odds ratio for staging of regional lymph nodes as well as for surveillance of lymph node involvement as compared to CT, positron emission tomography (PET), and PET-CT.[40] National Comprehensive Cancer Network (NCCN) Guidelines

(V2.2021) include nodal basin ultrasound surveillance as preferred over complete lymph node dissection (CLND) in the management and primary treatment of Stage III melanoma patients.[39] In the Multicenter Selective Lymphadenectomy Trial (MSLT-II), it was determined that CLND did not lead to an increase in melanoma-specific survival in patients with sentinel lymph-node metastases compared to observation with ultrasonography.[41] In sum, the evidence and management guidelines to date suggest a role for ultrasonography in the follow-up melanoma patients and supports implementation of ultrasonography in this study for participants with SLND only.

5.4.9 Rationale for MRI Surveillance of Head and Neck Mucosal Melanomas

Though mucosal melanomas of the head and neck are rare tumors, they account for 55.4% of cases of mucosal melanomas. The majority of these arise in the nasal cavity followed by paranasal sinuses, oral cavity, and rarely the pharynx and larynx. The risk of lymph node involvement is significantly higher in oral mucosal melanomas, occurring in about 26% of all cases of oral mucosal melanomas, as compared to nasal mucosal melanomas. Given the likelihood of lymph node spread, metastatic regions of spread may include the brain, lungs, and liver. Imaging plays a vital role for the evaluation of these melanomas given the invasion into adjacent soft tissue and bone erosion. Enhanced imaging techniques such as MRI are particularly helpful in identifying sino-nasal melanomas as iso-attenuating or hyperattenuating mass-like lesions, especially in cases of bone involvement due to regional bone remodeling, erosive, or destructive changes.[42]

5.5 Justification for Dose

5.5.1 Justification for Fixed Dose Combination Dosing

The proposed dose of the FDC product is 480 mg nivolumab + 160 mg relatlimab Q4W. The dose and dosing regimen for this study was primarily based on the benefit/risk profile in metastatic melanoma participants from Study CA224047 and CA224020 pharmacokinetics (PK), pharmacodynamics, and extensive nivolumab monotherapy clinical experience.[8,13] The flat E-R relationship for clinical efficacy and safety including data from higher doses supported the proposed dose for the adjuvant treatment of melanoma.

While administration of FDC (3:1) using a 30-minute infusion time has not been evaluated in participants with cancer, no clinically meaningful differences in the frequency of hypersensitivity/infusion-related reactions are expected when FDC is administered over a 30-minute infusion compared with the 60-minute infusion.[8] Clinical studies of FDC for the treatment of cancer used a 60-minute infusion duration. Infusion reactions, including high-grade hypersensitivity reactions, were uncommon across the relatlimab clinical program. The length of infusion of 30- or 60-minutes is not expected to impact the PK profile of nivolumab and relatlimab. Overall, an infusion duration of 30 minutes for nivo + rela FDC is likewise not anticipated to present significant safety concerns (ie, the frequency of hypersensitivity/infusion-related reactions). The shorter infusion will provide patient convenience by reducing the overall infusion duration and chair time.

Based on PPK analysis, relatlimab baseline CL in subjects receiving relatlimab monotherapy and nivolumab + relatlimab SAV (sequential or co-administered) was similar to participants receiving nivo + rela FDC (≤ 5% and ≤ 18% difference, respectively). Similarly, nivolumab baseline CL in subjects receiving nivolumab monotherapy or nivolumab + relatlimab was similar (≤ 5% difference) to participants receiving nivo + rela FDC, thus indicating no clinically relevant effect of FDC formulation on relatlimab or nivolumab PK. Nivolumab and relatlimab both exhibit time-varying clearance (CL) associated with improving disease status over time in metastatic solid tumor patient population. However, in the adjuvant setting, participants are expected to have improved disease status at baseline and in turn clearance is expected to be time invariant and lower than baseline CL observed in metastatic solid tumors patient population. For example, nivolumab CL in adjuvant melanoma participants was 40% lower than baseline CL and approximately 20% lower than steady-state CL relative to participants with advanced melanoma.[43] These changes in CL and resulting increase in exposure is not expected to be clinically relevant given the flat E-R for safety in the metastatic setting.[8]

5.5.2 Dose Rationale for Adolescent Participants

The nivo + rela FDC dose in adolescent patients for this indication is supported by evidence from RELATIVITY 047, a global Phase 3, double-blinded, randomized controlled study in adults with unresectable or metastatic melanoma; 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 pharmacokinetics of monoclonal antibodies 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 in an adjuvant setting is expected to be well within established adult safe and tolerable exposure margin. Relatlimab flat doses of 20 to 800 mg Q2W as monotherapy and up to 1440 mg Q4W in combination with nivolumab 480 mg have been studied in adults.[44]

Nivo + rela 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. Adolescents < 40 kg will be administered body weight adjusted nivo + rela FDC doses, up to the respective maximum adult flat-doses. Adolescent participants ≥ 12 years old who weigh ≥ 40 kg will be administered a flat-dose of nivo + rela FDC (nivolumab 480 mg and relatlimab 160 mg Q4W IV infusion [adult dosing]) or nivolumab monotherapy 480 mg Q4W IV infusion (adult dosing). Participants between ≥ 12 years and < 18 years of age who weigh < 40 kg will be administered body weight adjusted nivolumab [redacted] of nivo + rela FDC or nivolumab monotherapy 6 mg/kg Q4W IV infusion over approximately 30 minutes.

5.5.3 Justification for Nivolumab Monotherapy Dose

The nivolumab dose of 480 mg Q4W was selected based on clinical data and modeling and simulation approaches using population PK (PPK) and exposure-response (E-R) analyses of data from studies in multiple tumor types (melanoma, NSCLC, and RCC) where body weight normalized dosing (mg/kg) was used.

Nivolumab PK has been extensively studied in multiple tumor types, including melanoma, NSCLC, RCC, cHL, SCCHN, CRC, and urothelial carcinoma and has been safely administered at doses up to 10 mg/kg Q2W. Nivolumab monotherapy was originally approved as a body-weight based dose of 3 mg/kg Q2W, and was updated to 240 mg Q2W or 480 mg Q4W in multiple indications.[6,8] Nivolumab 360 mg Q3W is also under evaluation in monotherapy and in combination therapy studies. Less frequent 360 mg Q3W and 480 mg Q4W dosing regimens can reduce the burden to patients of frequent, lengthy IV treatments and allow combination of nivolumab with other agents using alternative dosing regimens.

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

Extensive E-R analyses of multiple PK measures (maximum serum concentration at Day 1[Cmax1], average serum concentration at Day 28 [Cavg28], and trough serum concentration at Day 28 [Cmin28]) and efficacy and safety endpoints indicated that the efficacy of the flat-dose 480 mg IV regimen are similar to that of 3 mg/kg Q2W IV regimen. In E-R efficacy analyses for OS and ORR conducted in melanoma, RCC, and NSCLC using Cavg28 as the exposure measure, probabilities of achieving a response and survival probabilities at 1 year and 2 years for IV

480 mg Q4W were similar to that of IV 3 mg/kg Q2W. In E-R safety analyses, it was demonstrated that the exposure margins for safety are maintained following nivolumab 480 mg Q4W, and the predicted risks of discontinuations due to AEs or death, AE Grade 3+, and immune-mediated AEs (IMAEs) Grade 2+ are similar following nivolumab 480 mg Q4W relative to nivolumab 3 mg/kg Q2W across tumor types. In addition, nivolumab exposures with 240 mg Q2W, 360 mg Q3W, and 480 mg Q4W flat-dose IV regimens across tumor types are maintained well below the corresponding exposures observed with the well-tolerated 10 mg/kg IV nivolumab Q2W dose regimen.

Additional details on nivolumab posologies and risk-benefit can be found in the nivolumab IB.

[redacted]

5.6 Clinical Pharmacology Summary

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

2 weeks. The predicted exposure (Cavg and Cmax) of nivolumab after a 30-minute infusion is comparable to that observed with a 60-minute infusion.

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

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

Hepatic Impairment: The effect of hepatic impairment on the clearance of nivolumab was evaluated by population PK analyses in patients with HCC and in patients with other tumors with mild hepatic impairment (total bilirubin [TB] less than or equal to the upper limit of normal (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 patients with mild/moderate hepatic impairment.

In addition, nivolumab pharmacokinetics (PK) was characterized in adults and pediatric participants with solid tumors who received nivolumab alone and in combination with relatlimab. Nivolumab exhibits linear and time-varying PK. Nivolumab baseline clearance (CL) in participants receiving nivolumab monotherapy or nivolumab + relatlimab was similar (≤ 5% difference) to participants receiving nivolumab + relatlimab FDC. [redacted] Thus, no PK interaction between nivolumab and relatlimab was observed when these agents were given in combination.

[redacted]

5.6.2 Relatlimab Clinical Pharmacology Summary

The PK of relatlimab was characterized over a wide range of doses; 20 mg to 800 mg Q2W when administered as monotherapy or 20 mg to 240 mg Q2W and 160 mg to 1440 mg Q4W when administered in combination with nivolumab.[8]

[redacted]

Relatlimab exhibits non-linear and time-varying PK. Nonlinearity in relatlimab CL represents ~31% of total CL of relatlimab at the relatlimab 160-mg dose Q4W in combination with nivolumab. Relatlimab clearance coefficient of variation% (CV%) is 9.7% lower (geometric mean, 5.48 mL/h [41.3%]) at steady state than after the first dose (6.06 mL/h [38.9%]) [redacted] The geometric mean value (CV%) for relatlimab volume of distribution at steady state is 6.65 L (19.8%), consistent with the expected distribution of monoclonal antibodies (mAbs) limited to the vascular space. Relatlimab baseline CL in participants receiving relatlimab monotherapy and nivolumab + relatlimab single-agent vial (SAV) (sequential or coadministered) was similar to participants receiving nivolumab + relatlimab FDC (≤ 5% and ≤ 18% difference, respectively), [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 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 tests, tumor biopsies, and other requirements of the study.

c) 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/has not been treated). If re-enrolled, the participant must be re-consented.

2) Type of Participant and Target Disease Characteristics

a) All participants must have been diagnosed with either Stage IIIA (> 1 mm tumor in lymph node)/B/C/D or Stage IV melanoma by AJCC v8 and have histologically confirmed melanoma that is completely surgically resected (free of disease) with negative margins in order to be eligible. All melanomas, except ocular melanoma, regardless of primary site of disease, will be allowed.

Note: Conjunctival melanoma is not considered to be ocular melanoma and is to be classified as mucosal melanoma.

b) Participants are eligible if central nervous system (CNS) metastases have been resected and participants are neurologically stable.
   i) Prior resected CNS metastases must be without evidence of recurrence, as determined by magnetic resonance imaging (MRI) performed at least 4 weeks after resection is complete and within 35 days prior to randomization.
   ii) Participants must be off immunosuppressive doses of systemic steroids (>10 mg/day prednisone or equivalent) for at least 14 days prior to study drug administration and must have returned to neurologic baseline post-operatively.
   iii) For CNS lesion(s), a pathology report indicating that there has been complete resection of CNS lesion(s) will suffice as confirmation of negative margins.

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

d) All participants must have disease-free status documented by a complete physical examination within 14 days prior to randomization and imaging studies within 35 days prior to randomization. Imaging studies must include CT scan of the chest, abdomen, pelvis, and all known sites of resected disease, and brain MRI. See Section 9.1.2 for details and exceptions.

e) [redacted]

f) Participants ≥ 18 years of age must have an ECOG performance status of ≤ 1. Adolescent participants between 12 and < 18 years of age must have a Lansky/Karnofsky performance score ≥ 80% (Appendix 6).

g) Not applicable - China only.

3) Age of Participant

a) Not applicable per Protocol Amendment 01.

b) Participant must be ≥ 12 years of age or local age of majority inclusive, at the time of signing the informed consent.

Except: Where local regulations do not allow for participants < 18 years of age (adolescent population) to participate. For those sites, the eligible participant population is ≥ 18 years of age. Refer to Appendix 9.

4) Reproductive Status

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

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

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

a) Female Participants:

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

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

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

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

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

v) The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

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

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

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

(1) Is not a WOCBP

OR

(2) Is a WOCBP and using a contraceptive method that is highly effective as described in Appendix 4 during screening and for the duration of treatment for a total of 5 months after the last dose and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction for the same time period.

b) Male Participants:

i) No additional contraceptive measures are required to be used.

6.2 Exclusion Criteria

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

1) Medical Conditions

a) History of ocular melanoma.

Note: Conjunctival melanoma is not considered to be ocular melanoma and is to be classified as mucosal melanoma.

b) Untreated/unresected CNS metastases or leptomeningeal metastases.

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

d) Participants with serious or uncontrolled medical disorder.

e) Previous severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection either suspected or confirmed within 4 weeks prior to screening. Acute symptoms must have resolved and based on investigator assessment, there are no sequelae that would place the participant at a higher risk of receiving investigational treatment.

f) [redacted]

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

h) Woman who are breastfeeding.

i) Participants with a history of myocarditis, regardless of etiology.

2) Prior/Concomitant Therapy

[redacted]

d) Treatment with complementary medications (eg, herbal supplements or traditional Chinese medicines) to treat the disease under study within 2 weeks prior to randomization. Such medications are permitted if they are used as supportive care. [redacted]

e) Treatment with any live/attenuated vaccine within 30 days of first study treatment (inactivated vaccines are permitted).

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

[redacted]

3) Physical and Laboratory Test Findings

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

Note: May not transfuse, use growth factors, and/or coagulation factors within 14 days of randomization to meet criteria 3b to 3e.

[redacted]

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

i) they have received antiretroviral therapy (ART dosing) for at least 4 weeks prior to randomizations as clinically indicated while enrolled on study

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

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

NOTE: Testing for HIV must be performed at sites where mandated locally. HIV positive participants must be excluded where mandated locally (see Appendix 9).

[redacted]

4) Allergies and Adverse Drug Reaction

a) Participants with history of allergy or hypersensitivity to study treatment components.

b) History of life-threatening toxicity related to prior immune therapy (e.g. anti-CTLA4 or anti-PD-1/PD-L1 treatment or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways) except those that are unlikely to re-occur with standard countermeasures (eg, hypothyroidism).

5) Other Exclusion Criteria

a) Prisoners or participants who are involuntarily incarcerated. (Note: Under certain specific circumstances and only in countries where local regulations permit, a person who has been imprisoned may be included or permitted to continue as a participant. Strict conditions apply, and BMS approval is required. [Please refer to Appendix 9 for Greece-specific differences.])

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

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

6.3 Lifestyle Restrictions

Not applicable. No restrictions are required.

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but 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 AEs.

6.4.1 Retesting During Screening or Lead-in Period

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

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

The most current result prior to randomization 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 Screening Procedural Outline (see Table 2-1), may be repeated in an effort to find all possible well-qualified participants. Consultation with the Medical Monitor/designee may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

[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.

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

7.1 Study Interventions Administered

Table 7.1-1: Study Interventions

ARM Name	Nivo + rela FDC	Nivolumab
Intervention Name	BMS-986213 (Nivolumab 240 mg / Relatlimab 80 mg) vial	Nivolumab 100 mg/vial
Type	Drug	Drug
Dose Formulation	Solution for injection	Solution for injection
Unit Dose Strength(s)	16 mg/mL	10 mg/mL
Dosage Level(s) for Adults (≥ 18 years of age) and Adolescents (≥ 12 years to < 18 years of age) ≥ 40 kg	Nivolumab 480 mg Relatlimab 160 mg Total: 640 mg Once every 4 weeks	Nivolumab 480 mg Once every 4 weeks
Dosage Level(s) for Adolescents (≥ 12 years to < 18 years of age) < 40 kg (weight-based)	[redacted]	Nivolumab 6 mg/kg Once every 4 weeks
Route of Administration	IV infusion	IV infusion
Use	Experimental	Active comparator
IMP and Non-IMP/AxMP	IMP	IMP
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 (Relatlimab 80 mg/Nivolumab 240 mg/vial)[a] Opdualag™	BMS-936558 Opdivo™

Abbreviations: AxMP, auxiliary medical product; FDC, fixed dose combination; IMP, investigational medicinal product; IP, investigational product; IV, intravenous; nivo, nivolumab; rela, relatlimab.

[a] Study Intervention for Nivo + Rela FDC Arm is currently BMS-986213 (Relatlimab 80 mg/Nivolumab 240 mg/vial) and will be updated to BMS-986213 (Nivolumab 240 mg/Relatlimab 80 mg/vial) approximately 1Q-2Q 2023.

For body weight dosing, the dosing calculations should be based on the body weight assessed at screening. [redacted]

7.1.1 Study Treatment Details

Participants will receive nivo + rela FDC or nivolumab monotherapy on Day 1 of every 4-week cycle. Blinded study drug will be administered in a single bag IV over approximately 30 minutes. Participants should be carefully monitored for infusion reactions during IV administration. If an acute infusion reaction is noted, participant should be managed according to Section 7.4.4.

