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Clinical Protocol CA224047

A Randomized, Double-Blind Phase 2/3 Study of Relatlimab Combined with Nivolumab versus Nivolumab in Participants with Previously Untreated Metastatic or Unresectable Melanoma

Protocol Amendment Number: 03

[redacted]

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DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Protocol Amendment 03	23-Nov-2020	The following changes have been made to this protocol: 1) Revised the order of the Phase 3 secondary endpoints hierarchical testing strategy (1. Overall survival [OS] 2. Overall response rate [ORR]). 2) Added two interim analyses of OS. 3) Revision of dose delay, criteria to resume treatment, and discontinuation criteria to align with CTCAE V5. 4) Updated contraceptive guidance for participants. In addition, minor changes were made to improve overall clarity and to clarify necessary communication with the BMS Medical Monitor/designee.
Revised Protocol 02	22-Feb-2019	The following changes have been made to this protocol: 1) Incorporated changes from Administrative Letters 04, 05, and 06. 2) Added PFS2 as an exploratory objective. 3) Re-added pregnancy testing during follow-up visits. Made additional minor changes to clarify timing of procedures and improve overall clarity of protocol.
Administrative Letter 06	05-Nov-2018	Updated Medical Monitor and Study Director information.
Administrative Letter 05	07-Sep-2018	Corrected study design statement error in Section 5.1.
Administrative Letter 04	05-Sep-2018	Updated CTCAE version from 4 to 5. As such, also instructed sites that Grade 1 myocarditis is no longer an event term and all troponin elevations should be coded as troponin elevation regardless of myocardial inflammation.
Revised Protocol 01	15-Aug-2018	The following changes have been made to this protocol: • Incorporated changes from Administrative Letters 01, 02, and 03. • Changed Phase 2 primary objective from ORR to PFS. • Updated interim analysis to include all 400 participants from Phase 2. • Clarified procedures for interim analysis and results. • Updated timing of procedures throughout for clarity. • Updated PK analyses for current preferred methods. • Updated Immuno-Oncology (IO) algorithms for current methods. • Added myocarditis IO algorithm. Updated headers to include full fixed-dose combination product.
Administrative Letter 03	18-Jun-2018	Corrected an error in Appendix 8, Country Specific Requirement. The section indicates that HIV testing at site is locally mandated in countries listed. The test is not required in Italy and Spain.
Administrative Letter 02	17-May-2018	Corrected an error in Appendix 8, Country Specific Requirement. The section indicates that HIV testing at site is locally mandated in countries listed. The test is not required in France.

Document	Date of Issue	Summary of Change
Administrative Letter 01	09-Mar-2018	Corrected an error in Section 9.4.4, Safety Laboratory Assessment, Table 9.4.4-1 section of the protocol. The serology tests indicate incorrectly that the HPV status should be done at screening. The test is not needed as part of the inclusion/exclusion criteria.
Original Protocol	18-Dec-2017	Not applicable

OVERALL RATIONALE FOR REVISED PROTOCOL 03:

The key change to the protocol includes the secondary endpoints statistical hierarchy evaluation to overall survival (OS) followed by overall response rate (ORR). Importantly, the primary endpoint has not been changed. In addition, revisions including interim analyses to be performed during the study (1 of progression-free survival [PFS] and up to 2 of OS) are included.

OS is considered a more relevant endpoint for evaluation of clinical benefit in the melanoma landscape compared with ORR. In study CA209-067 in previously untreated metastatic melanoma, overall survival at 5 years was remarkable at 52% in the nivolumab-plus-ipilimumab group and 44% in the nivolumab group, as compared with 26% in the ipilimumab group.[1] In addition, in the event of a statistically significant PFS result, evaluating OS more formally would be considered more clinically meaningful than ORR.[2] Therefore, OS will be tested hierarchically at the time of statistically significant PFS followed by ORR (if OS is statistically significant and at the time that ORR data are mature).

The final target number of OS events is 300, and the OS interim analyses present the opportunity to identify if a clear statistical significance is present at earlier information fractions between both treatment arms, indicating a survival benefit.

In addition, dose modification criteria and immuno-oncology (IO) agent management algorithms have been updated to align with the current Common Terminology Criteria for Adverse Event (CTCAE) version (v5). Monitoring for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-related AE/SAE has been added. In addition, minor changes were made to improve clarity throughout the protocol were made. This revised protocol applies to all participants.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03