- There will be no dose escalations or reductions of immunotherapy allowed.
- Premedications are not recommended for the first dose of immunotherapy.
- Participants should be carefully monitored for infusion reactions during immunotherapy administration.
- If an acute infusion reaction is noted, participants should be managed according to Section 7.4.4.
- Participants should receive immunotherapy until recurrence [redacted], unacceptable toxicity, withdrawal of consent, a maximum treatment duration of 1 year from first dose (maximum of 13 doses), or the study ends, whichever occurs first.
- Doses of immunotherapy may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment according to Section 7.4.1.
- Dosing visits must not be skipped, only delayed. See Section 7.4 and Section 8.1.

All infusions must be promptly followed by a diluent flush to clear the line of IP before starting infusion(s) of any additional treatment. Instruction for dilution and infusion of study drug injections will be provided in the Pharmacy Manual. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent. For details on prepared drug storage, preparation, and administration, please refer to the IBs and/or Pharmacy Manual. The selection and timing of dose for each participant is provided in Table 7.1-1.

Study treatment will be dispensed by interactive response technology (IRT) at the study visits as listed in Section 2 (Schedule of Activities). Further details regarding preparation and administration will be provided separately in site/pharmacy training materials.

7.2 Method of Study Intervention Assignment

All participants will be centrally randomized using Interactive Response Technology (IRT). Before the study is initiated, each user will receive log-in information and directions on how to access the IRT. 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 the participant

number. Every participant who signs the ICF 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:

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

After enrollment in the IRT, participants who have met all eligibility criteria will be randomized through the IRT. The following information is required for participant randomization:

- Participant number
- Year of birth
- Melanoma type (cutaneous or mucosal)
- AJCC v8 stage at screening (cutaneous melanoma only)

Participants will be randomized in a 1:1 ratio (see Figure 5.1-1) and stratified by geographic region (USA/Canada/Australia vs Europe vs ROW) and AJCC v8 stage as described in Section 5.2.

The randomization procedures will be carried out via permuted blocks within each stratum, defined by combination of geographic region and AJCC v8 stage. The exact procedures for using the IRT will be detailed in the IRT manual.

7.3 Blinding

This is a double-blind study. Access to treatment codes will be restricted from all participants, and site and Sponsor personnel prior to primary database lock, with exceptions as specified below.

Blinding of study treatment assignment is critical to the integrity of this clinical study. However, in the event of a medical emergency or pregnancy in an individual participant in which knowledge of the IP is critical to the participant's management, the blind for that participant may be broken by the investigator. The participant's safety takes priority over any other considerations in determining if a treatment assignment should be unblinded.

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

For information on how to unblind in an emergency, consult the IRT manual.

In cases of accidental unblinding, contact the Medical Monitor/designee and ensure every attempt is made to minimize additional disclosure and the impact of unblinding.

Any request to unblind a participant for nonemergency purposes should be discussed with the Medical Monitor/designee. Discussions regarding unblinding with the Medical Monitor/designee must be documented.

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

A scientist in the NonClinical Disposition and Bioanalysis department of BMS (and/or a designee in the external bioanalytical laboratory) will be unblinded to the randomized treatment assignments in order to minimize unnecessary bioanalytical analysis of samples. Any results shared by the NonClinical Disposition and Bioanalysis group with the Sponsor's study team will be blinded to ensure integrity of the study.

Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study. In order to maintain this blind, an otherwise uninvolved third party will be responsible for the reconstitution and dispensation of all study intervention and will endeavor to ensure that there are no differences in time taken to dispense following randomization.

In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately.

The DMC will assess safety and risk-benefit on an ongoing basis, and will have access to unblinded treatment codes for individual subjects. An external analysis team (external to BMS), including a reporting statistician and programming support, who are not involved with the conduct of the study, will provide analyses to the DMC. [redacted]

7.4 Dosage Modification

Dose reductions or dose escalations are not permitted. All dose modification rules apply to all arms, given the blinded nature of this study.

7.4.1 Dose Delay Criteria

Dose delay criteria apply for all drug-related AE. Delay administration of study treatment if any of the delay criteria in Table 7.4.1-1 are met. Delay dosing for any AE, laboratory abnormality, or intercurrent illness which, in the judgement of the investigator, warrants delaying the dose of study medication.

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

For participants who require delay of study treatment, re-evaluate weekly, or more frequently, if clinically indicated, and resume dosing when criteria to resume treatment are met (see Section 7.4.2). Continue tumor assessments per protocol even if dosing is delayed.

Table 7.4.1-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Treatment

Drug-Related Adverse Event (AE) per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Gastrointestinal			
Colitis or Diarrhea	Grade 2	Delay dose	Dosing may resume when AE resolves to baseline
	Grade 3	Delay dose	Dosing may resume when AE resolves to baseline
	Grade 4	Permanently discontinue	
Renal			
Serum Creatinine Increased	Grade 2 or 3	Delay dose	Dosing may resume when AE resolves to Grade ≤ 1 or baseline value
	Grade 4	Permanently discontinue	
Pulmonary			
Pneumonitis	Grade 2	Delay dose	Dosing may resume after pneumonitis has resolved to ≤ Grade 1.
	Grade 3 or 4	Permanently discontinue	
Hepatic			
Aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin (T.bili) increased	AST or ALT > 3 × and ≤ 5 × upper limit of normal (ULN) or T.bili >1.5 × and ≤ 3 × ULN, regardless of baseline value	Delay dose	Dosing may resume when laboratory values return to baseline.
	AST or ALT > 5 × ULN or T.bili > 3 × ULN, regardless of baseline value	Permanently discontinue	
	Concurrent AST or ALT > 3 × ULN and T.bili > 2 × ULN, regardless of baseline value	Permanently discontinue	

Table 7.4.1-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Treatment

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

Table 7.4.1-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Treatment

Drug-Related Adverse Event (AE) per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Skin			
Rash	Grade 2 rash covering > 30% body surface area or Grade 3 rash	Delay dose	Dosing may resume when rash reduces to ≤ 10% body surface area
	Suspected Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or drug reaction with eosinophilia and systemic symptoms (DRESS)	Delay dose	Dosing may resume if SJS, TEN, or DRESS is ruled out and rash reduces to is ≤ 10% body surface area
	Grade 4 rash or confirmed SJS, TEN, or DRESS	Permanently discontinue	
Neurological			
Guillain-Barre Syndrome (GBS)	Any Grade	Permanently discontinue	
Myasthenia Gravis (MG)	Any Grade	Permanently discontinue	
Encephalitis	Any Grade encephalitis	Delay dose	After workup for differential diagnosis, (i.e. 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, (i.e. 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	

Table 7.4.1-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Treatment

Drug-Related Adverse Event (AE) per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Cardiovascular			
[redacted]			
Myocarditis			
Myocarditis	Symptoms induced from mild to moderate activity or exertion	Delay dose	Dosing may resume after myocarditis has resolved
	Severe or life threatening, with symptoms at rest or with minimal activity or exertion, and/or where intervention indicated.	Permanently discontinue	
Other Clinical AE			
Pancreatitis: Amylase or Lipase increased	Grade 3 with symptoms	Delay dose	Note: Grade 3 increased amylase or lipase without signs or symptoms of pancreatitis does not require dose delay. Dosing may resume when patient 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 patient requires oral steroids for uveitis, then permanently discontinue study drug.
	Grade 3 or 4 uveitis	Permanently discontinue	

Table 7.4.1-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Treatment

Drug-Related Adverse Event (AE) per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resume Criteria
Other Drug-Related AE **(not listed above)**	Grade 2 non-skin AE, except fatigue	Delay dose	Dosing may resume when AE resolves to Grade ≤ 1 or baseline value.
	Grade 3 AE - First occurrence lasting ≤ 7 days	Delay dose	Dosing may resume when AE resolves to Grade ≤ 1 or baseline value.
	Grade 3 AE- First occurrence lasting > 7 days	Permanently discontinue	
	Recurrence of Grade 3 AE of any duration	Permanently discontinue	
	Grade 4 or Life-threatening adverse reaction	Permanently discontinue	
Other Lab abnormalities			
Other Drug-Related lab abnormality (not listed above)	Grade 3	Delay dose	Exceptions: No delay required for: Grade 3 lymphopenia Permanent Discontinuation for: Grade 3 thrombocytopenia > 7 days or associated with bleeding.
	Grade 4	Permanently discontinue	Exceptions: The following events do not require discontinuation of study drug: • Grade 4 neutropenia ≤ 7 days • Grade 4 lymphopenia or leukopenia • Grade 4 isolated electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are responding to supplementation/appropriate management within 72 hours of their onset
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; BMS, Bristol Myers Squibb; CTCAE, Common Terminology Criteria for Adverse Events; DRESS, drug reaction with eosinophilia and systemic symptoms; GBS, Guillain Barre syndrome; MG, myasthenia gravis; SJS, Stevens-Johnson syndrome; T.bili, total bilirubin; TEN, toxic epidermal necrolysis; ULN, upper limit of normal.

7.4.2 Criteria to Resume Treatment

Participants may resume treatment with study intervention if they have completed AE management (ie, corticosteroid taper) or are on ≤ 10 mg prednisone or equivalent, and meet the requirements per Table 7.4.1-1.

[redacted]

7.4.4 Treatment of Infusion-Related Reactions

Since relatlimab and nivolumab contain only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a

reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. Report all Grade 3 or 4 infusion reactions within 24 hours as an SAE if it meets the criteria.

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

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

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

For Grade 2 symptoms: (Therapy or infusion interruption indicated but responds promptly to symptomatic treatment [e.g., antihistamines, NSAIDS, narcotics, IV fluid]; prophylactic medications indicated for ≤ 24 hours):

- Stop the study drug infusion, begin an IV infusion of normal saline, and treat the participant with diphenhydramine 50 mg intravenous (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor participant until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor participant closely. If symptoms recur, then no further study medication will be administered at that visit.
- For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg should be administered at least 30 minutes before study treatment infusions. If necessary, corticosteroids (up to 25 mg of hydrocortisone or equivalent) may be used.

For Grade 3 or 4 symptoms: (severe reaction, Grade 3: prolonged [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae. Grade 4: Life threatening consequences; urgent intervention indicated):

- Immediately discontinue infusion of study drug. Begin an IV infusion of normal saline and treat the participant as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for intravenous administration, and/or diphenhydramine 50 mg intravenous with methylprednisolone 100 mg intravenous (or equivalent), as needed. Monitor participant until the Investigator judges that the symptoms will not recur. Study drug will be permanently

discontinued. Follow institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor participant until recovery of the symptoms.

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

7.5 Preparation/Handling/Storage/Accountability

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

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

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

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

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

7.5.1 Retained Samples for Bioavailability/Bioequivalence/Biocomparability

Not Applicable.

7.6 Treatment Compliance

Treatment compliance will be monitored by drug accountability as well as the participant's medical record and electronic case report form (eCRF). This will be source data reviewed through regularly scheduled monitoring visits.

7.7 Concomitant Therapy

7.7.1 Prohibited and/or Restricted Treatments

7.7.1.1 Prohibited Treatments

[redacted]

7.7.2 Other Restrictions and Precautions

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

Participants are prohibited from joining another interventional clinical trial if they are still on study treatment. Participation in observation only studies is allowed at any time.

7.7.2.1 SARS-CoV-2 Vaccination Guidelines

[redacted]

[redacted]

7.7.2.2 Imaging Restriction and Precautions

It is the local imaging facility's responsibility to determine, based on participant attributes (eg, allergy history, diabetic history, and renal status), the appropriate imaging modality and contrast regimen per imaging study. Imaging contraindications and contrast risks are to be considered in this assessment. Participants with renal insufficiency are to be assessed as to whether or not they should receive contrast and if so, which contrast agent and dose is appropriate based on local standard of care.

Specific to MRI, participants with severe renal insufficiency (ie, estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2) are at increased risk of nephrogenic systemic fibrosis, therefore MRI contrast is contraindicated. Participants may be excluded from MRI if they have tattoos, metallic implants, pacemakers, etc., following local standard of care.

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

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

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

BMS reserves the right to terminate access to BMS-supplied study intervention if any of the following occur: a) the study is terminated due to safety concerns; b) the development of nivo + rela FDC 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

8.1 Discontinuation From Study Treatment

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

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

- Any clinical AE, laboratory abnormality, or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant
- Termination of the study by BMS
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness. (Note: Under specific circumstances and only in countries where local regulations permit, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply, and BMS approval is required.)
- Disease recurrence [redacted]
- Pregnancy (refer to Section 9.2.5)
- Significant noncompliance with protocol (eg, procedures, assessments, medications, etc.). The investigator should discuss such issues with the Medical Monitor/designee and be documented.

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

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

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

8.1.1 Dose Discontinuation

Study treatment must be permanently discontinued per criteria in Table 7.4.1-1 in Section 7.4.

Discontinue study treatment for any AE, laboratory abnormality, or intercurrent illness which in the judgment of the Investigator, presents a substantial clinical risk to the participant with continued dosing.

Any event that leads to delay in dosing lasting > 10 weeks from the previous dose requires discontinuation of study drug, with the following exceptions:

- Dosing delays to allow for prolonged steroid tapers to manage drug-related AE are allowed.
- Dosing delays lasting > 10 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the Medical Monitor/ designee.

Note: dosing delays that are approved by the Medical Monitor/designee must be documented.

8.1.2 Post-study Intervention Study Follow-up

In this study, RFS is a key endpoint of the study. Post-study follow-up is of critical importance and is essential to preserving participant safety and the integrity of the study. Participants who discontinue study intervention must continue to be followed (in this study or a rollover study) for collection of outcome and/or survival follow-up data as required and in line with Section 5.3 until death or the conclusion of the study. [redacted]

BMS may request that survival data be collected on all randomized participants outside of the protocol defined window as defined in Section 2. At the time of this request, each participant will be contacted to determine their survival status unless the participant has withdrawn consent for all contacts 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 eCRF 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.
- Site should document if subject is unwilling to attend future visits, accept phone calls, allow contact with their personal physician, or allow review of medical records for health status information.

- At the time of discontinuing from the study, an immediate follow-up visit may be needed. See the Schedule of Activities (Section 2) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

8.3 Lost to Follow-up

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

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

9 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and timing are summarized in the Schedule of Activities.

Protocol waivers or exemptions are not allowed.

All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.

Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before 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 (e.g., blood count) and obtained before signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Schedule of Activities.

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

Evaluate participant immediately to rule out cardiac or pulmonary toxicity if participant shows cardiac or pulmonary-related signs (hypoxia, abnormal heart rate or changes from baseline) or symptoms (eg, dyspnea, cough, chest pain, fatigue, palpitations).

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

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will be at approximately 775 mL. However, the volume of blood drawn for local safety assessments, done before every dose, and in follow-up, will depend on local institutional practices and will vary from institution to institution.

9.1 Efficacy Assessments

9.1.1 Efficacy Assessment for the Study

Study evaluations will take place in accordance with Section 2, Schedule of Activities. Surveillance for recurrence will be performed until investigator assessed [redacted] recurrence [redacted]

Contrast-enhanced CT of the chest, abdomen, pelvis, and all suspected sites of disease must be performed every 12 weeks (± 7 days) from randomization for the first 2 years, and every 26 weeks (± 14 days) beyond the Week 108 imaging time point thereafter until investigator assessed [redacted]

Imaging should be obtained anytime there is suspected disease. In cases of suspected lesions of the extremities, contrast-enhanced MRI may be substituted for contrast-enhanced CT. Please refer to Appendix 9 for Germany-specific imaging language.

Participants with a history of brain metastasis or symptoms should have a surveillance MRI (without and with contrast) approximately every 12 weeks ± 7 days from randomization for the first 2 years and subsequently every 26 weeks (± 14 days) beyond the Week 108 imaging time point thereafter until investigator assessed [redacted] recurrence [redacted] or sooner if clinically indicated. Participants without history of brain metastases should have MRI if clinically indicated.

9.1.2 Imaging Assessment for the Study

Images will be submitted to a central imaging vendor and may undergo blinded independent central review (BICR) at any time during the study. 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. Tumor assessments at other time points may be performed if clinically indicated and should be submitted to the central imaging vendor as soon as possible. All imaging that may demonstrate disease recurrence (including scans performed at unscheduled time points and/or at an outside institution) should be collected and submitted to the imaging vendor.

Assessments for recurrence should continue on the protocol defined imaging schedule regardless if dosing is delayed or discontinued. [redacted]

The same method of assessment used at Screening should be used for on-study time points. CT images should be acquired with slice thickness of 5 mm or less with no intervening gap (contiguous). Every attempt should be made to image each participant using an identical acquisition protocol on the same scanner for all imaging time points.

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

MRI of brain (without and with contrast) must 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.

Other imaging may be collected per local standards, as clinically indicated. See Section 7.7.2.2.

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

9.1.3 Investigator Assessment of Baseline Disease Status

Participant eligibility (disease-free status) must be confirmed by investigator prior to randomization. Baseline disease assessments should be performed within 35 days prior to randomization, including contrast-enhanced CT of the chest, abdomen, pelvis, and all suspected sites of disease. Baseline MRI of the brain (with and without contrast) is required for ALL participants during screening to rule out brain metastases, within 35 days prior to randomization. CT of the brain (without and with contrast) can be performed if MRI is contraindicated. Please refer to Appendix 9 for Germany-specific imaging language.

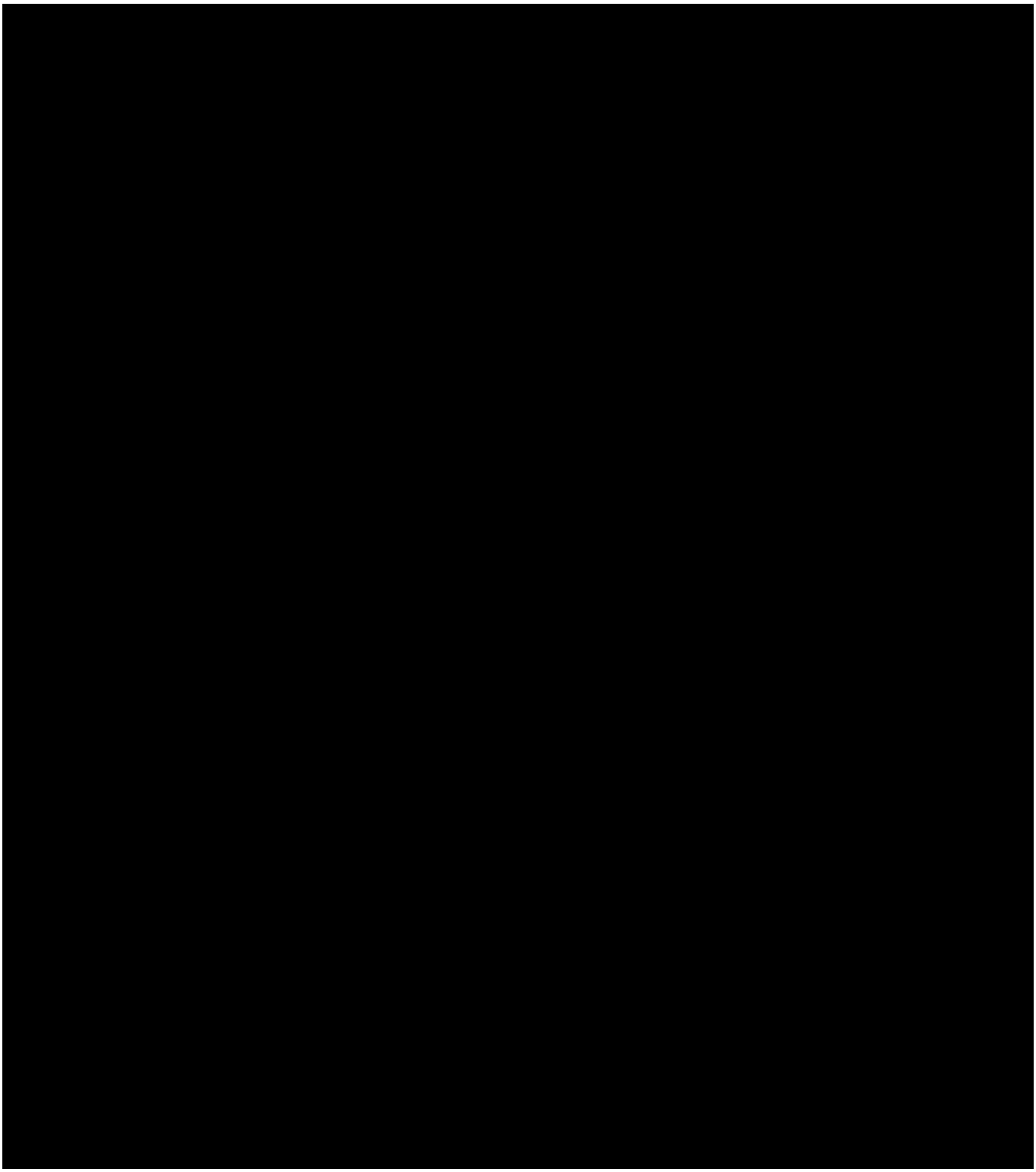
All participants must have disease-free status defined as no clinical or radiographic evidence of recurrence of disease documented by a complete physical examination within 14 days prior to randomization and imaging studies within 35 days prior to randomization. [redacted]

9.1.4 Investigator Assessment of Recurrence

The same method of assessment used at Screening should be used for on-study time points. Post-baseline assessments will be performed at the time points described in Table 2-2 and Table 2-3 until [redacted] recurrence [redacted]

Tumor assessments for ongoing study treatment decisions will be completed by the investigator. Additional imaging of potential disease sites should be performed whenever disease recurrence or occurrence of a secondary malignancy is suspected.

Cytology and/or histology are mandatory to confirm recurrence in solitary or in doubtful/suspect lesions, cutaneous, subcutaneous, or lymph node lesions. Histological or cytological evidence of recurrence should be attempted in all cases, except for brain metastases, when safe and clinically feasible. Tumor markers or auto-antibodies alone cannot be used to assess recurrence.



[redacted]

[redacted]

9.1.5 Patient-Reported Outcomes

Health-related quality of life (HRQoL) will be assessed by [redacted] in participants who are ≥ 18 years of age at the time of informed consent as outlined in Section 2. Adolescent participants (≥ 12 and < 18 years of age) only complete [redacted] Adolescent participants will continue to complete only the [redacted] even if they become ≥ 18 years of age during treatment or follow-up.

If Health Outcomes Assessments are collected but the dose is subsequently delayed, a data change form should be submitted to move the original data entry to an unscheduled visit.

If the participant withdraws from the study prematurely, all attempts should be made to obtain [redacted] prior to withdrawal from the study in participants who are ≥ 18 years of age at the time of informed consent, or [redacted] for participants who are ≥ 12 and < 18 years of age at the time of informed consent. Reasons for missing patient-reported outcomes questionnaires should also be documented so that the appropriate imputation method can be employed to correct for missing data in the analysis.

The questionnaire will be completed by the participants before any clinical assessments are performed and treatments administered at any given visit. If participants refuse to complete all or any part of a questionnaire, this will be documented. Questionnaires should be completed in the language most familiar to each participant (if available), and participants should be given adequate time and space to complete the questionnaire. In order to preserve the integrity of trial data, no patient-reported data can be changed after the patient initially provides it.

[redacted] assessments in Long-term Follow Up (visits beyond Follow Up 2) may be completed by other modes of administration (eg, telephone) if deemed necessary by the study team. If exceptional circumstances preclude the continued administration of measures using planned modalities, then alternate administration methods may be required, after consultation with the Sponsor.

[redacted]

[redacted]

9.2 Adverse Events

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

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

The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up

on AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue before completing the study.

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

Immune-mediated adverse events 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.

Refer to Appendix 3 for SAE reporting.

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

Collect all nonserious adverse events (not only those deemed to be treatment related) continuously during the treatment period and for a minimum of 135 days following discontinuation of study treatment. All AEs associated with SARS-CoV-2 infection must be collected from time of consent and during the treatment period. All SAEs must be collected from the time of signing the consent, including those thought to be associated with protocol-specified procedures, and within 135 days following discontinuation of dosing, except in cases where a study participant has started a new anti-neoplastic therapy. However, any SAE occurring after the start of a new treatment that is suspected to be related to study intervention by the investigator will be reported.

For participants randomized to treatment and never treated with study drug, collect SAEs for 30 days from the date of randomization.

All SAEs, and 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. Collect all nonserious adverse events, not only those deemed to be treatment-related, (with the exception of non-serious AEs related to SARS-CoV-2 infection) continuously during the treatment period and for a minimum of 135 days following discontinuation of study treatment.

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

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

Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant

has been discharged from the study, and he/she considers the event reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

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

9.2.2 Method of Detecting AEs and SAEs

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

All nonserious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 135 days following discontinuation of study treatment.

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 test result abnormalities that are reported/identified during the study.

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

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

9.2.4 Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the Sponsor of SAEs is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a product under clinical investigation are met.

An investigator who receives an investigator safety report describing SAEs or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

The Sponsor or designee must report AEs to regulatory authorities and ethics committees according to local applicable laws and regulations. A SUSAR (suspected, unexpected serious

adverse reaction) is a subset of SAEs and must be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

9.2.5 Pregnancy

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

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

For WOCBP who are partners of male participants in the study, pregnancy reporting is not required.

9.2.6 Laboratory Test Result Abnormalities

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

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

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

9.2.7 Potential Drug-induced Liver Injury

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

Potential DILI is defined as:

- Aminotransferase (AT) ALT or AST elevation > 3 times upper limit of normal (ULN)

  AND

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

AND

- No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

9.2.8 Other Safety Considerations

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

9.3 Overdose

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

In the event of an overdose, the investigator should:

- Contact the 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 Medical Monitor/designee based on the clinical evaluation of the participant and documented.

9.4 Safety

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

9.4.1 Physical Examinations

Refer to Schedule of Activities, Section 2.

9.4.2 Vital signs

Refer to Schedule of Activities, Section 2.

9.4.3 Electrocardiograms

Refer to Schedule of Activities, Section 2.

9.4.4 Clinical Safety Laboratory Assessments

Investigators must document their review of each laboratory safety report.

All clinical safety laboratory assessments will be performed locally per Section 2 (Schedule of Activities).

Table 9.4.4-1: Clinical Laboratory Assessments

Hematology - CBC	
Hemoglobin Hematocrit Total leukocyte count, including differential Platelet count	
Chemistry	
Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Total bilirubin Alkaline phosphatase (ALP) Lactate dehydrogenase (LDH) Creatinine Blood urea nitrogen (BUN) or serum urea level Glucose	Albumin - screening only Sodium Potassium Chloride Calcium [redacted] Phosphorus TSH, free (or total) T3 and free (or total) T4 - screening TSH, with reflexive f(or t)T3 and f(or t)T4 if TSH is abnormal - on treatment
[redacted]	
Serology	
Hepatitis B/C [redacted], (screening only; testing for HIV must be performed at sites where mandated by local requirements [see Appendix 9]).	
Other Analyses	
Pregnancy test (WOCBP only; minimum sensitivity 25 IU/L or equivalent units of HCG; screening, predose, and, follow-up. During follow-up, [redacted]	
Follicle stimulating hormone (FSH) screening - only required to confirm menopause in women < age 55. If FSH does not confirm postmenopausal status, pregnancy testing is required as per SOA.	

Abbreviations: CBC, complete blood count; [redacted]; ft3, free T3; ft4, free T4; HBsAG, hepatitis B virus surface antigen; HCG, human chorionic gonadotropin; HCV, hepatitis C virus; HIV, human immunodeficiency virus; [redacted] SOA, Schedule of Activities; T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone; tT3, total T3; tT4, total T4; WOCBP, women of child bearing potential.

[redacted]

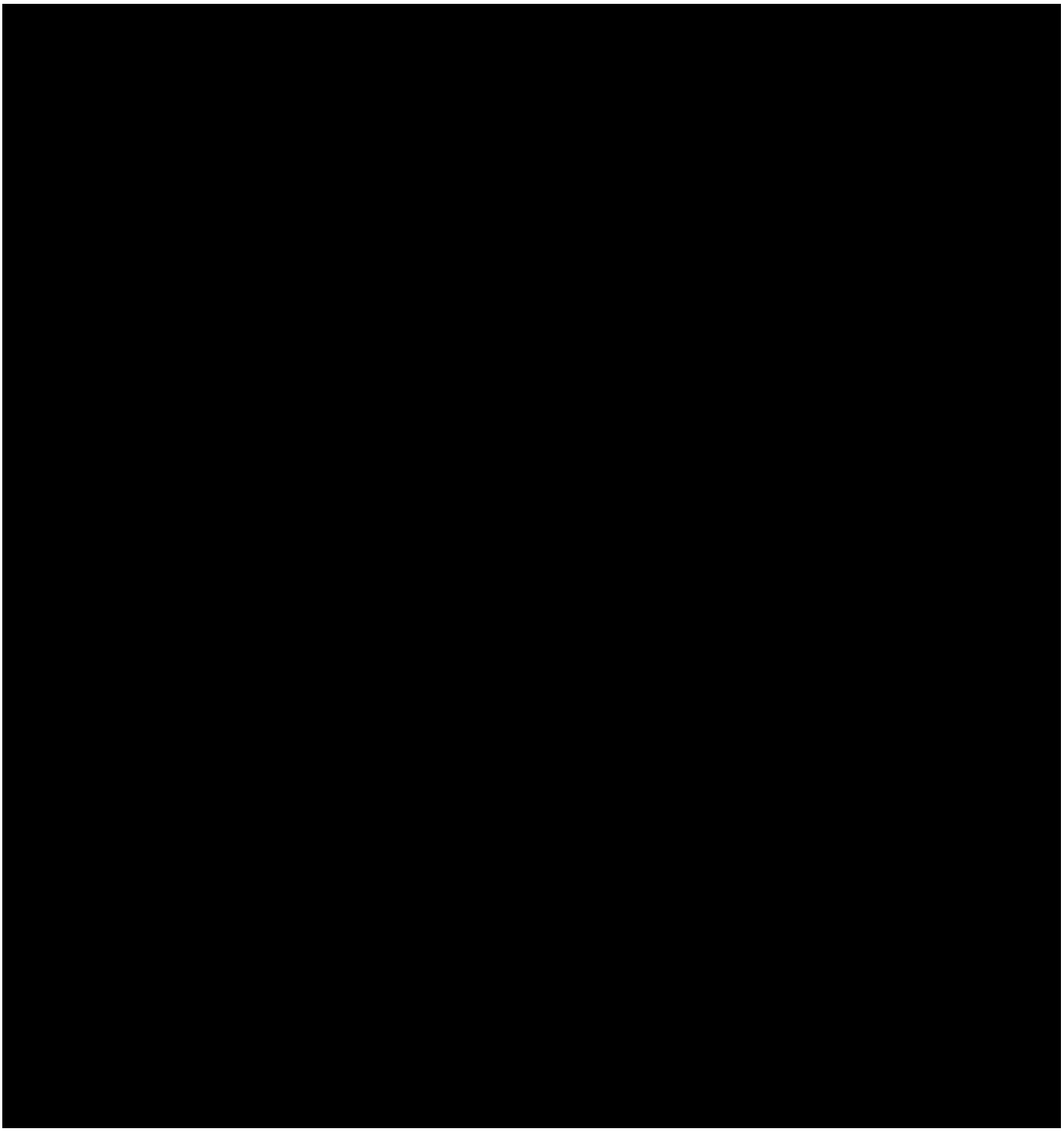
[redacted]

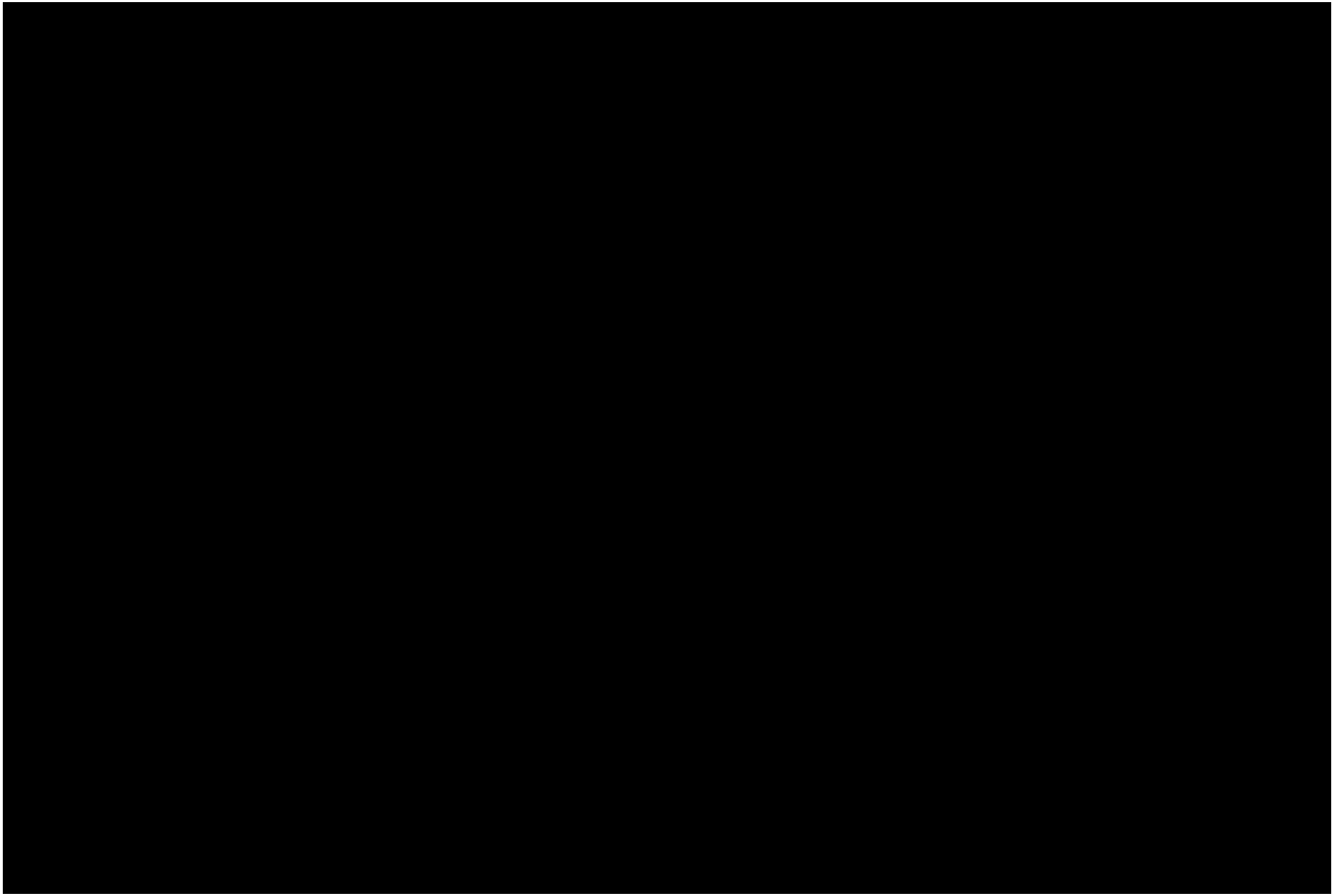
9.4.6 Imaging/Other Safety Assessment

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

[redacted]