Section Number & Title	Description of Change	Brief Rationale
Title Page	Updated Medical Monitor Contact Information	Update
Section 2, Schedule of Activities; Table 2-2: On-Study Assessments; Section 9.8.2, Tumor Samples; Section 9.8.2.6, Tumor Sample Collection	• Added a note regarding collection of SARS-Cov-2-associated AEs/SAEs • Added clarification regarding biopsied lesions • Added clarification regarding pediatric participants; they would only complete EQ-5D-3L and not the WPAI:GH or FACT-M assessments	• AE/SAE collection in the context of SARS-CoV-2 was added in the event that coronavirus disease 2019 (COVID-19) sequelae may increase toxicity or impact interpretation of study events/results. • Biopsy language, clarification only. • Pediatric EQ-5D-3L clarification only.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 2, Schedule of Activities; Table 2-3: Follow-Up Procedural Outline	Added a note regarding collection and follow-up of SARS-CoV-2 infection.	AE/SAE collection in the context of SARS-CoV-2 was added in the event that COVID-19 sequelae may increase toxicity or impact interpretation of study events/results.
Section 3.1, Study Rationale	Revised to remove ORR from Phase 2 evaluations and to include OS and response rate and duration in the Phase 3 study evaluations.	This was a correction. This edit was part of revisions made in revised protocol 02.
Synopsis; Section 4, Objective and Endpoints; Table 4-1: Objectives and Endpoints	Phase 3 Exploratory • Added an objective regarding evaluations of FACIT GP5 • Added evaluation of TFI Phase 2 Secondary Objectives • Added definition for OS rate • Removal of "median" DOR Phase 2 Exploratory Objective • Removal of "median" DOR	Treatment-free interval (TFI) is an emerging exploratory endpoint of interest in melanoma. Data suggest that TFI can positively impact quality of life (QoL) and may improve the cost-effectiveness of immune checkpoint inhibitors. TFI can be analyzed in conjunction with safety, health-related QoL to give another representation of outcomes for off-treatment patients.
Section 5.1, Overall Design; Section 10.2.5, Interim Analyses	Timing on PFS interim analysis has been added.	Clarification on PFS analysis timing as been added.
Section 5.1.1, Data Monitoring Committee	Revised to clarify that Data Monitoring Committee (DMC) will convene for assessment of the interim analysis.	Clarification regarding DMC involvement in interim analysis.
Section 5.2, Number of Participants	Revised to clarify that the interim PFS analysis is a futility analysis and that the threshold for positivity determines continuation to Phase 3 study will be defined in the SAP.	Clarification of the PFS interim analysis.
Section 5.3, End of Study Definition	Revised to clarify the timing of the final analyses for the Phase 2 study, and the total duration of the assessment of PFS in the Phase 3 study.	Clarification on the PFS analysis timing.
Section 7.3, Blinding	• Specified when Sponsor and sites/participants will be unblinded to individual treatment assignments and to analysis results. • Specified that the analysis team reporting to the DMC is external to BMS.	• Necessary with the inclusion of interim analyses for OS. • Clarification only.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 7.4, Dosage Modification	Added Table 7.4-1: AE Criteria for Delay, Resume, and Discontinuation of Treatment	• Reorganized dose delay, resume, and discontinuation criteria for improved readability and to align with the current CTCAE version (v5).
Section 7.4.2, Dose Delay Criteria	Added suspected or confirmed SARS-CoV-2 infection as a criterion to delay treatment.	Updated dose delay criteria to include expectations in cases of confirmed or suspected SARS-CoV-2 infection.
Section 7.4.2, Dose Delay Criteria; Section 7.4.3, Criteria to Resume Treatment; Section 8.1.1: Dose Discontinuation	Modified text to align criteria for dose delay, resume, and discontinuation of treatment with Table 7.4-1.	Updated dose delay, resume, and discontinuation criteria to align with the current CTCAE version (v5).
Section 9.3.1, Patient-Reported Outcomes	Language added to allow alternative collection methods.	Permit alternative PRO collections should SARs-CoV-2 limit patient contact.
Section 9.1.3.2, FACT-M; Section 10.2.4.3 Outcomes Research	Add clarification regarding the use of GP-5 in FACT-M to assess burden due to treatment toxicities.	Clarification only.
Section 9.2.1, Time Period and Frequency of AE and SAE Information	The following updates were made: • Removed bullet related to Reference Safety Information in Investigator's Brochure (IB). • Added text to describe collection of AEs and SAEs in the context of SARS-CoV-2 infection. • Removed bullet related to SAE collection for participants who signed a pre-screening consent.	These changes were made to: • Align references to IB in the protocol with current IB template. • Include language for AE/SAE collection in the context of SARS-CoV-2 in the event that COVID-19 sequelae may increase toxicity or impact interpretation of study events/results. Remove inconsistent text to ensure alignment of this section with Table 2-1.
Section 9.2.3, Follow-up of AEs and SAEs	Updated last paragraph to include details related to follow-up of SAEs and non-serious AEs associated with confirmed or suspected SARS-CoV-2 infection.	Included language for AE/SAE follow-up in the context of SARS-CoV-2 in the event that COVID-19 sequelae may increase toxicity or impact interpretation of study events/results.
Section 9.4.4, Clinical Safety Assessments; Table 9.4.4-1 Clinical Laboratory Assessments	Added additional information regarding cardiac evaluation in the event of troponin elevations.	Clarification that troponin elevations will require cardiac evaluation in participants receiving ongoing treatment with relatlimab.
Section 9.5.1, Pharmacokinetics: Collection and Processing; Table 9.5.1-1 PK and ADA Sampling Schedule for Relatlimab and Nivolumab	Updated footnotes to clarify End of Infusion (EOI) collection with respect to utilization of IV flush.	Clarification for the sites regarding timing of EOI collection.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 9.8.1.5, Circulating Tumor DNA Analysis (Plasma) Biomarkers	Updated to contain rationale for ctDNA and plasma samples.	Clarification of rationale for collection.
Section 10.1, Sample Size Determination	Added text on non-proportional hazards for sample size justification for Phase 2 PFS estimation	Additional information added to provide clarity.
Section 10.2.2, Efficacy Analyses	Revised the Phase 3 secondary endpoints hierarchy (1. OS, 2. ORR).	OS is a validated relevant endpoint in the current clinical landscape as described above. The testing strategy was changed to include an interim analysis of OS at the same time as a successful PFS analysis. This changes OS to be second in the hierarchy.
	Provided more detail on the Phase 2 Primary statistical methods.	Clarified Phase 2 PFS analysis.
	Divided the "Testing Strategy" into separate sections for Phase 2 and Phase 3.	Separation of Phase 2 and Phase 3 testing improves document clarity.
	Updated the Phase 3 Testing Strategy text to include overall alpha, and the plan and conditions for analysis of OS.	Provided potential subsequent analysis of OS secondary endpoint (if PFS is statistically significant), including alpha-spending approach.
	Updated the Phase 2 Testing Strategy text to include the stopping at Phase 2, and when the Sponsor would be unblinded in that case.	Clarified intention to unblind sponsor after 183 events if enrollment is stopped.
Appendix 2, Study Governance Consideration	Updated definition of "serious breach"; provided additional criteria for the CSR Signatory Investigator; added publication policy.	Updated to most current definition in alignment with current standards.
Appendix 4, Women of Childbearing Potential Definitions and Methods of Contraception	• Language regarding contraception for male participants was removed from the appendix. • Updated the definition of end of relevant systemic exposure from 24 weeks to 5 months.	• Male contraception language removed due to no genotoxicity and no transmission of biologically relevant amount to WOCBP partner. • Updated relevant exposure duration for females to align with most recent IB for nivolumab.
Appendix 9, Immuno-oncology Agent Management Algorithms	Replaced IO agent management algorithms with those aligned with CTCAE v5.	Updated management algorithms for immune-mediated AEs to align with current CTCAE version (v5) and nivolumab IB.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
All	Minor formatting and typographical corrections.	Minor, therefore have not been summarized.

References:

[1] Larkin J, Chiarion-Sileni V, Gonzalez R, Grob J-J, et al. Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med. 2019;381(16):1535-1546.

[2] Ritchie G, Gasper H, Man J, et al. Defining the most appropriate primary end point in Phase 2 trials of immune checkpoint inhibitors for advanced solid cancers: a systematic review and meta-analysis. JAMA Oncol. 2018;4(4):522-528.

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1 SYNOPSIS

Protocol Title: A Randomized, Double-Blind Phase 2/3 Study of Relatlimab Combined with Nivolumab versus Nivolumab in Participants with Previously Untreated Metastatic or Unresectable Melanoma

Study Phase: 2/3

Rationale:

Individually targeting immune checkpoint receptors such as CTLA-4 and PD-1 has been clinically successful across multiple tumor types. It is possible, however, that combination therapies could potentially lead to greater depth of response and overall survival as has been noted with anti-PD-1 and anti-CTLA-4 combination therapy in advanced melanoma patients. Targeting additional checkpoints, such as LAG-3, is considered a promising, novel approach. Blockage of LAG-3 in combination with anti-PD-1 has potential to improve efficacy in comparison with blocking anti-PD-1 alone without adding significant toxicity.

This study aims to demonstrate that treatment with BMS-986213 shows increased progression-free survival (PFS) compared with nivolumab monotherapy in participants with previously untreated, unresectable, or metastatic melanoma. Additional objectives include the evaluation of OS, response rate and duration, characterization of safety and tolerability, pharmacokinetics, potential predictive biomarkers, and changes in patient-reported outcomes for quality-of-life assessments.

Study Population:

The study population includes adults and adolescents ≥ 12 years of age with unresectable or metastatic melanoma with no prior systemic anticancer therapy for their disease.

Key Inclusion Criteria:

- Participants must have an ECOG performance status of ≤ 1/Lansky Performance Score ≥ 80% for minors (ages 12-17) ONLY
- Participants must have histologically confirmed Stage III (unresectable) or Stage IV melanoma, per the AJCC staging system (8th edition)
- Participants must be treatment-naïve (ie, no prior systemic anticancer therapy for unresectable or metastatic melanoma).
  - Note that the following prior adjuvant or neoadjuvant melanoma therapies are allowed if all related adverse events have either returned to baseline or stabilized.
    - Anti-PD-1 or anti-CTLA-4 therapy with at least 6 months between the last dose and date of recurrence.
    - Interferon therapy with the last dose at least 6 weeks prior to randomization.
    - BRAF- or MEK-inhibitor-containing adjuvant therapy regimens with at least 6 months between the last dose and date of recurrence.
- Participants must have measurable disease by CT or MRI per RECIST v1.1 criteria

- Tumor tissue from an unresectable or metastatic site of disease must be provided for biomarker analyses. In order to be randomized, a participant must be classified as PD-L1 positive or PD-L1 negative as well as LAG-3 positive or LAG-3 negative. If an insufficient amount of tumor tissue from an unresectable or metastatic site is available prior to the start of the screening phase, participants must consent to allow the acquisition of additional tumor tissue during the screening period for performance of biomarker analyses.
- Participants must have known BRAF V600 mutation status or consent to BRAF V600 mutation testing per local institutional standards during the screening period.
- Prior radiotherapy must have been completed at least 2 weeks prior to study treatment administration.
- Women must not be pregnant or breastfeeding.