[redacted]





[redacted]

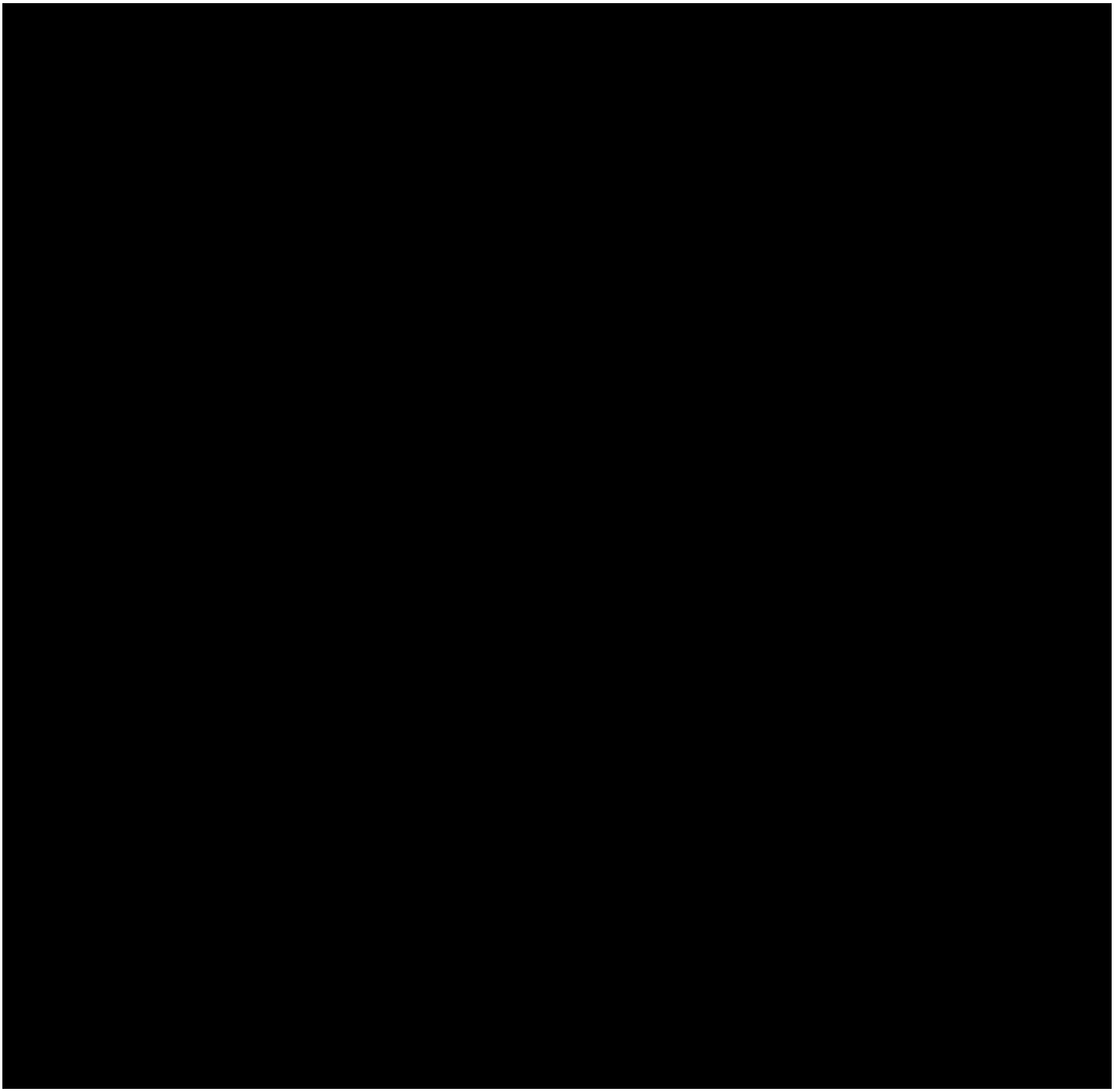
[redacted]

[redacted]

9.8.2.1 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]



9.9 Additional Research

This protocol will include residual sample storage for additional research.

For All US Sites

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

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

For non-US Sites

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

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

Sample Collection and Storage

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

[redacted]

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

The manager of these samples will ensure they are properly used throughout their usable life and will destroy the samples at the end of the scheduled storage period, [redacted] after the end of the study or the maximum allowed by applicable law.

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

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

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

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

Sample Type	Time points for which residual samples will be retained
[redacted]	All
[redacted]	All
[redacted]	All
[redacted]	All
[redacted]	All
[redacted]	All
[redacted]	All
[redacted]	All
[redacted]	All
Other derived/extracted materials from primary collection samples	All

[redacted]

9.10 Other Assessments

Not applicable.

[redacted]

10 STATISTICAL CONSIDERATIONS

10.1 Statistical Hypotheses

The primary hypothesis for the study is that nivo + rela FDC is superior to nivolumab monotherapy in achieving RFS as assessed by the investigator.

The null hypothesis to be tested in relation to the primary endpoint is as follows:

1) Nivo + rela FDC is not different from nivolumab monotherapy with respect to RFS per investigator.

The null hypothesis corresponding to the key secondary endpoint is as follows:

1) Nivo + rela FDC is not different from nivolumab monotherapy with respect to overall survival.

[redacted]

10.2 Sample Size Determination

10.2.1 Recurrence-free Survival

The primary objective of the study is to compare RFS of nivo + rela FDC to nivolumab monotherapy in participants with completely resected Stage IIIA (> 1 mm tumor in lymph node), Stage IIIB/C/D, or Stage IV NED melanoma. [redacted] The sample size calculations were simulated using East® and Statistical Analysis System (SAS®) software (SAS Institute, North Carolina, USA).

[redacted]

[redacted]

[redacted]

10.3 Analysis Sets

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

Population	Description
Enrolled	All participants or their legally acceptable representative who signed an informed consent and were registered into IRT.
Randomized	All participants who were randomized to any treatment arm in the study.
Safety	All participants who take at least 1 dose of double-blind study treatment. Data in this data set will be analyzed based on randomized treatment, except if a participant received the same incorrect treatment throughout the study, then the participant will be analyzed based on the treatment received.
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Abbreviations: [redacted] IRT, interactive response technology; [redacted]

Defined Analysis Data Sets	Description
Analysis set for [redacted] of RFS	All randomized participants. Refer to Table 10.4.1-2 for details of intercurrent strategy.
Analysis set for [redacted] of DMFS	All randomized Stage III/IVA/IVB participants. Refer to Table 10.4.1-2 for details of intercurrent strategy.
Analysis set for [redacted] of OS	All randomized participants. [redacted]
Analysis set for safety	All safety events reported for all randomized participants who are exposed to study drug. For participants who discontinue study intervention, all events post-discontinuation up to Day 135 post last dose of study intervention will be included in the safety summaries.

Abbreviations: DMFS, distant metastasis-free survival; OS, overall survival; RFS, recurrence-free survival.

10.4 Statistical Analyses

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

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

10.4.1 General Considerations

RFS will be programmatically determined based on the disease recurrence date provided by the investigator and is defined as the time between the date of randomization and the first date of documented recurrence [redacted], or death (whatever the cause), [redacted]

Table 10.4.1-1: Censoring Scheme for Definition of Recurrence-free Survival

[redacted]

The stratification factors for analysis are:

- AJCC v8 stage: Stage IIIA/IIIB vs Stage IIIC vs Stage IIID/IV (including all participants with mucosal melanoma, Stage III, Stage IVA, Stage IVB, and Stage IVC)
- Geographic region (USA/Canada/Australia vs Europe vs ROW)

[redacted]

DMFS, by investigator, is defined as the time between the date of randomization and the date of first distant metastasis or date of death (whatever the cause), whichever occurs first. [redacted]

OS is defined as the time between the date of randomization and the date of death. [redacted] OS will be followed continuously while participants are on the study drug and every 12 weeks via in-person or phone contact after participants discontinue the study drug.

Table 10.4.1-2: Definition of Estimands for Primary and Secondary Endpoints

Objective	Endpoint	Estimand
Primary		
To compare the efficacy, as measured by RFS, provided by nivo + rela FDC vs nivolumab monotherapy in participants with completely resected Stage III/IV NED melanoma.	Recurrence or death per investigator	**Population:** All randomized participants with completely resected Stage III/IV NED melanoma. [redacted] **Treatment:** Nivo + rela FDC compared to nivolumab monotherapy [redacted]
Key Secondary Efficacy		
To compare the OS provided by nivo + rela FDC vs nivolumab monotherapy in participants with completely resected Stage III/IV NED melanoma.	OS	**Population:** All randomized participants with completely resected Stage III/IV NED melanoma. [redacted] **Treatment:** Nivo + rela FDC compared to nivolumab monotherapy [redacted]
Other Secondary Efficacy		
To assess the efficacy as measured by distant metastasis-free survival (DMFS), provided by nivo + rela FDC vs nivolumab monotherapy in participants with completely resected Stage III/IVA/IVB NED melanoma.	Distant recurrence or death per investigator	**Population:** All randomized Stage III/IVA/IVB NED participants **Population level summary:** [redacted] **Treatment:** Nivo + rela FDC compared to nivolumab monotherapy [redacted]

Table 10.4.1-2: Definition of Estimands for Primary and Secondary Endpoints

Objective	Endpoint	Estimand
		[redacted]
To compare PFS2 between nivo + rela FDC vs nivolumab monotherapy in randomized participants.	PFS2	**Population:** All randomized participants [redacted] **Treatment:** Nivo + rela FDC compared to nivolumab monotherapy [redacted]
Safety		
To assess safety and toxicity of nivo + rela FDC vs nivolumab monotherapy in participants with completely resected Stage III/IV NED melanoma.	Incidence and severity of AE, SAEs, IMAEs, drug-related AE/SAE, AEs leading to discontinuation, deaths, other select AEs and laboratory abnormalities.	**Population:** Safety analysis population (defined in Section 10.3) [redacted] **Treatment:** Nivo + rela FDC compared to nivolumab monotherapy [redacted]

Abbreviations: AE, adverse event; [redacted] CI, confidence interval; DMFS, distant metastasis-free survival; FDC, fixed dose combination; [redacted] NED, no evidence of disease; OS, overall survival; PFS2, progression-free survival 2; RFS, recurrence free survival; SAEs, serious adverse events; [redacted].

[a] [redacted]

10.4.2 Primary Endpoint(s)

Table 10.4.2-1: Primary Endpoints

Primary Endpoint	Description	Timeframe
Primary Efficacy		
Recurrence Free Survival (RFS)	Time from randomization to the first documentation of recurrence [redacted] or death due to any cause, whichever occurs first.	[redacted]

Table 10.4.2-2: Summary of Primary Endpoint Analysis

Endpoint	Statistical Analysis Methods
RFS as assessed by the investigator. RFS is defined as the time between the date of randomization and the first date of documented recurrence [redacted] or death due to any cause, whichever occurs first.	RFS distributions will be compared between treatment groups (nivo + rela FDC vs nivolumab monotherapy) [redacted] in all randomized population. [redacted]

Abbreviations: [redacted] FDC, fixed dose combination; [redacted] RFS, recurrence-free survival.

[redacted]

[redacted]

10.4.3 Secondary Endpoint(s)

Table 10.4.3-1: Secondary Efficacy Endpoints

Secondary Endpoints	Description	Timeframe
Key Secondary Efficacy		
Overall Survival	Time from randomization date until death (whatever the cause)	[redacted]
Other Secondary Efficacy		
Distant metastasis-free survival	Time from date of randomization to the date of first distant metastasis or date of death (whatever the cause, whichever occurs first).	[redacted]

Table 10.4.3-2: Summary of Secondary Endpoint Analysis

Secondary Endpoints	Statistical Analysis Methods
Key Secondary	
OS is defined as the time between the date of randomization and the date of death (whatever the cause).	[redacted]
Other Secondary	
DMFS, by investigator, is defined as the time between the date of randomization and the date of first distant metastasis or date of death (whatever the cause), whichever occurs first.	[redacted]
PFS2 defined as time from randomization to second recurrence/objective disease progression on next-line systemic therapy per investigator, or death from any cause, whichever occurs first.	[redacted]

Abbreviations: [redacted] DMFS, distant metastasis free survival; FDC, fixed dose combination; [redacted] overall survival; PFS2, progression-free survival 2.

10.4.3.1 Safety Analysis

Table 10.4.3.1-1: Safety Analysis

Safety Endpoint	Description	Timeframe
Safety		
Incidence and severity of AEs, SAEs, IMAEs, other select AEs, laboratory abnormalities, drug related AEs/SAEs, death	Incidence and severity (i.e. CTC grade) of AEs, SAEs, IMAEs, other select AEs, laboratory abnormalities, drug related AEs/SAEs, death	Up to 135 days after the last dose of study treatment
Incidence of AEs leading to discontinuation	Incidence and severity of AEs leading to discontinuation of study treatment	Up to discontinuation of study treatment

Abbreviations: AE, adverse event; CTC, Common Terminology Criteria; IMAEs, immune mediated adverse events; SAE, serious adverse event.

[redacted]

10.4.5 Other Safety Analysis

All safety analyses will be performed using the Safety analysis population.

Endpoint	Statistical Analysis Methods
The Safety and tolerability objective will be measured by the incidence and severity of adverse events (AEs), serious adverse events (SAEs), and adverse events leading to discontinuation study drug, select AEs, immune-mediated AEs (IMAEs), other events of special interest (OESIs), deaths, and laboratory abnormalities in each arm.	All safety analyses will be performed using the safety analysis population. The frequency of deaths, adverse events (AEs), serious adverse events (SAEs), AEs leading to discontinuation of study drug, select AEs, immune-mediated AEs (IMAEs), other events of special interest (OESIs), and abnormalities in specific clinical laboratory assessments will be presented. The safety summaries will be presented by severity were applicable. Analyses will be conducted using the 30-day and/or 135-day safety window from day of last dose received. AEs will be coded using the most recent Medical Dictionary for Regulatory Activities (MedDRA) version available during the conduct of the study. AEs and laboratory values will be graded for severity according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

[redacted]

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12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
ADA	anti-drug antibodies
AE(s)	adverse event(s)
AIDS	acquired immunodeficiency syndrome
AJCC	American Joint Committee on Cancer
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ART	antiretroviral therapy
AST	aspartate aminotransferase
AUC(TAU)	area under the plasma concentration-time curve over dosing interval
AxMP	auxiliary medical product
[redacted]	[redacted]
BICR	blinded independent central review
BMS	Bristol Myers Squibb
BRAF	B-RAF proto-oncogene
BUN	blood urea nitrogen
Cavgss	steady state average concentration
CBC	complete blood count
C	cycle
CD	cluster of differentiation
CFR	Code of Federal Regulations
cHL	classical Hodgkin's lymphoma
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CL	clearance
CrCl	creatinine clearance
CLNR	nonrenal clearance
CLND	complete lymph node dissection
CLss	steady-state clearance
Cmax	maximum observed concentration

Term	Definition
CNS	central nervous system
COVID-19	coronavirus disease 2019
[redacted]	[redacted]
CRC	colorectal cancer
CrCl	creatinine clearance
CRF	case Report Form, paper or electronic (eCRF)
CSR	clinical study report
CT	computed tomography
CTAg	clinical trial agreement
CTCAE	common terminology criteria for adverse events
[redacted]	[redacted]
CTLA	cytotoxic T-lymphocyte-associated protein 4
CV%	coefficient of variation %
D	day
DAB	dabrafenib
dL	deciliter
DILI	drug induced liver injury
DLT	dose limiting toxicity
DMC	data monitoring committee
DMFS	distant metastasis-free survival
[redacted]	[redacted]
DRESS	drug reaction with eosinophilia and systemic symptoms
eCOA	electronic clinical outcome assessments
ECG(s)	electrocardiogram(s)
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EC50	half-maximal effective concentration
eg	exempli gratia (for example)
eGFR	estimated glomerular filtration rate
EOI	end of infusion