Key Exclusion Criteria:

- Participants must not have active brain metastases or leptomeningeal metastases. Participants with brain metastases are eligible if these have been treated and there is no MRI evidence of progression for at least 4 weeks after treatment is complete and within 28 days prior to first dose of study treatment administration. There must also be no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study treatment administration. Participants with brain disease treated with whole brain radiation are not eligible.
- Participants must not have uveal melanoma
- Participants must not have an active, known, or suspected autoimmune disease. Participants may enroll with the following conditions:
  - type 1 diabetes mellitus
  - hypothyroidism only requiring hormone replacement
  - skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment
  - conditions not expected to recur in the absence of an external trigger are permitted to enroll.
- Participants must not have a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of start of study treatment. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
- Participants must not have a history of myocarditis
- Participant must not have had prior treatment with an anti-PD-1 (except if given as adjuvant or neoadjuvant therapy for melanoma), anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody (except if given as adjuvant or neoadjuvant therapy for melanoma), or any other antibody or drug specifically targeting T-cell costimulation or immune checkpoint pathways (except for interferon given as adjuvant or neoadjuvant therapy for melanoma). Prior treatment with relatlimab or any other with LAG-3 targeted agents.

Objectives and Endpoints:

Objectives	Endpoints
Phase 3 Primary Objective	
• The Phase 3 primary objective is to compare PFS of BMS-986213 to nivolumab monotherapy in participants with previously untreated, unresectable or metastatic melanoma.	• PFS time as assessed by a Blinded Independent Central Review (BICR), using RECIST v1.1. PFS is defined as the time between the date of randomization and the first date of documented progression, or death due to any cause, whichever occurs first.
1. **Phase 3 Safety Objective:**	
• To assess the overall safety and tolerability of BMS-986213 and of nivolumab monotherapy.	• Incidence of AEs, SAEs, AEs leading to discontinuation of treatment, deaths, and laboratory abnormalities.
Phase 3 Secondary Objectives	
The Phase 3 secondary objectives are: • To compare overall survival (OS) of BMS-986213 to nivolumab monotherapy in participants with previously untreated, unresectable or metastatic melanoma.	• OS is defined as the time between the date of randomization and the date of death due to any cause.
• To compare ORR of BMS-986213 to nivolumab monotherapy in participants with unresectable or metastatic melanoma.	• ORR as assessed by a BICR. The ORR is defined as the number of subjects with a BOR of CR or PR divided by the number of randomized subjects for each treatment group. The BOR is defined as the best response designation, recorded between the date of randomization and the date of objectively documented progression per RECIST v1.1 or the date of subsequent anti-cancer therapy, whichever occurs first.
Phase 2 Primary Objective	
• The Phase 2 primary objective is to compare PFS of BMS-986213 to nivolumab monotherapy in participants with previously untreated, unresectable, or metastatic melanoma.	• PFS time as assessed by a Blinded Independent Central Review (BICR), using RECIST v1.1. PFS time is defined as the time between the date of randomization and the first date of documented progression, or death due to any cause, whichever occurs first.

Objectives	Endpoints
2. Phase 2 Safety Objective:	
• To assess the overall safety and tolerability of BMS-986213 and of nivolumab monotherapy.	• Incidence of AEs, SAEs, AEs leading to discontinuation of treatment, deaths, and laboratory abnormalities.
Phase 2 Secondary Objectives	
The Phase 2 secondary objectives are: • To estimate the treatment effect, measured by ORR, as determined by BICR using RECIST v1.1 in all-comers and in subgroups based on combinations of LAG-3 expression (≥ 1% expression versus < 1% expression) and PD-L1 status (≥ 1% tumor cell surface expression versus < 1% tumor cell surface expression) among participants with unresectable or metastatic melanoma treated with BMS-986213 compared to those treated with nivolumab monotherapy.	• ORR as assessed by a BICR.
• To evaluate DOR and PFS rates at pre-specified time points (eg, 24 weeks) based on BICR assessments using RECIST v1.1 in the randomized population (for DOR) and in subgroups based on combinations of LAG-3 expression (≥ 1% expression versus < 1% expression and PD-L1 status (≥ 1% tumor cell surface expression versus < 1% tumor cell surface expression) among subjects with unresectable or metastatic melanoma treated with BMS-986213 and those treated with nivolumab monotherapy.	• DOR • PFS time as assessed by a BICR using RECIST v1.1.
• To assess the 1- and 2-year OS rate in the randomized population and in subgroups based on combinations of LAG-3 expression (≥ 1% expression versus < 1% expression) and PD-L1 status (≥ 1% tumor cell surface expression versus < 1% tumor cell surface expression) among subjects with unresectable or metastatic melanoma treated with BMS-986213 and those treated with nivolumab monotherapy.	• OS is defined as the time between the date of randomization and the date of death due to any cause.

Overall Design:

This is a Phase 2/3, randomized, double-blind study of BMS-986213 (fixed-dose combination relatlimab/nivolumab at a 1:3 ratio) versus nivolumab monotherapy in adult and adolescent participants (ages ≥ 12 to 17 years of age) with previously untreated, unresectable, or metastatic melanoma.

- Depending on the treatment arm, the participant will receive BMS-986213 or nivolumab in a blinded manner.
- One cycle of treatment is defined as 4 weeks. Treatment beyond initial investigator-assessed RECIST v1.1-defined progression is permitted if the participant has investigator-assessed clinical benefit, is tolerating study treatment. Dose reductions will not be allowed.
- On-study tumor assessments will begin 12 weeks after randomization and will continue every 8 weeks until Week 52 and every 12 weeks thereafter until BICR-confirmed disease progression or treatment discontinuation, whichever occurs later.

Number of Participants:

The Phase 2 part of the study will enroll approximately 400 participants. An interim analysis of PFS will be performed when a minimum follow-up of 12 weeks is achieved for approximately 400 randomized subjects or at least 150 PFS events have been observed using BICR. If the interim analysis of PFS is positive (based on a pre-specified threshold as defined in the Statistical Analysis Plan (SAP) and the DMC Charter), then the study will continue to Phase 3 and remain blinded. If the interim analysis of PFS does not support continuing to the Phase 3 study, the study will allow the Phase 2 data to mature and then unblind the sponsor for analysis. If the latter scenario takes place, approximately 575 participants will need to be enrolled in order to randomize 400 participants assuming a screen failure rate of 30%.

If the study does continue to Phase 3, it is expected that approximately 1000 participants will need to be enrolled to randomize at least 700 participants, assuming a screen failure rate of approximately 30%.

Participants will be randomized 1:1 to one of two parallel treatment groups:

- BMS-986213 IV Q4W
- nivolumab IV Q4W

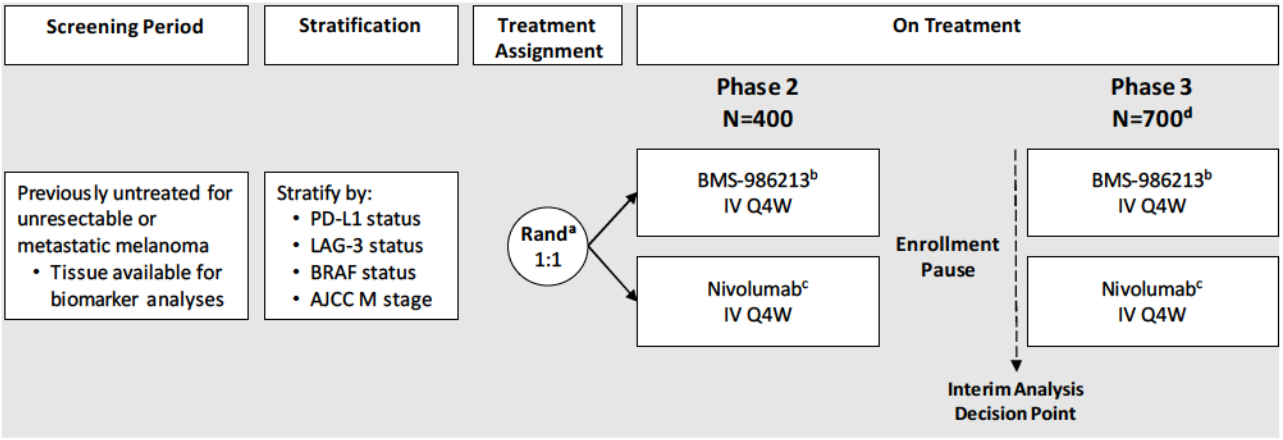
Treatment Arms and Duration:

Study Treatment:

Study Treatments for CA224047		
Medication	**Potency**	**IP/Non-IP**
BMS-986213 (Relatlimab 160 mg/ Nivolumab 480 mg)	16 mg/mL	IP
Nivolumab 480 mg	10 mg/mL	IP

The study design schematic for adults and adolescents is presented below.

Figure 1-1: Study Design Schematic



[a] A safety lead-in evaluation will be performed on the first (up to) 18 participants.

[b] BMS-986213 is the fixed-dose combination relatlimab/nivolumab at a 1:3 ratio. For adults, dosing is relatlimab 160 mg/nivolumab 480 mg. Adolescents ≥ 40 kg will receive adult dosing; for adolescents < 40 kg, dosing is relatlimab 2 mg/kg/nivolumab 6 mg/kg.

[c] Nivolumab monotherapy dosing for adults is 480 mg. Adolescents ≥ 40 kg will receive adult dosing; for adolescents < 40 kg, dosing is 6 mg/kg.

[d] The 700 subjects in Phase 3 will consist of the 400 from Phase 2 and an additional 300 from the Phase 3 part of the trial.

During the treatment phase, participants will receive the following treatments in a blinded manner:

- BMS-986213 IV Q4W (for adolescent participants < 40 kg, the dose will be weight-based relatlimab 2 mg/kg Q4W, nivolumab 6 mg/kg Q4W) or,

- Nivolumab 480 mg IV Q4W (for adolescent participants < 40 kg, the dose will be weight-based; nivolumab 6 mg/kg Q4W)
- Dose reductions are not permitted for either study treatment.

Doses of relatlimab and nivolumab should be delayed due to treatment-related adverse events as outlined in the protocol. Treatment may be discontinued due to unacceptable toxicity, withdrawal of consent, disease progression, or termination of the study, whichever occurs first. A DMC will provide independent oversight of safety, study conduct, and efficacy of the study treatments. The DMC will convene to assess the results of the interim analysis and provide its recommendations.