Term	Definition
[redacted]	
E-R	exposure-response
EUDAMED	European Databank on Medical Devices
[redacted]	[redacted]
FDA	Food and Drug Administration
FDC	Fixed-dose combination
FDG	fluorodeoxyglucose
[redacted]	[redacted]
FFR	Freedom From Relapse
FGL-1	fibrinogen-like protein 1
FSH	follicle stimulating hormone
fT3	free T3
fT4	free T4
FU	follow-up
GBS	Guillain-Barre Syndrome
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GI	gastrointestinal
h	hour
HBsAg	hepatitis B virus surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCG	human chorionic gonadotropin
HCV	hepatitis C virus
H&E	hematoxylin & eosin
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HR	hazard ratio
HRQoL	health-related quality of life
HRT	hormone replacement therapy

Term	Definition
IA	interim analysis
IB	Investigator's Brochure
IC50	half-maximal inhibitory concentration
[redacted]	[redacted]
ICF	informed consent form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDO	indoleamine 2,3-dioxygenase
ie	id est (that is)
IEC	Independent Ethics Committee
[redacted]	[redacted]
[redacted]	[redacted]
IgG4	immunoglobulin G4
IHC	immunohistochemistry
IMAE	immune-mediated adverse event
IMG	immunogenicity
IP/IMP	investigational [medicinal] products
IND	Investigational New Drug Exemption
IO	immuno-oncology
IPI	ipilimumab
IUS	intrauterine hormone-releasing system
IRB	Institutional Review Board
IRT	Interactive Response Technology
IU	International Unit
IV	intravenous
kg	kilogram
K-M	Kaplan Meier
LAG-3	lymphocyte activation gene-3
LAM	lactational amenorrhea method
LD	longest diameter

Term	Definition
LDH	lactate dehydrogenase
LN	lymph node
MedDRA	Medical Dictionary for Regulatory Activities
MEK	mitogen-activated protein kinase
mg	milligram
MG	Myasthenia Gravis
MHC	major histocompatibility complex
min	minute
mL	milliliter
mmHg	millimeters of mercury
[redacted]	[redacted]
MMR	measles, mumps, rubella
[redacted]	[redacted]
MRI	magnetic resonance imaging
MSLT-II	Multicenter Selective Lymphadenectomy Trial
MSS	melanoma specific survival rate
MTD	maximum tolerated dose
µg	microgram
N	number of subjects or observations
N/A	not applicable
NCCN	National Comprehensive Cancer Network
NCT	National clinical trial number
NED	no evidence of disease
ng	nanogram
NGS	next generation sequencing
NIMP	non-investigational medicinal products
Nivo	nivolumab
NK	natural killer
[redacted]	[redacted]
NSAID	nonsteroidal anti-inflammatory drug

Term	Definition
NSCLC	non-small cell lung cancer
OESI	other events of special interest
ORR	objective response rate
OS	overall survival
[redacted]	[redacted]
PD-1	programmed death-1
PD-L1	programmed death ligand-1
PD-L2	programmed death ligand-2
PEMBRO	pembrolizumab
PET	positron emission tomography
PET-CT	positron emission tomography-computed tomography
PFS	progression-free survival
PFS2	progression-free survival 2
PK	pharmacokinetics
PPK	population pharmacokinetics
PRO	patient reported outcome
Q2W	every 2 weeks
Q3W	every 3 weeks
Q4W	every 4 weeks
[redacted]	[redacted]
R&D	Research and Development
RCC	renal cell carcinoma
Rela	relatlimab
RFS	recurrence free survival
[redacted]	[redacted]
RO	receptor occupancy
ROW	rest of the world
RT-PCR	reverse transcription polymerase chain reaction
SAE(s)	serious adverse event(s)
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2

Term	Definition
SAP	statistical analysis plan
SAV	single agent vial
[redacted]	[redacted]
SCCHN	squamous cell carcinoma of the head and neck
SJS	Stevens-Johnson syndrome
SLN	sentinel lymph nodes
SLNB	sentinel lymph node biopsy
SOA	Schedule of Activities
SPSD	Site Process and Source Documentation
SUSAR	suspected, unexpected serious adverse reaction
T3	triiodothyronine
T4	thyroxine
TB	total bilirubin
T.Bili	total bilirubin
TEN	toxic epidermal necrolysis
[redacted]	[redacted]
TME	tumor microenvironment
TILs	tumor infiltrating lymphocytes
[redacted]	[redacted]
TNM	tumor/node/metastasis
[redacted]	[redacted]
TRAE	treatment-related adverse event
TRAM	trametinib
TSH	thyroid stimulating hormone
TSST	time to second subsequent therapy
tT3	total T3
tT4	total T4
ULN	upper limit of normal
USA	United States of America
USPI	United States Prescribing Information

Term	Definition
VAS	visual analog scale
Vss/F (or Vss)	apparent volume of distribution at steady state
Vz	Volume of distribution of terminal phase (if IV and if multi-exponential decline)
WES	whole exome sequencing
WOCBP	women of childbearing potential
WS	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 Institutional Review Board/Independent Ethics Committee (IRB/IEC), and regulatory authorities according to applicable regulations prior to initiation of the study.

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

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

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

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

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

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

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

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

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

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

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

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

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

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

FINANCIAL DISCLOSURE

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

INFORMED CONSENT PROCESS

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

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

The investigator or his/her representative must:

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

Obtain an ICF signed and personally dated by participant or his/her legally acceptable representative and by the person who conducted the informed consent discussion.

- Include a statement in participant's medical record that written informed consent was obtained before participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Re-consent participant to the most current version of the ICF(s) during his/her participation in the study, as applicable.

Revise the ICF whenever important new information becomes available that is relevant to the participant's consent. The investigator, or a person designated by the investigator, should fully inform the participant or his/her legally acceptable representativeof 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. The explicit wish of a minor, who is capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the clinical study at any time, should be considered by the investigator.

Minors who are judged to be of an age of reason must also give their written consent. Minors who reach the age of majority (legal adulthood) during the clinical study must 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.

BMS COMMITMENT TO DIVERSITY IN CLINICAL TRIALS

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

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

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

DATA PROTECTION, DATA PRIVACY, AND DATA SECURITY

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

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

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

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

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

SOURCE DOCUMENTS

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

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

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

The investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original, and attributable, whether the data are handwritten on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of 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: • amount received and placed in storage area • amount currently in storage area • label identification number or batch number • amount dispensed to and returned by each participant, including unique participant identifiers • amount transferred to another area/site for dispensing or storage • nonstudy disposition (eg, lost, wasted) • amount destroyed at study site, if applicable • amount returned to BMS • retain samples for bioavailability/bioequivalence/biocomparability, if applicable • dates and initials of person responsible for Investigational Product dispensing / accountability, as per the Delegation of Authority Form
Sourced by site and not supplied by BMS or its vendors (examples include IP sourced from the sites stock or commercial supply or a specialty pharmacy)	The investigator or designee accepts responsibility for documenting traceability and study treatment integrity in accordance with requirements applicable under law and the standard operating procedures/standards of the sourcing pharmacy

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

CASE REPORT FORMS

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

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

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

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

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

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

MONITORING

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

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

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

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

RECORDS RETENTION

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

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

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

RETURN OF STUDY TREATMENT

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

If	Then
Study treatments supplied by BMS (including its vendors)	Any unused study interventions supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor, unless study treatments containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics). Partially used study interventions and/or empty containers may be destroyed after proper reconciliation and documentation. But unused IMP must be reconciled by site monitor/Clinical Research Associate prior to destruction. If study treatments will be returned, the return will be arranged by the responsible Study Monitor.

Study treatments sourced by site, not supplied by BMS (or its vendors; eg, study treatments sourced from the site's stock or commercial supply or a specialty pharmacy)	It is the investigator's or designee's responsibility to dispose of all containers according to the institutional guidelines and procedures.

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

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

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

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

STUDY AND SITE START AND CLOSURE

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

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local Health Authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator

- Discontinuation of further study intervention development

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

DISSEMINATION OF CLINICAL STUDY DATA

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

CLINICAL STUDY REPORT

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

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

- Participant recruitment (eg, among the top quartile of enrollers)
- External Principal Investigator designated at protocol development
- National Coordinating Investigator
- Study Steering Committee chair or their designee
- Involvement in trial design
- Regional representation (eg, among top quartile of enrollers from a specified region or country)
- Other criteria (as determined by the study team)

SCIENTIFIC PUBLICATIONS

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

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

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

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

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

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

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

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

ADVERSE EVENTS

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

DEFINITION OF SAE

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

SERIOUS ADVERSE EVENTS

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

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

EVALUATING AES AND SAES

Assessment of Causality

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

Follow-up of AEs and SAEs

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

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

All SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

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

SAE Email Address: [redacted]

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

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

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

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

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP:

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

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

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

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

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

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

End of Relevant Systemic Exposure

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

METHODS OF CONTRACEPTION

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

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

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

- Vasectomized partner

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

- Sexual abstinence

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

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

NOTES:

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

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

[c] IUSs are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness. For information specific to this study regarding permissibility of hormonal contraception, refer to Sections 6.1 INCLUSION CRITERIA and 7.7.1 PROHIBITED AND/OR RESTRICTED TREATMENTS of the protocol.

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

COLLECTION OF PREGNANCY INFORMATION

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

APPENDIX 5 MANAGEMENT ALGORITHMS FOR STUDIES UNDER CTCAE VERSION 5.0

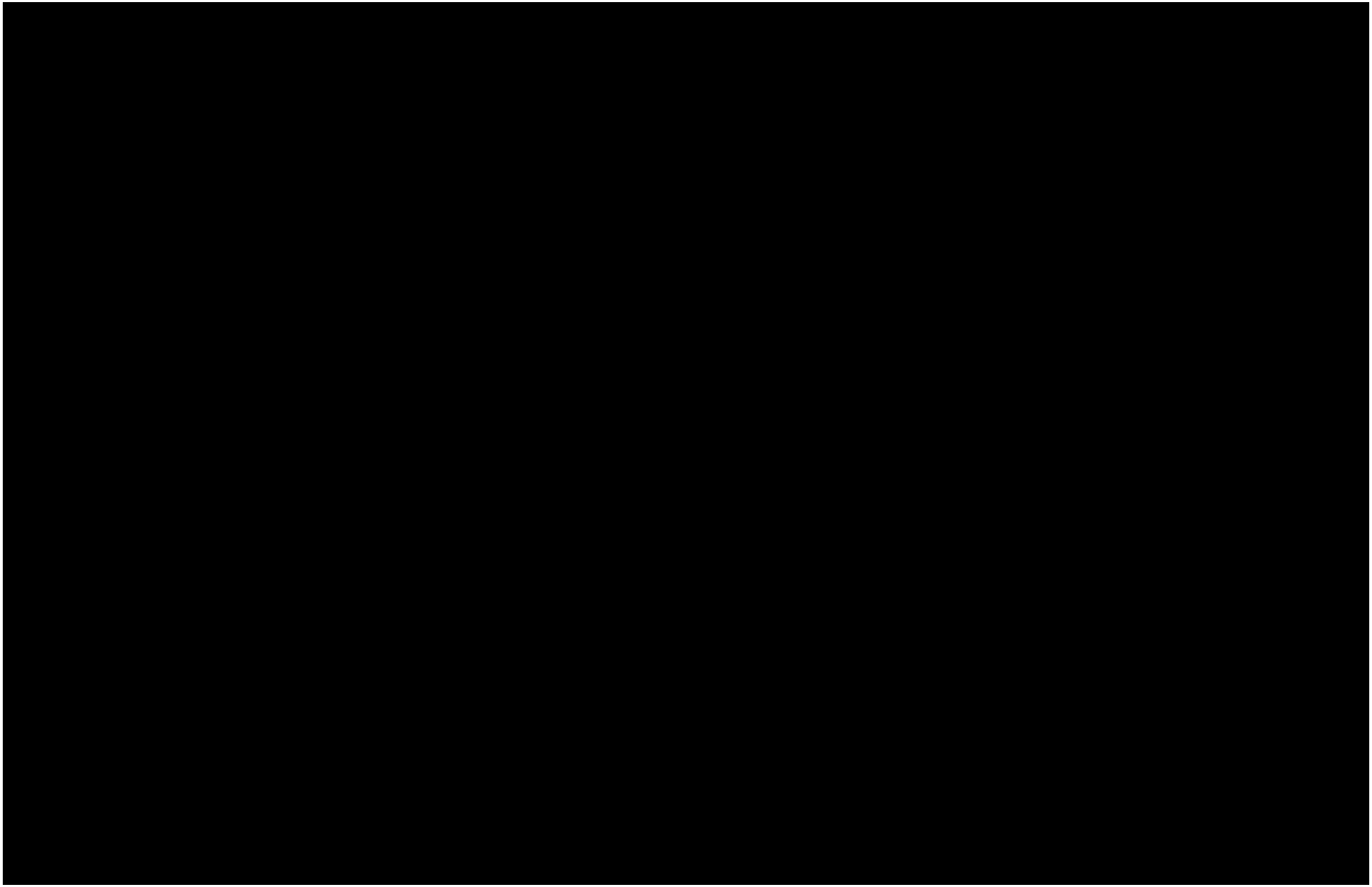
These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology agents and regimens.

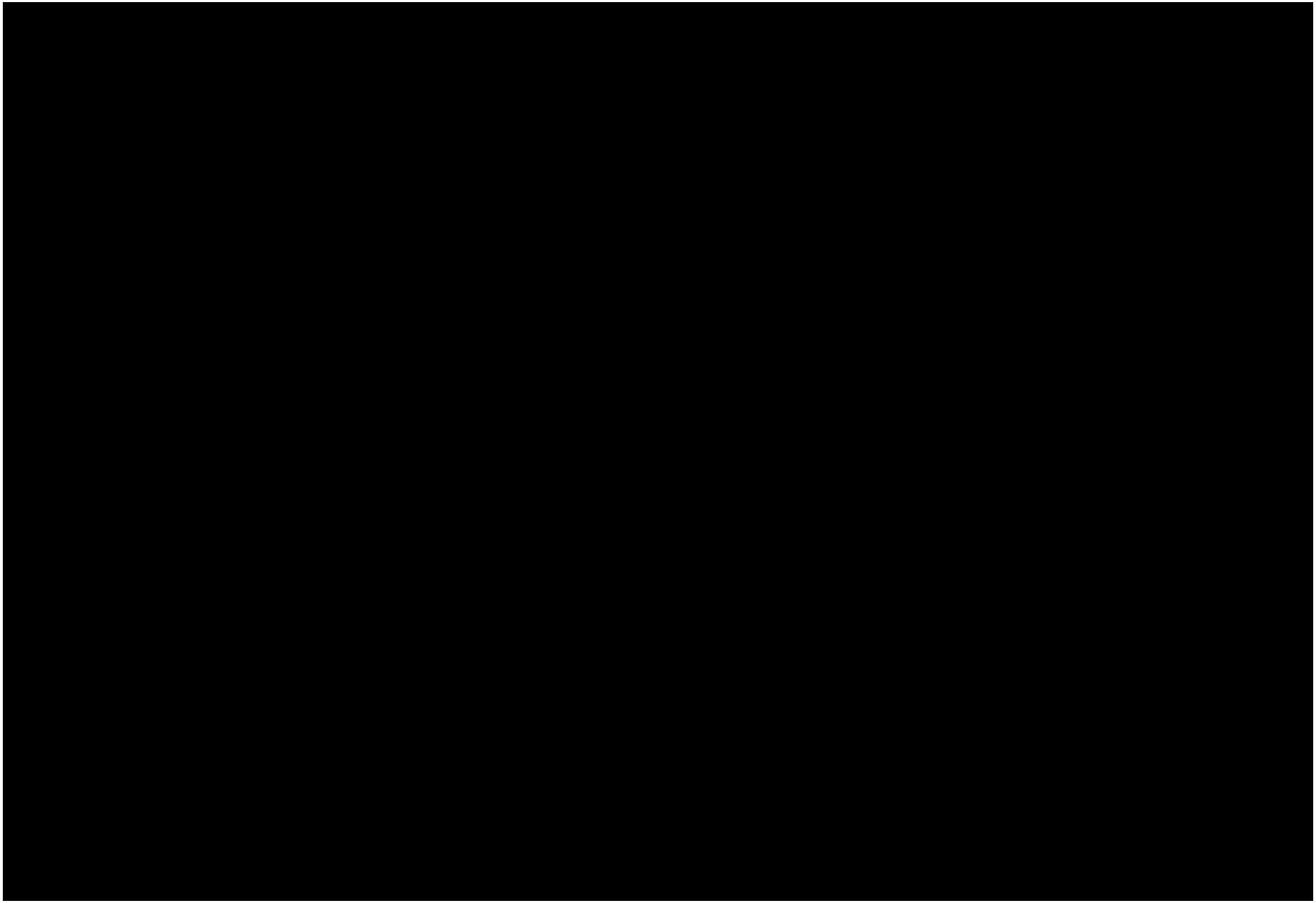
A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

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.