Duration

An interim PFS analysis will be performed when a minimum follow-up of 12 weeks is achieved for approximately 400 randomized subjects or at least 150 PFS events have been observed using BICR.

If the decision from the PFS interim is not to proceed to Phase 3, the study will stop enrollment and remain blinded until the final analysis of the Phase 2 study which will be performed with a minimum of 183 PFS events.

The total duration of the study for the Phase 3 primary endpoint of PFS will be determined by accrual of events. This is estimated to occur approximately 27 months after the first participant is randomized (which includes a potential 6-month delay in enrollment at the time of the interim analysis).

Additional follow-up for OS may be conducted up to approximately 5 years after the randomization of the last participant.

2 SCHEDULE OF ACTIVITIES

Table 2-1: Screening Procedural Outline (CA224047)

Procedure	Screening Visit	Notes
Eligibility Assessments		
Informed Consent	X	Prior to any screening procedures.
Contact IRT	X	For participant number assignment at time informed consent is obtained.
Inclusion/Exclusion Criteria	X	All inclusion/exclusion criteria should be assessed at screening.
Medical History	X	Including concomitant medications, disease state related to the study, AJCC M stage, and BRAF mutation status.
Tumor Tissue Samples	X	All participants must have tumor tissue available, either recent archival sample (obtained within 3 months of enrollment and with no intervening treatment between time of acquisition and enrollment) or a fresh pre-treatment biopsy obtained during the screening period. Tissue may be from a core biopsy, punch biopsy, excisional biopsy, or surgical specimen. Sufficient quantities must be available: a block or a minimum of 20 slides is requested. The analytical laboratory must provide IRT with related results prior to randomization. In order to be randomized, a participant must have quantifiable PD-L1 expression (≥ 1% or < 1% tumor cell membrane staining), and LAG-3 expression (≥ 1% or < 1%). Please refer to Section 9.8.2 for additional information.
BRAF Status		Results from a previous or new BRAF mutation test or a new sample must be processed per local institutional standard. Although this will be conducted on all participants, the results will be required for entry into IRT by the site prior to randomization.
NRAS and KIT Status		Results from a previous or new NRAS and KIT mutational test, if available, must be documented.
Safety Assessments		
Physical Examination	X	Within 14 days prior to randomization.
Physical Measurements (including performance status)	X	Within 14 days prior to randomization. Height, weight, and ECOG Performance Status/Lansky Performance Score for minors ONLY (see Appendix 6).
Vital Signs	X	Within 14 days prior to randomization. Including BP, heart rate, and temperature.

Table 2-1: Screening Procedural Outline (CA224047)

Procedure	Screening Visit	Notes
Assessment of Signs and Symptoms	X	Within 14 days prior to randomization.
Concomitant Medication Use	X	Within 14 days prior to randomization.
Serious Adverse Events Assessment	X	Serious Adverse Events ongoing from time of consent.
Laboratory Tests	X	Hematology, Serum Chemistry, and Urinalysis as outlined in Table 9.4.4-1 within 14 days of randomization. Serology as outlined in Table 9.4.4-1 within 28 days of randomization. For HIV: testing at sites where locally mandated, see Appendix 8.
Troponin	X	Within 14 days prior to randomization.
ECG	X	Within 14 days prior to randomization.
Pregnancy Test (WOCBP only)	X	Serum or urine (minimum sensitivity equivalent units 25 IU/L or equivalent units of HCG).
Follicle-stimulating hormone (FSH)	X	If needed to document post-menopausal status as defined in Table 9.4.4-1.
Efficacy Assessments		
Body Imaging	X	Contrast-enhanced CT of the chest, abdomen, pelvis, and all known sites of disease within 28 days prior to randomization. See Table 9.1.2-1 for preferred and alternative imaging methods.
Brain Imaging	X	MRI of the brain without and with contrast is required for ALL participants during screening to rule out brain metastases within 28 days prior to randomization. CT of the brain (without and with contrast) can be performed if MRI is contraindicated. See Table 9.1.2-1 for preferred and alternative imaging methods.

Table 2-2: On-Study Assessments (CA224047)

Procedure[a]	Day 1 of each cycle (Cycle = 4 weeks)	Other Time Points Relative to Dosing Schedule	Notes
Safety Assessments			
Inclusion/Exclusion Criteria		X	All inclusion/exclusion criteria should be confirmed prior to randomization.
Targeted Physical Examination	X		To be performed only as clinically indicated within 3 calendar days prior to dosing.
Vital Signs	X		Including BP, heart rate, and temperature within 3 calendar days prior to dosing.
Physical Measurements (including performance status)	X		Weight and ECOG Performance Status/Lansky Performance Score for minors ONLY (see Appendix 6) within 3 calendar days prior to dosing.
Adverse Events Assessment	Continuously		All AEs (SAEs or non-serious AEs), including those associated with SARS-CoV-2 infection, must be collected continuously during the treatment period.
Concomitant Medication Assessment	Continuously		
Laboratory Tests	X		Within 3 calendar days prior to dosing including Hematology, Serum Chemistry, Urinalysis as outlined in Table 9.4.4-1. All labs should be checked prior to dosing.
Troponin		X	C1D1 (predose)* and C1D14 (± 5 days). C2D1 (predose) and C2D14 (± 5 days). C3D1 (predose). * Only if not done at screening. Predose: Within 3 calendar days prior to dosing. All labs should be checked prior to dosing. Day 14 lab should be checked as soon as possible. In case of high troponin, perform cardiac imaging via echocardiography or cardiac MRI.

Table 2-2: On-Study Assessments (CA224047)

Procedure[a]	Day 1 of each cycle (Cycle = 4 weeks)	Other Time Points Relative to Dosing Schedule	Notes
ECG	X		Within 3 calendar days prior to dosing; all ECGs should be checked prior to dosing.
Pregnancy Test (WOCBP only)		X	Serum or urine (minimum sensitivity equivalent units 25 IU/L or equivalent units of HCG) within 24 hours prior to administration of first dose of study treatment and then every 4 weeks (± 7 days) regardless of dosing schedule. Home pregnancy test that meets the minimum sensitivity requirements can be used as necessary.
Efficacy Assessments			
Body Imaging		X	FIRST tumor assessment should be performed at 12 weeks (± 1 week) relative to date of randomization. SUBSEQUENT tumor assessments should occur every 8 weeks (± 1 week) up to Week 52 (relative to date of randomization) and then every 12 weeks (± 1 week) (relative to date of randomization). Tumor assessments should continue until disease progression is confirmed by BICR or discontinuation of study treatment, whichever occurs later. Contrast enhanced CT chest, CT (or MRI with and without contrast) abdomen, pelvis, and all known sites of disease. Use same imaging method as was used at screening/baseline. See Section 9.1.
Brain Imaging		X	Participants with a history of brain metastasis or symptoms should have a surveillance MRI (without and with contrast) study per standard of care (approximately every 12 weeks), or sooner if clinically indicated. CT of the brain without and with contrast can be performed if MRI is contraindicated. See Section 9.1. See Table 9.1.2-1 for instructions on performance of scans in participants with contrast allergies.
Pharmacokinetic and Immunogenicity Assessments			
PK and Immunogenicity blood sample		X	Refer to Table 9.5.1-1.

Table 2-2: On-Study Assessments (CA224047)

Procedure[a]	Day 1 of each cycle (Cycle = 4 weeks)	Other Time Points Relative to Dosing Schedule	Notes
Exploratory Biomarkers			
On treatment tumor biopsy		X	On-treatment tumor biopsy optional for all participants (see Table 9.8.2.6-1). Biopsied lesions should be distinct from index lesion(s) being evaluated for radiological response, if clinically feasible.
Exploratory Serum & Plasma Biomarkers, Peripheral Blood Mononuclear Cells (PBMCs)		X	Refer to Table 9.8.2.6-1.
Whole Blood Sample (DNA)		X	The whole blood sample (DNA) is to be collected predose for the first dose only (only one time point). See Table 9.8.2.6-1.
Additional Research Sampling		X	See Section 9.8.2.7.
Patient-Reported Outcomes Assessments			
EQ-5D-3L	X		Each assessment should be completed at the start of the clinic visit prior to dosing. Pediatric participants (≥12 and <18 years of age) should only complete the EQ-5D-3L and not the WPAI:GH or FACT-M assessments
FACT-M	X		
WPAI:GH	X		
Health Care Resource Utilization	X		Health care resource utilization data will be collected at each visit by study site staff using the CRF.
Clinical Drug Supplies			
Administer Study Treatment	X		The first dose is to be administered within 3 calendar days following randomization. Study treatments will be administered via a single IV bag in a single 1-hour infusion. Treatment will continue until progression, unacceptable toxicity, or study ends.

[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, except for body imaging and pregnancy testing.

Table 2-3: Follow-Up Procedural Outline (CA224047)

Procedure	Follow-Up[a] Visits 1 and 2	Survival Follow-Up Visits[b]	Notes
Safety Assessments			
Targeted Physical Examination	X		Weight, BP, heart rate, and temperature. Targeted physical examination to be performed only as clinically indicated.
Serious Adverse Events Assessment / Adverse Events Assessment	X		All SAEs and non-serious AEs should be collected continuously during the treatment period and for a minimum of 100 days following discontinuation of study treatment. Participants will be followed for all SAEs, non-serious AEs of special interest (as defined in Section 9.2.3), and all AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection until resolution, the condition stabilizes, the event is otherwise explained, the event is deemed irreversible, the participant is lost to follow-up (as defined in Section 8.3), or for suspected cases, until SARS-CoV-2 infection is ruled out.
Laboratory Tests	X		For Follow-Up Visit 1, onsite/local including Hematology, Serum Chemistry, and Urinalysis as outlined in Table 9.4.4-1. Repeat at Follow-Up Visit 2 if study treatment related toxicity persists.
Pregnancy Test (WOCBP only)	X		Pregnancy testing is only required at FU Visits 1 and 2 unless increased frequency and duration is required per local regulations.
Efficacy Assessments			
Body Imaging	X	X	Only for participants without BICR-confirmed progression on study therapy. Tumor assessments subsequent to the first assessment should occur every 8 weeks (± 1 week) up to Week 52 and then every 12 weeks (± 1 week) until disease progression is documented or study treatment is discontinued, whichever occurs later Contrast enhanced CT chest, CT (or MRI with and without contrast) abdomen, pelvis, and all known sites of disease. Use same imaging method as was used at screening/baseline. See Section 9.1.