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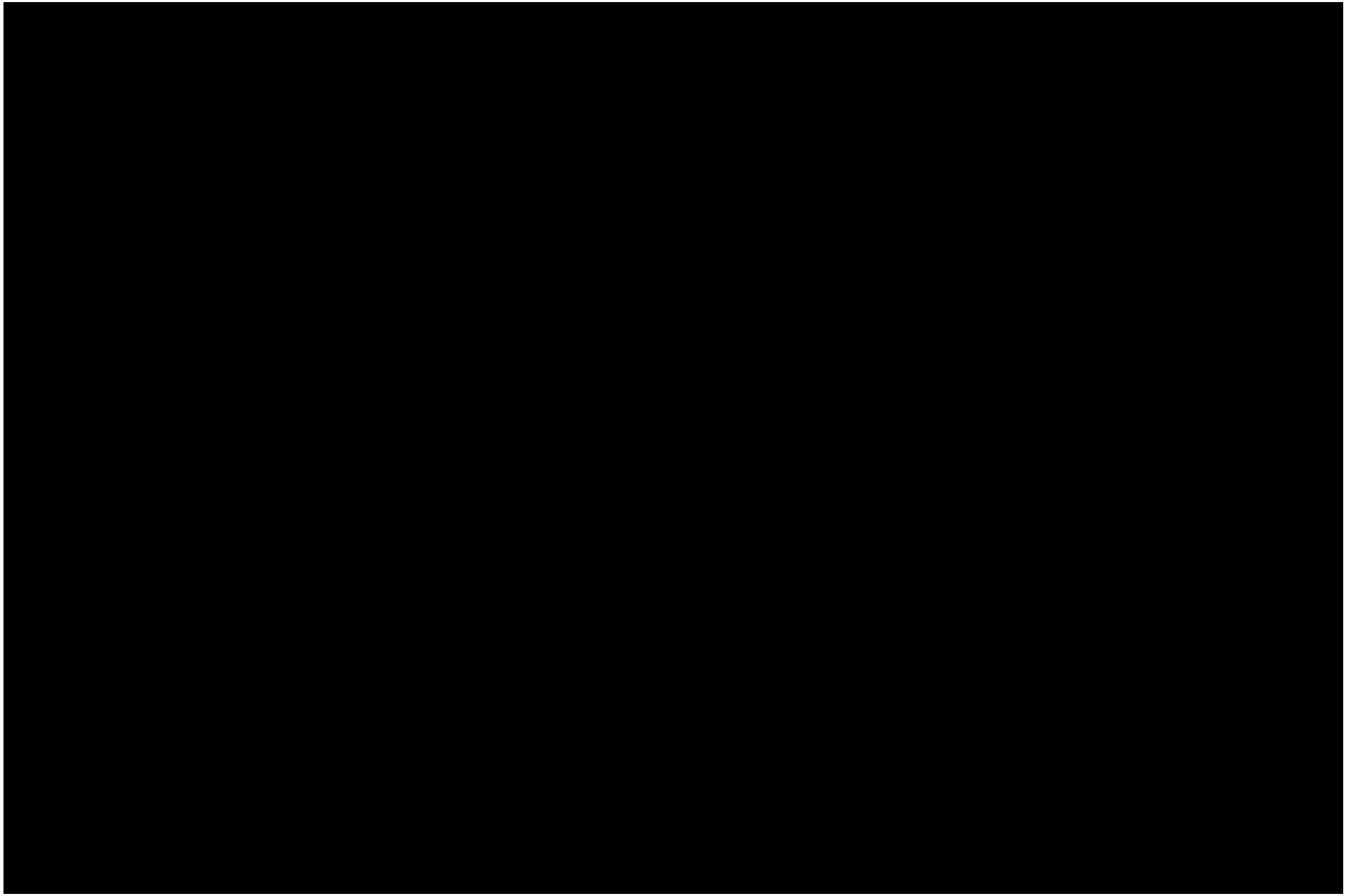

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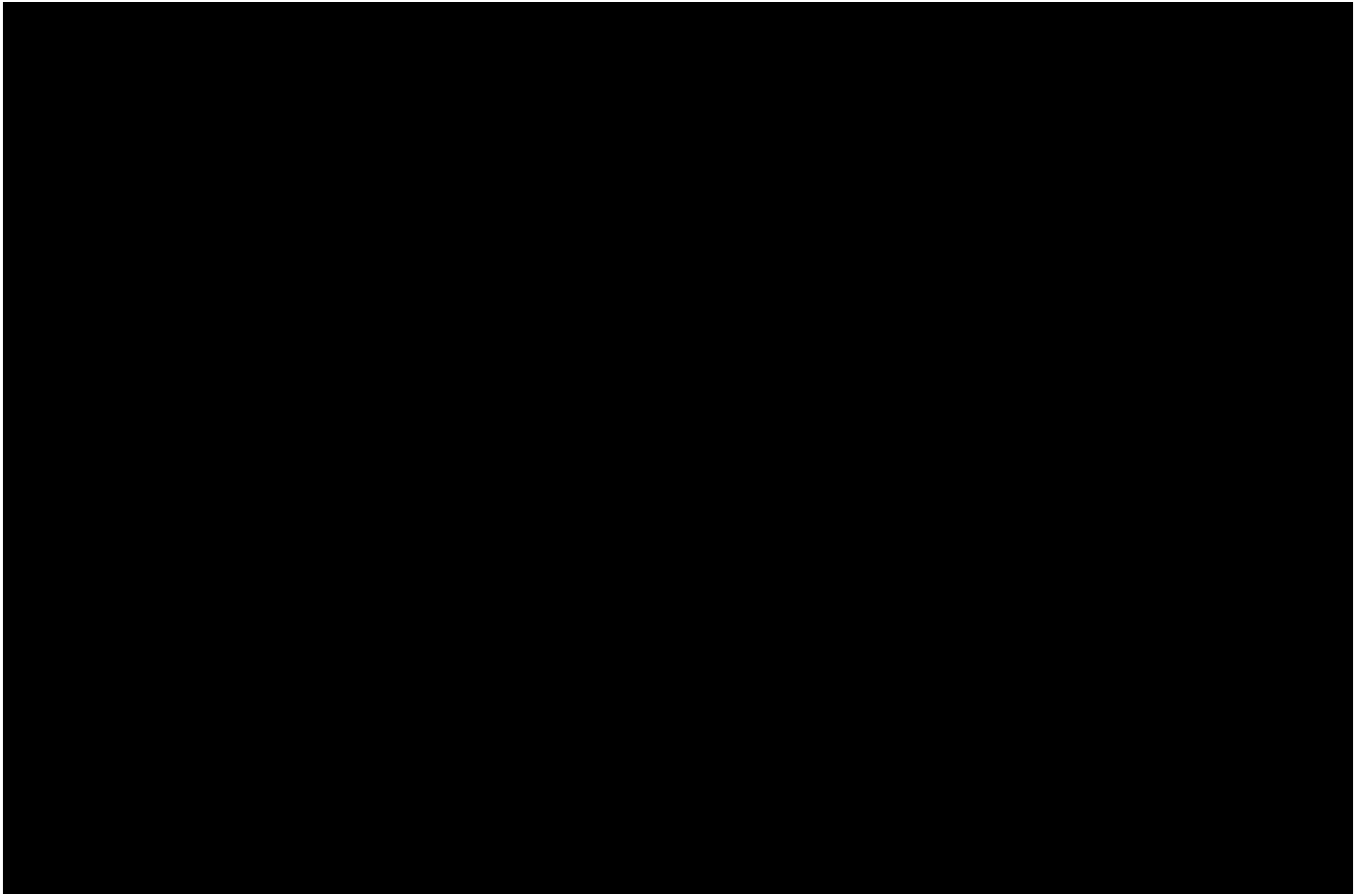

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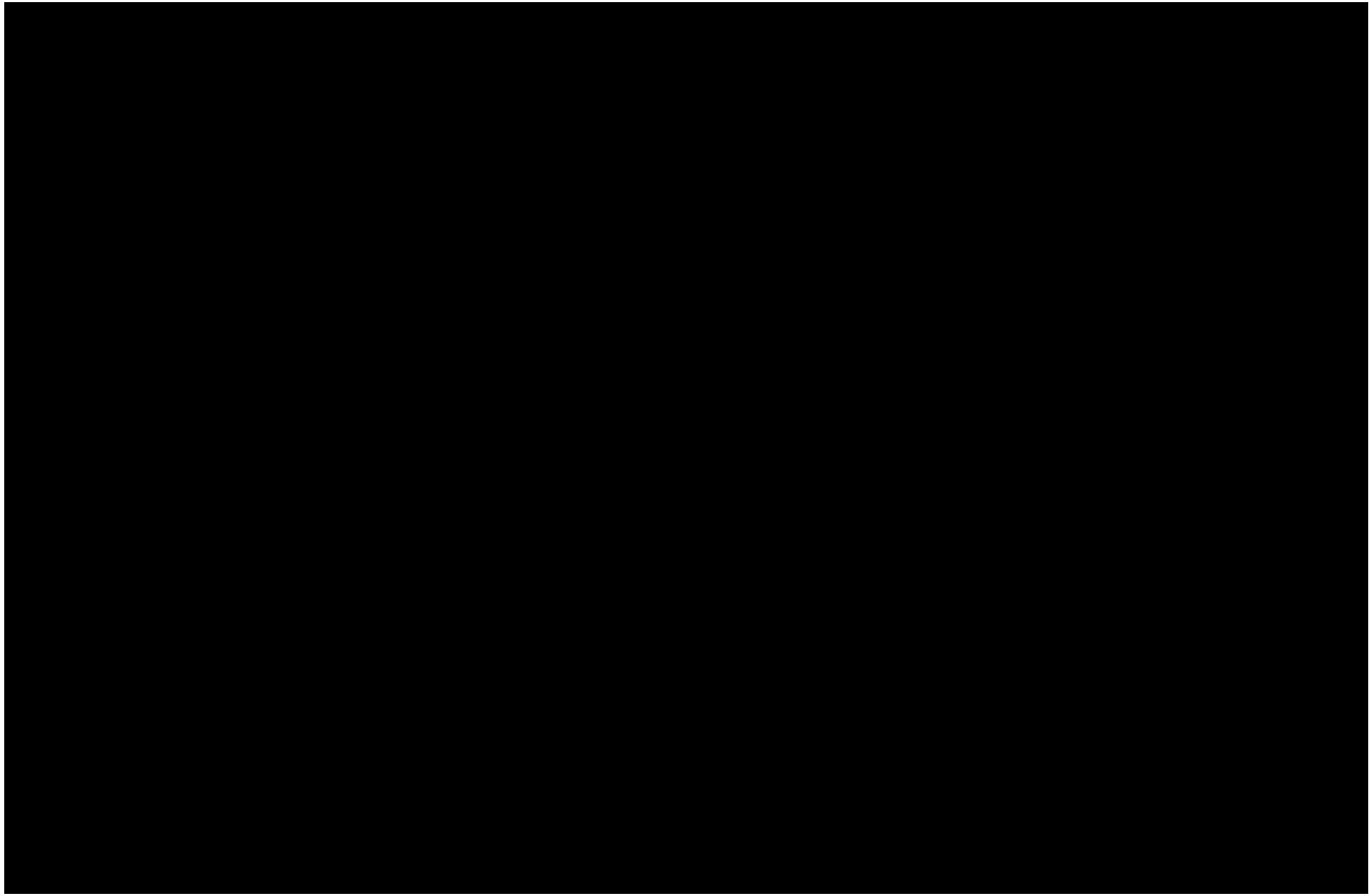


APPENDIX 6 ECOG AND LANSKY/KARNOFSKY PERFORMANCE STATUS SCALE

PERFORMANCE STATUS CRITERIA: ECOG Score	
ECOG (Zubrod)	
Score	**Description**
0	Fully active; able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of alight or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all self care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of only limited self care; confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self care; totally confined to bed or chair.

PERFORMANCE STATUS CRITERIA: Karnofsky and Lansky		
Score	**Karnofsky Description (≥ 16 years of age)**	**Lansky Description (12 years to < 16 years age)**
100	Normal; no complaints; no evidence of disease.	Fully active, normal.
90	Able to carry on normal activity; minor signs or symptoms of disease.	Minor restrictions in physically strenuous activity.
80	Normal activity with effort; some signs or symptoms of disease.	Active, but tires more quickly.
70	Cares for self; unable to carry on normal activity or to do active work.	Substantial restriction of, and less time spent, in play activity.
60	Requires occasional assistance, but is able to care for most of their personal needs.	Out of bed, but minimal active play; keeps busy with quiet activities.
50	Requires considerable assistance and frequent medical care.	Gets dressed, but inactive much of day; no active play, able to participate in quiet play.
40	Disabled; requires special care and assistance.	Mostly in bed; participates in some quiet activities.
30	Severely disabled; hospital admission is indicated although death not imminent.	In bed; needs assistance even for quiet play.
20	Very sick; hospital admission necessary; active supportive treatment necessary.	Often sleeping; play limited to passive activities.
10	Moribund; fatal processes progressing rapidly.	No play; does not get out of bed.
0	Dead	Unresponsive

APPENDIX 7 AJCC MELANOMA STAGING (CANCER STAGING MANUAL 8TH EDITION)

Definition of Primary Tumor (T)

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

Definition of Distant Metastasis (M)

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

Definition of Regional Lymph Node (N)

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

AJCC Prognostic Stage Groups

Clinical (cTNM)

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

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

PATHOLOGICAL (pTNM)

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

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

When T is....	And N is.....	And M is....	The pathological stage is...
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 or 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 [redacted] and T1 do not require pathological evaluation of lymph nodes to complete pathological staging; use cN information to assign their pathological stage.			

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

APPENDIX 8 MUCOSAL MELANOMA STAGING

All mucosal melanoma, regardless of anatomical location, should be staged using the following classification.

The American Joint Committee on Cancer (AJCC) TNM Staging System for Mucosal Melanoma of the Head and Neck[a,b,c,d]

Primary Tumor (T)		Characteristics
T3		Tumors limited to the mucosa and immediately underlying soft tissue, regardless of thickness or greatest dimension; for example, polypoid nasal disease, pigmented or nonpigmented lesions of the oral cavity, pharynx, or larynx
T4		Moderately advanced or very advanced disease
	T4a	Moderately advanced disease - Tumor involving deep soft tissue, cartilage, bone, or overlying skin
	T4b	Very advanced disease - Tumor involving brain, dura, skull base, lower cranial nerves (IX, X, XI, XII), masticator space, carotid artery, prevertebral space, or mediastinal structures

Regional Lymph Nodes (N)	Characteristics
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis present

Distant Metastasis (M)	Characteristics
M0	No distant metastasis
M1	Distant metastasis

Staging group	Tumor	Node	Metastases
III	T3	N0	M0
IVA	T3-T4a	N1	M0
IVA	T4a	N0	M0
IVB	T4b	Any N	M0
IVC	Any T	Any N	M1

[a] NCCN Clinical Practice Guidelines in Oncology: Head and Neck Cancers. National Comprehensive Cancer Network. Version 1.2020 - February 12, 2020. Assessed March 22, 2020.

[b] Head and Neck. American Joint Committee on Cancer. AJCC Cancer Staging Manual. 8th edition. New York, NY: Springer, 2016.

[c] Histologic Grade (G): There is no recommended histologic grading system at this time.

[d] Prognostic Stage Groups: Currently, there is no clear ability to determine prognosis based on histologic differences.

APPENDIX 9 COUNTRY-SPECIFIC REQUIREMENTS

Country	Section Number and Title	Original Language	Country-specific Language or Differences
Argentina, Czech Republic, Germany, Romania, and Any Other Countries Where Exclusion of HIV Positive Participants is Locally Mandated	Table 2-1, Screening Procedural Outline - Clinical Laboratory Assessments		Add "HIV" to the list of laboratory tests
Argentina, Czech Republic, Germany, Romania, and Any Other Countries Where Exclusion of HIV Positive Participants is Locally Mandated	Section 6.2, Exclusion Criteria - 3k Table 9.4.4-1, Clinical Laboratory Assessments	Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)	Positive test for HIV.
Denmark, Germany, Greece, and Sweden	Table 2-1, Screening Procedural Outline - Informed Consent Section 6.1, Inclusion Criteria - 3b		Adolescents can no longer be enrolled in these countries; participants must be ≥ 18 years of age.
Denmark			
Denmark	Table 4-1, Objectives and Endpoints - Exploratory	*Objective:* [redacted]	*Objective:* [redacted]

Country	Section Number and Title	Original Language	Country-specific Language or Differences
		Endpoint: [redacted]	*Endpoint:* [redacted]
Denmark	Table 4-1, Objectives and Endpoints - Exploratory	*Objective:* [redacted]	[redacted]
Denmark	Table 4-1, Objectives and Endpoints - Exploratory Endpoint	[redacted]	[redacted]
Denmark	Section 5.4.6, Rationale for Evaluation of [redacted]	[redacted]	[redacted]
Denmark	[redacted]		[redacted]
Denmark	[redacted]		[redacted]
Denmark	[redacted]		[redacted]

Country	Section Number and Title	Original Language	Country-specific Language or Differences
[redacted]	[redacted]		
Denmark	[redacted]		[redacted]
Denmark	[redacted]	[redacted]	[redacted]
Germany			
Germany	Table 2-1, Screening Procedural Outline - Body Imaging	Contrast-enhanced CT of the chest, abdomen, pelvis, and all suspected sites of disease, within 35 days prior to randomization. See Section 9.1.2 for further details and exceptions. For head and neck mucosal melanomas, contrast-enhanced CT of the neck also required at screening as reference for on-treatment nodal surveillance.	Contrast-enhanced CT of the chest, abdomen, pelvis, and all suspected sites of disease, within 35 days prior to randomization. See Section 9.1.2 for further details and exceptions. For head and neck mucosal melanomas, contrast-enhanced CT of the neck also required at screening as reference for on-treatment nodal surveillance. MRI may be used as an alternative imaging modality to CT at screening, during treatment, and in follow-up.

Country	Section Number and Title	Original Language	Country-specific Language or Differences
Germany	Table 2-2, On Study Treatment Procedural Outline - Body Imaging	In case of suspected lesions in the extremities, contrast-enhanced MRI can be substituted for contrast-enhanced CT. For head and neck mucosal melanomas, contrast-enhanced MRI of the head and neck is required at every time point for nodal surveillance.	MRI may be used as an alternative imaging modality to CT at screening, during treatment, and in follow-up.
Germany	Table 2-3, Follow-up Assessments - Body Imaging	In cases of suspected lesions of the extremities, contrast-enhanced MRI may be substituted for contrast-enhanced CT. For head and neck mucosal melanoma, contrast-enhanced MRI of the head and neck is required at every time point for nodal surveillance.	MRI may be used as an alternative imaging modality to CT at screening, during treatment, and in follow-up.
Germany	[redacted]	[redacted]	[redacted]

Country	Section Number and Title	Original Language	Country-specific Language or Differences
Germany	[redacted]	[redacted]	[redacted]
Germany	Section 9.1.1, Efficacy Assessment for the Study	In cases of suspected lesions of the extremities, MRI (with and without contrast) may be substituted for contrast-enhanced CT.	MRI may be used as an alternative imaging modality to CT at screening, during treatment and in follow-up.
Germany	Section 9.1.3, Investigator Assessment of Baseline Disease Status	Participant eligibility (disease-free status) must be confirmed by investigator prior to randomization. Baseline disease assessments should be performed within 35 days prior to randomization, including contrast-enhanced CT of the chest, abdomen, pelvis, and all suspected sites of disease. Baseline MRI of the brain (with and without contrast) is required for ALL participants during screening to rule out brain metastases, within 35 days prior to randomization. CT of the brain (without and with contrast) can be performed if MRI is contraindicated.	Participant eligibility (disease-free status) must be confirmed by investigator prior to randomization. Baseline disease assessments should be performed within 35 days prior to randomization, including contrast-enhanced CT of the chest, abdomen, pelvis, and all suspected sites of disease. MRI may be used as an alternative imaging modality to CT at screening, during treatment, and in follow-up.

Country	Section Number and Title	Original Language	Country-specific Language or Differences
Germany	[redacted]	[redacted]	[redacted]
Greece			
Greece	Section 6.2, Exclusion Criteria, 5a	Per Administrative Letter effective 13-Jul-2021: Greek sites should follow the stricter local regulations according to the Ministerial Decision G5a/59676/21-11-2016 (Government Gazette Issue No 4131/B/22-12-2016) - Article 11, and not allow participants in prison to participate in the trial.	
		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.)	Prisoners or participants who are involuntarily incarcerated.
Norway			
Norway	[redacted]	[redacted]	[redacted]

APPENDIX 10 PROTOCOL AMENDMENT SUMMARY OF CHANGE HISTORY

Overall Rationale for Protocol Amendment 02, 22-Feb-2023

The main reasons for this amendment are the following:

- [redacted]
- [redacted]
- The population for the distant metastasis-free survival (DMFS) secondary objective was limited to randomized participants with Stage III/IVA/IVB no evidence of disease (NED) melanoma.
- An additional clarification for neck magnetic resonance imaging (MRI) was provided for head and neck mucosal melanomas, since imaging plays a vital role for the evaluation of these melanomas given the invasion into adjacent soft tissue.
- In order to consolidate the previously published and implemented country-specific amendments for Denmark, Germany, Greece, and Sweden with the global amendment in preparation for the European Union Clinical Trials Regulation (EU CTR) transition, certain country-specific paragraphs were delineated while others were consolidated for easier reading without changing context.

These revisions are specified below and have been incorporated into the Protocol Summary.

Revisions apply to all participants currently enrolled.

Summary of Key Changes for Protocol Amendment 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-1: Screening Procedural Outline	Added sentence about local regulations that do not allow adolescents (< 18 years) to participate in the study. [redacted]	Wording already present in country-specific amendments modified and/or added to consolidate with global amendment in preparation for EU CTR.

Summary of Key Changes for Protocol Amendment 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-2: On Study Treatment Procedural Outline	[redacted]	
Section 6.2: Exclusion Criteria	[redacted]	
Table 7.4.1-1: AE Criteria for Delay, Resume, and Discontinue of Treatment	[redacted]	
Table 9.4.4-1: Clinical Laboratory Assessments	[redacted]	
[redacted]	[redacted]	
[redacted]	[redacted]	
Appendix 9: Country-Specific Requirements	Added and revised rows for Denmark-, Germany-, Greece-, and Sweden-specific requirements and differences.	
Table 2-1: Screening Procedural Outline Table 2-2: On Study Treatment Procedural Outline Table 2-3: Follow-up Assessments	Added that ultrasounds should not be submitted to imaging vendor.	To align with current BMS processes.
Table 2-2: On Study Treatment Procedural Outline Table 2-3: Follow-up Assessments Section 9.1.1: Efficacy Assessment for the Study	For body/brain imaging and ultrasounds, added that the assessments at every 26 weeks (± 14 days) should be "beyond the Week 108 imaging time point thereafter."	Clarification for the timing when sites should switch to imaging every 26 weeks.

Summary of Key Changes for Protocol Amendment 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-2: On Study Treatment Procedural Outline Table 2-3: Follow-up Assessments Section 8.1.2 Post-study Intervention Study Follow-up Section 9.1.1: Efficacy Assessment for the Study Section 9.1.2: Imaging Assessment for the Study Section 9.1.4: Investigator Assessment of Recurrence	[redacted]	To align with the tumor/node/ metastasis (TNM) staging system for Mucosal Melanoma of the Head and Neck from the American Joint Committee on Cancer (AJCC v8).
Table 2-2: On Study Treatment Procedural Outline Table 2-3: Follow-up Assessments	Added imaging requirements for mucosal melanoma of the head and neck to require MRI at every time point.	To ensure surveillance for mucosal head and neck participants is using the most clinically appropriate modality.
Table 2-2: On Study Treatment Procedural Outline Table 2-3: Follow-up Assessments Section 9.1.5: Patient-Reported Outcomes	Added that Health Outcomes assessments [redacted] Added that adolescent participants will continue to complete only the [redacted] even if they become ≥ 18 years of age during treatment or follow-up. Added that if dose is delayed after collection of Health Outcomes, submit data change form to move original data entry to unscheduled visit.	To align with current BMS processes and for clarity.
Table 2-3: Follow-up Assessments [redacted]	[redacted]	[redacted]
Table 2-2: On Study Treatment Procedural Outline Table 2-3: Follow-up Assessments [redacted]	[redacted]	[redacted]

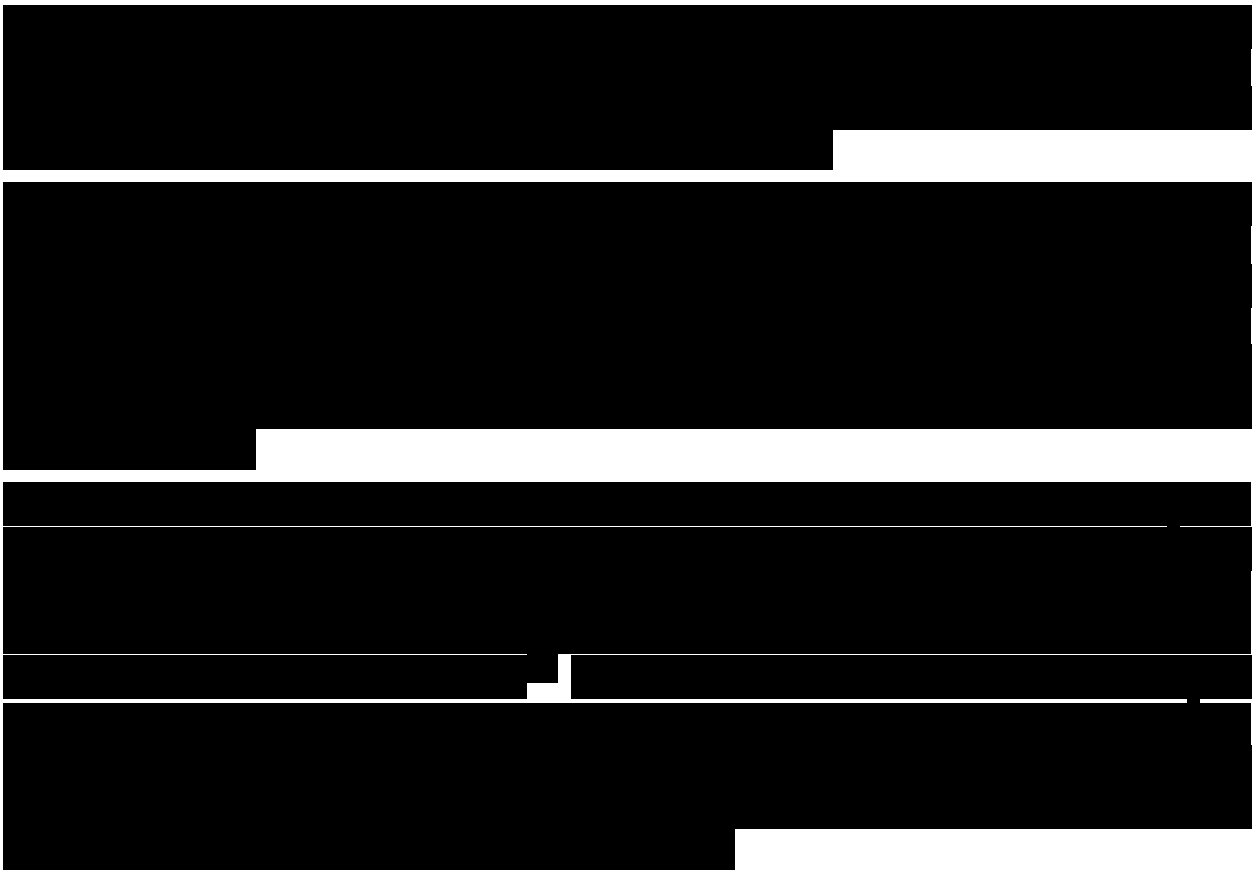
Summary of Key Changes for Protocol Amendment 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-3: Follow-up Assessments	Removed collection of corticosteroids and other immune-modulating medications beyond 135 days of last dose for AE/SAEs related to study drug.	Section 9.2.1 states that investigators are not obligated to actively seek AEs/SAEs in former study participants, but are required to continue to report drug-related AEs/SAEs and their management; therefore, this sentence was removed for consistency.
	Revised footnote that defines timing of Long-Term Follow-up and Survival visits.	In cases where a Follow-up visit is unable to be completed, timing of Survival Follow-up visit has been clarified.
Section 3.3: Benefit/Risk Assessment	Added paragraph with data from safety memo.	To ensure pertinent study information is included to support patient safety.
Table 4-1: Objectives and Endpoints Section 10.3: Analysis Sets Table 10.4.1-2: Definition of Estimands for Primary and Secondary Endpoints	In the DMFS secondary efficacy objective, changed "Stage III/IV" to "Stage III/IVA/IVB" in the description of participants with completely resected NED melanoma.	To align with prior adjuvant studies CM238 and CM915 as well as clinical relevance of occurrence of distant metastasis in Stage III disease rather than Stage IV.
Table 4-1: Objectives and Endpoints Table 10.4.1-2: Definition of Estimands for Primary and Secondary Endpoints Table 10.4.3-2: Summary of Secondary Endpoint Analysis	[redacted]	[redacted]
	[redacted]	[redacted]
Section 5.4.2: Rationale for Use of Nivolumab + Relatlimab Fixed Dose Combination	Removed text regarding characteristics of effector T cells.	To align with updated BMS standards for relatlimab protocols.
Section 5.4.9: Rationale for MRI Surveillance of Head and Neck Mucosal Melanomas	Added section.	To align with changes in protocol.
Section 7.3: Blinding	Removed paragraph regarding randomization schedules.	Included in error in previous amendment but not applicable to the study.

Summary of Key Changes for Protocol Amendment 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 8.1: Discontinuation From Study Treatment	Added "or new primary melanoma" to disease recurrence as reason for discontinuation.	To clarify existing discontinuation reason.
Section 9.1.1: Efficacy Assessment for the Study	Revised text regarding the discontinuation of follow-up scans for Stage III and IV participants.	To ensure comprehensive data collection for all Stage III and Stage IV participants regardless of initiation of subsequent systemic therapy or not.
[redacted]	Added "but no later than 12 weeks" to timeframe of subsequent scan from the time when recurrence is suspected.	To define an expected timeframe for confirmation of recurrence.
	Added that even though ultrasounds are not to be submitted to imaging vendor, any recurrence identified by ultrasound must be recorded as recurrence event.	To clarify ultrasound-identified recurrence events.
[redacted]	[redacted]	[redacted]
[redacted]	Removal of reference to minimal important differences not existing.	New minimal important difference estimates were recently released.
Section 9.2.3: Follow-up of AEs and SAEs	Updated text to current practice.	To align with updated BMS processes.
Section 9.2.5: Pregnancy	Added that pregnancy reporting is not required for WOCBP partners of male participants.	For clarity.
[redacted]	[redacted]	For clarity.

Summary of Key Changes for Protocol Amendment 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 10.2.1: Recurrence-free Survival [redacted] Section 10.3: Analysis Sets Table 10.4.2-1: Primary Endpoints [redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Throughout	[redacted]	The copyright holder has updated the preferred name.
	Added references to Appendix 9 where appropriate.	For clarity.
All	Minor formatting and typographical corrections.	Changes are minor and therefore have not been summarized.

Overall Rationale for Protocol Amendment 01, 18-May-2022

Despite limited clinical studies evaluating immuno-oncologic treatment outcomes in adolescent melanoma, with the small number of participants in these studies, results have shown that the safety profiles and treatment effects in pediatric participants are generally comparable to adult participants.[1,2,3,4,5] Surgical and medical management of adolescent melanoma continues to derive guidelines from adult melanoma treatment. Hence the addition of adolescent participants ≥ 12 years through < 18 years of age covers an unmet need within the melanoma population under study. The Food and Drug Administration (FDA) approval in Mar-2022 of Opdualag™ for the treatment of adult and adolescent patients (12 years and older and weighing at least 40 kg) with unresectable or metastatic melanoma provides further justification for the inclusion of this population in future studies.



Existing data and National Comprehensive Cancer Network guidelines support ultrasonography as a preferred modality compared to other imaging modalities in the management of Stage III melanoma patients based on sensitivity, specificity, and surveillance benefit.[9] Ultrasonography was updated as a study requirement for surveillance of participants who have a sentinel lymph node biopsy but do not undergo complete lymph node dissection (CLND) and left as optional for those with CLND.

The benefit/risk section of the protocol was updated to reflect updated data from the publication of the combination dosing study in first-line metastatic melanoma, which continues to suggest a favorable safety profile of the combination therapy.

Additional minor changes include protocol clarifications, harmonization of collection durations (days or weeks versus months), and formatting changes. Revisions to the protocol summary have been made to align with changes throughout the protocol. This amendment includes changes from approved Administrative Letters 01, 02 and 04 and those changes are not listed in the table below.

References

1 Longo MI, Lázaro P, Bueno C, et al. Fluorodeoxyglucose-positron emission tomography imaging versus sentinel node biopsy in the primary staging of melanoma patients. Dermatol Surg 2003;29:245-8.

2 Balch CM, Soong SJ, Smith T, et al. Long-term results of a prospective surgical trial comparing 2 cm vs. 4 cm excision margins for 740 patients with 1-4 mm melanomas. Ann Surg Oncol 2001;8:101-8.

3 Harris MN, Shapiro RL, Roses DF. Malignant melanoma. Primary surgical management (excision and node dissection) based on pathology and staging. Cancer 1995;75(2 Suppl):715-25.

4 Jen M, Murphy M, Grant-Kels JM. Childhood melanoma. Clin Dermatol 2009;27:529-36.

5 Saiyed FK, Hamilton EC, Austin MT. Pediatric melanoma: incidence, treatment, and prognosis. Pediatric Health Med Ther 2017;8:39-45.

[redacted]

9 Xing Y, Bronstein Y, Ross MI, et al. Contemporary diagnostic imaging modalities for the staging and surveillance of melanoma patients: a meta-analysis. J Natl Cancer Inst 2011;103: 129-42.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Throughout	To align with the naming convention in the United States prescribing information (USPI), nivolumab will precede relatlimab when in reference to any combination therapy, and relatlimab and nivolumab FDC has been renamed to nivolumab + relatlimab (nivo + rela) fixed-dose combination (FDC) throughout the protocol.	To align the naming convention with the USPI.
Protocol Summary	Text has been updated to align with changes made throughout the protocol.	Alignment between Protocol Summary and body of the protocol.
Table 2-1: Screening Procedural Outline (CA224098)	Specified complete physical examination at screening.	Clarification only.
Table 2-1: Screening Procedural Outline (CA224098)	In regard to the informed consent for adolescent participants, a note was added referencing Appendix 2 for details regarding minor assent.	Hyperlink added to reference to further details for minor assent.
Table 2-1: Screening Procedural Outline (CA224098) Section 6.1: Inclusion Criteria [redacted]	For tumor sample submission procedures at baseline, the timeline for submission was updated from 3 months to 90 days for specificity.	Clarification on timing added for specificity.
Table 2-1: Screening Procedural Outline (CA224098) Table 2-2: On Study Treatment Procedural Outline (CA224098) Table 2-3: Follow-up Assessments (CA224098) Section 9.1.1: Efficacy Assessment for the Study Section 9.1.3: Investigator Assessment of Baseline Disease Status	Under the body imaging assessment, clarified that contrast-enhanced computed tomography (CT) scans for the listed body scans are required.	Clarified the requirement for contrast-enhanced CT imaging.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-1: Screening Procedural Outline (CA224098) Table 2-2: On Study Treatment Procedural Outline (CA224098) Table 2-3: Follow-up Assessments (CA224098) Section 5.4.8: Rationale for Ultrasound in Disease Surveillance	The following changes were made to the ultrasound assessments: • Ultrasound will now be required of all participants with positive sentinel lymph node biopsy and who do not undergo immediate complete lymph node dissection (CLND). A note has also been added to indicate ultrasound is optional if the participant has undergone CLND. • The ultrasound assessment interval on study and during follow-up was updated from 6 months to 26 weeks. • A new section that provides the rationale for requiring ultrasound for surveillance has been added.	Updated to make ultrasound a study requirement for all sentinel lymph node dissection (SLND) participants (rather than optional) based on the sensitivity and specificity of ultrasound as a surveillance modality, and to harmonize this requirement across the global and country-specific protocols. Clarified timing to align with language previously used in the protocol (weeks vs months) for imaging duration.
Table 2-1: Screening Procedural Outline (CA224098 Table 2-2: On Study Treatment Procedural Outline (CA224098)	Performance status assessment has been updated to include both Eastern Cooperative Oncology Group (ECOG) and Lansky/Karnofsky assessments depending on participant age.	Performance scale has been updated to be used depending on participant age (adults vs adolescent age group).
Table 2-1: Screening Procedural Outline (CA224098) Table 9.4.4-1: Clinical Laboratory Assessments	[redacted]	[redacted]
Table 2-2: On Study Treatment Procedural Outline (CA224098)	Participants must receive their first dose of study intervention within 3 days of randomization, changed from IRT drug assignment.	Consistency with other assessments that are based off randomization.
Table 2-2: On Study Treatment Procedural Outline (CA224098) Table 2-3: Follow-up Assessments (CA224098) Appendix 9: Country Specific Requirements	[redacted]	Added detailed [redacted]

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-2: On Study Treatment Procedural Outline (CA224098) Table 2-3: Follow-up Assessments (CA224098) Section 9.1.1: Efficacy Assessment for the Study	The interval of timing between body imaging, brain imaging, and ultrasound has been updated from 6 months to 26 weeks, and 2 years has been clarified as 104 weeks.	Clarified timing to harmonize with language previously used in the protocol (weeks vs. months) for imaging duration.
Table 2-2: On Study Treatment Procedural Outline (CA224098) Table 2-3: Follow-up Assessments (CA224098) Section 9.1.1: Efficacy Assessment for the Study	Follow-up body and brain imaging scans has been discontinued during follow-up, once systemic therapy starts for a melanoma recurrence or for a new non-melanoma tumor after study drug discontinuation. In Section 9.1.1, clarified when follow-up scans may be discontinued (ie, in cases when participant has started systemic therapy after unequivocal recurrence or for a new non-melanoma tumor after study drug discontinuation).	Clarification for when discontinuing imaging collections is allowed (after unequivocal recurrence or new non primary melanoma requiring systemic therapy).
Table 2-2: On Study Treatment Procedural Outline (CA224098) Table 2-3: Follow-up Assessments (CA224098) Section 9.1.5: Patient Reported Outcomes	Adolescent participants will only be required to complete the [redacted] assessment for the patient-reported outcomes.	Adolescent population is [redacted]
Table 2-2: On Study Treatment Procedural Outline (CA224098) Table 2-3: Follow-up Assessments (CA224098) [redacted]	Tumor tissue collection via biopsy or surgical resection at disease recurrence must be performed if medically feasible and must be submitted to the central laboratory within 30 days of collection.	Clarification of protocol requirement and incorporation of a timeframe for submission of tissue specimen to the central laboratory.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-3: Follow-up Assessments (CA224098)	For concomitant medications, removed reference to subsequent therapy and specified collection of corticosteroid/immune-modulating medications only for AE/SAE considered study drug related.	Removal of subsequent therapy as it is addressed elsewhere and redundant and limiting the collection of corticosteroid/immune-modulating medications for safety.
Table 2-3: Follow-up Assessments (CA224098) Figure 5.1-1: Study Design Schema Section 5.3: End of Study Definition Section 10.3: Analysis Sets Section 10.4.1: General Considerations	For survival status in long-term follow-up, further specified timing of 12 weeks instead of 3 months and a window of 14 days was included for consistency with the footnote. [redacted]	Harmonize timing of months to weeks and addition of window for scheduling flexibility. [redacted]
Table 2-3: Follow-up Assessments (CA224098) Table 4.1: Objectives and Endpoints Table 10.4.3-2: Summary of Secondary Endpoint Analysis	Clarified the wording and intent of collecting subsequent therapy and associated outcomes for participants who recur.	Clarification only.
Table 2-3: Follow-up Assessments (CA224098) [redacted]	[redacted]	[redacted]
Section 3: Introduction	[redacted]	[redacted]

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 3.1: Study Rationale Section 3.2.2: Nivolumab Combined with Relatlimab Clinical Activity Section 3.2.6: Nivolumab Combined with Relatlimab Clinical Safety Section 3.3: Benefit/Risk Assessment	Additional data from the CA224047 study has been provided to support the clinical efficacy and safety of nivo + rela FDC.	Data from publication of combination dosing study in first-line metastatic melanoma updated to support rationale for combined clinical efficacy and safety.
Section 3.2.2: Nivolumab Combined with Relatlimab Clinical Activity Section 3.2.6: Nivolumab Combined with Relatlimab Clinical Safety	• Clinical efficacy and safety sections have been updated and streamlined. • Efficacy numbers for Study [redacted] and CA224047 overall survival/overall response rate have been updated. • Updated safety information added for study CA224020.	Updates per nivolumab + relatlimab FDC IB.
Section 3.2.6: Nivolumab Combined with Relatlimab Clinical Safety	[redacted]	Safety data information updated and clarified for earlier identification of cardiac risk based on actual study information.
Section 3.3: Benefit/Risk Assessment	Updated benefit/risk assessment for nivolumab and relatlimab combination therapy.	Updates per nivolumab + relatlimab FDC IB.
Table 3.3.1-1: Risk Assessment	Ultrasound added as a study procedure risk for comprehensiveness.	For treatment of imaging risks in the study, ultrasound was added.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 4-1: Objectives and Endpoints Section 10.1: Statistical Hypotheses Section 10.4.1: General Considerations Table 10.4.1-2: Definition of Estimands for Primary and Secondary Endpoints Table 10.4.3-1: Secondary Efficacy Endpoints Table 10.4.3-2: Summary of Secondary Endpoint Analysis	[redacted]	[redacted]
Table 4-1: Objectives and Endpoints [redacted] Section 10.4.1: General Considerations Table 10.4.1-1: Censoring Scheme for Primary Definition of Recurrence-free Survival Table 10.4.2-1: Primary Endpoints Table 10.4.2-2: Summary of Primary Endpoint Analysis.	[redacted]	[redacted]
Table 4-1: Objectives and Endpoints	[redacted]	[redacted]
Table 4-1: Objectives and Endpoints	[redacted]	[redacted]

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.1: Overall Design Section 5.4.7: Rationale for Inclusion of Adolescent Participants Section 5.5.2: Dose Rationale for Adolescent Participants Table 7.1-1: Study Interventions	Adolescent participants ≥ 12 years are now eligible to participate in the study. The protocol has been updated throughout to include pediatric dosing information, which for a subset of pediatric participants will be weight based. Rationale for the inclusion of adolescent participants and dosing rationale for this population have been added.	Addition of adolescent participants. Addition of dosing for adolescent participants aged ≥ 12 years to 18 years, including weight-based differences for this group of participants.
Figure 5.1-1: Study Design Schema	The study design schema and associated footnotes were updated per the changes to Protocol Amendment 01.	Addition of dosing for pediatric participants for nivo + rela FDC and nivolumab only added to study schema including footnotes.
Section 5.1.1: Data Monitoring Committee and Other Committees [redacted]	[redacted]	[redacted]
Section 5.4.6: Rationale for Evaluation of [redacted]	[redacted]	[redacted]
Section 5.5.1: Justification for Fixed Dose Combination Dosing	• Minor rewording throughout the section and updated infusion safety data have been provided. • Also updated text in regard to population pharmacokinetic (PPK) analysis. • Updated language for dose justification for [redacted] infusion.	Clarification of protocol verbiage and updates per nivolumab + relatlimab FDC IB
Section 5.6.1: Nivolumab Clinical Pharmacology Summary Section 5.6.2: Relatlimab Clinical Pharmacology Summary	Updated language for clinical pharmacology of nivolumab and relatlimab.	Updates per nivolumab + relatlimab FDC IB.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 6.1: Inclusion Criteria Section 9.2: Adverse Events Section 10.3: Analysis Sets Appendix 2: Study Governance Considerations	Multiple changes were made throughout the protocol to include legally acceptable representatives (LAR): Inclusion criterion 1) a) was modified to permit legally acceptable representatives (LAR) with the inclusion of pediatric participants. Added participant's LAR as an individual who may report AEs if applicable. Redefined enrolled population as participant or their LAR who signed informed consent and were registered into Interactive Response Technology. Inclusion of LAR in the informed consent process given inclusion of pediatric participants.	Updated the informed consent and AE reporting section for participants to conform with required regulatory and ethics guidelines for a legally acceptable representative.
Section 6.1: Inclusion Criteria Section 6.2: Exclusion Criteria	Inclusion criterion 2) a) and exclusion criteria 1) a) were modified to exclude participants with ocular melanoma.	Terminology change from uveal to ocular.
Section 6.1: Inclusion Criteria	Inclusion criterion 2) c) was modified regarding timing of complete resection prior to randomization, from 12 weeks to 90 days.	Clarified timing to harmonize with language used in the protocol (days vs weeks).
Section 6.1: Inclusion Criteria	Inclusion criterion 2) d) was modified to require a brain magnetic resonance imaging (MRI) scan at screening.	Clarification on procedures required at study screening.
Section 6.1: Inclusion Criteria	Inclusion criterion 2) f) was modified to include both ECOG and Lansky/Karnofsky performance status scores, depending on participant age.	Clarification on performance scale for assessment of pediatric participants.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 6.1: Inclusion Criteria	Inclusion criterion 2) g) was added as a placeholder to align formatting with country-specific protocol amendments.	Added for formatting alignment with country-specific amendments.
Section 6.1: Inclusion Criteria	Inclusion criterion 3)a) was updated to criterion 3)b) to permit pediatric participants ≥ 12 years of age to participate unless local regulations do not permit participants < 18 years of age.	Clarification provided for pediatric participant inclusion to conform with local regulatory and institutional policies.
Section 6.2: Exclusion Criteria	Exclusion criterion 1) f) was updated to specify concurrent non-melanoma malignancy.	Clarification that the criterion is referring to non-melanoma malignancy.
Section 6.2: Exclusion Criteria	[redacted]	[redacted]
Section 6.2: Exclusion Criteria	[redacted]	[redacted]
Section 6.2: Exclusion Criteria	[redacted]	[redacted]
Section 6.2: Exclusion Criteria	[redacted]	[redacted]
Table 7.1-1: Study Interventions	Added approved Opdualag™ to the current name of BMS-986213.	Naming update.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 7.1: Study Interventions Administered	A note regarding the pediatric dosing calculations for body weight dosing was included.	Clarification on using cumulative weight change for dose adjustments for newly added pediatric population.
Section 7.1.1: Study Treatment Details	• The final bullet point regarding participant discontinuation was deleted as it is addressed in the discontinuation section of the protocol. • The term study treatment has been replaced with immunotherapy. • As all infusions are diluted, we have removed an inaccurate statement.	Minor rewording and corrections to the protocol as these items are addressed in different sections.
Section 7.3: Blinding	Text added to clarify that randomization schedules are provided directly to the individual dispensing blinded study intervention, but who are not involved in the study in any other aspect.	To indicate that the blinding is maintained throughout the study by differentiating blinded versus unblinded individuals.
Section 7.3: Blinding	Details regarding DMC access to unblinded treatment codes, and the timing of participant, investigator, site staff, and sponsor access to unblinded treatment assignments has been included.	Clarifying information regarding timing of unblinding for DMC, sponsor, participants, investigator, site staff, and sponsor access to unblinded treatment assignments is added.
Section 7.4.2: Criteria to Resume Treatment	For consistency with Section 8.1.1, an exception regarding delays due to steroid taper in management of drug related-adverse events (AEs) was included.	Clarification for consistency.
Section 7.6: Treatment Compliance	Clarified that source data will be reviewed at routine monitoring visits.	Reworded for accuracy.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 7.7.1.1: Prohibited Treatments	[redacted]	[redacted]
Section 7.7.2: Other Restrictions and Precautions	Revised wording of text detailing restrictions of participation in other interventional clinical trials.	Clarification on restrictions for participating in interventional trials vs observational studies.
Section 7.7.2.1: SARS-CoV-2 Vaccination Guidelines	[redacted]	[redacted]
Section 8.2.1: Individual Discontinuation Criteria	Clarified that at the time of discontinuation from the study, an immediate follow-up visit may be required.	Removed statement about an early termination visit as there is no such visit and clarified visit requirements at study drug discontinuation.
Section 9.1.2: Imaging Assessment for the Study	Removed a statement that assessments should be performed by the same investigator or delegate at all time points.	To reduce site burden of having the same investigator perform the assessment at all time points.
Section 9.1.3: Investigator Assessment of Baseline Disease Status [redacted]	[redacted]	[redacted]
Section 9.1.4: Investigator Assessment of Recurrence [redacted]	[redacted]	[redacted]

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]	Minor clarification that questionnaires should be obtained prior to participant withdrawal from the study.	Clarification only.
Section 9.2.1: Time Period and Frequency for Collecting AE and SAE Information	For collection of nonserious adverse events, a timeframe of all study treatment and 135 days following discontinuation of study intervention was added, and added that adverse events associated with severe acute respiratory syndrome coronavirus-2 must be collected from time of consent and during treatment period.	The timeframe for the collection of non-serious AEs was added.
Table 9.4.4-1: Clinical Laboratory Assessments	Updated TSH assessment to add total T3 and total T4.	Updated to align with the local lab collection parameters.
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01

Section Number & Title	Description of Change	Brief Rationale
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted] Table 10.4.2-1: Primary Endpoints [redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 10.3: Analysis Sets Table 10.4.1-1: Censoring Scheme for Primary Definition of Recurrence-free Survival Table 10.4.1-2: Definition of Estimands for Primary and Secondary Endpoints	[redacted]	[redacted]
[redacted]	[redacted]	Clarification of the [redacted]
[redacted]	[redacted]	Clarification only.
Appendix 2: Study Governance Considerations	Added text for legally acceptable representatives in the informed consent process.	Added text based on inclusion of adolescent participants and participants who may not be able to provide consent.
Appendix 2: Study Governance Considerations	Added 2 new sections titled: • BMS Commitment to Diversity in Clinical Trials • Data Protection, Data Privacy, and Data Security	Added text for BMS' commitment to diversity in clinical trials, and to align BMS practice and comply with EU-CTR requirements.
Appendix 6: ECOG and Lansky/ Karnofsky Performance Status Scale	Lansky/Karnofsky performance status scale has been added.	Addition of performance assessment scale for pediatric participants.
Appendix 9: Country Specific Requirements	Germany's requirements have been removed from the global protocol and will be included in their country-specific protocol.	Removed Germany-specific requirements as Germany has a country-specific amendment.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Appendix 9: Country Specific Requirements	[redacted]	[redacted]
All	Minor formatting and typographical corrections.	Changes are minor and therefore have not been summarized.