Table 2-3: Follow-Up Procedural Outline (CA224047)

Procedure	Follow-Up[a] Visits 1 and 2	Survival Follow-Up Visits[b]	Notes
Brain Imaging	X	X	Only for participants without BICR-confirmed progression on study therapy. Participants with a history of brain metastasis or symptoms should have surveillance MRIs per standard of care (approximately every 12 weeks) or sooner if clinically indicated. CT of the brain without and with contrast can be performed if MRI is contraindicated. See Section 9.1. See Table 9.1.2-1 for instructions on performance of scans in participants with contrast allergies.
PFS2 Assessment	X	X	Following first progression, participants will continue to be followed during the safety and survival Follow-Up Visits. Time of second progression per investigator's assessment will be documented.
Pharmacokinetic (PK) Assessments			
PK and Immunogenicity blood sample	X		Refer to Table 9.5.1-1 for details regarding specific sample timing.
Outcomes Research Assessments			
EQ-5D-3L	X	X	For survival visits, questionnaire can be administered by phone. Pediatric participants (≥12 and <18 years of age) should only complete the EQ-5D-3L and not the WPAI:GH or FACT-M assessments
FACT-M	X		
FACT-M melanoma subscale (MS)		X	For survival visits, MS questionnaire can be administered by phone.
WPAI:GH	X		
Health Care Utilization	X		Health care resource utilization data will be collected by study site staff using the CRF.

Table 2-3: Follow-Up Procedural Outline (CA224047)

Procedure	Follow-Up[a] Visits 1 and 2	Survival Follow-Up Visits[b]	Notes
Exploratory Biomarker Testing			
Tumor Tissue Biopsy and Biomarker Assessments			See Table 9.8.2.6-1.

[a] Follow-up visits occur as follows: Follow-up Visit 1 = 30 days from the last dose (±7 days) or coincide with the date of discontinuation (±7 days) if date of discontinuation is greater than 42 days after last dose. Follow-up Visit 2 = 100 days (±7 days) from last dose of study treatment. Participants must be followed for at least 100 days after last dose of study treatment. Both follow-up visits should be conducted in person.

b Survival follow up visits may be conducted in clinic or by phone. Survival visits: first Survival Follow-up visit 3 months (± 14 Days) after FU 2, subsequent survival FU visits every 3 months (± 14 days). BMS may request that survival data be collected on all treated participants outside of the 3 month specified window. 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.

3 INTRODUCTION

Study CA224047 is a Phase 2/3, randomized, double-blind study of BMS-986213 (fixed-dose combination [FDC] relatlimab/nivolumab at a 1:3 ratio) versus nivolumab monotherapy in participants with previously untreated, unresectable, or metastatic melanoma. 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 with high affinity and prevents binding of this receptor to cells bearing its ligand, major histocompatibility complex (MHC) Class II, the peptide antigen presentation molecule recognized by CD4+ T cells. Relatlimab binding inhibits the negative regulatory function of LAG-3 in vitro. By blocking the normal down regulatory 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) monoclonal antibodies (mAbs).

Nivolumab is a human mAb (IgG4-S228P) that targets the programmed death-1 (PD-1) cluster of differentiation 279 (CD279) cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes.[1] Binding of PD-1 to its ligands, programmed death-ligands 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens.

BMS-986213 is being developed for use in patients with advanced malignancies, including melanoma. This is the first randomized study for BMS-986213 and will allow for direct comparison of BMS-986213 versus nivolumab monotherapy in participants with unresectable or metastatic melanoma.

3.1 Study Rationale

Individually targeting immune checkpoint receptors such as CTLA-4 and PD-1 has been clinically successful across multiple tumor types. It is possible, however, that combination therapies could potentially lead to greater depth of response and overall survival (OS) as has been noted with the combination of anti-PD-1 and anti-CTLA-4 in advanced melanoma patients.[2,3] Targeting additional checkpoints, such as by targeting LAG-3, is considered a promising novel approach. The combination blockage of LAG-3 and anti-PD-1 has potential to improve efficacy without adding significant toxicity compared to blocking anti-PD-1 alone.

This study aims to demonstrate that treatment with BMS-986213 shows increased progression-free survival (PFS) compared with nivolumab monotherapy in participants with previously untreated, unresectable, or metastatic melanoma. Additional objectives of the study include evaluation of OS, response rate and duration, characterization of safety and tolerability, pharmacokinetics, potential predictive biomarkers, and changes in patient -reported outcomes for quality-of-life assessments.

3.1.1 Research Hypothesis

Treatment with BMS-986213 will improve PFS when compared to nivolumab monotherapy in previously untreated participants with unresectable or metastatic melanoma.

3.2 Background

3.2.1 Indication Background

Melanoma, the most serious form of skin cancer, accounts for approximately 1-2% of all cancer deaths and approximately 5% of all new cases of cancer in the United States (US) with a 5-year survival rate of 18% for late-stage disease.[4]

Prior to 2011, approved therapies for the treatment of metastatic melanoma were limited and included chemotherapy (DTIC) and immunotherapy (interleukin-2 [IL-2]). Since then, three new therapeutic classes have been added to the treatment armamentarium and include seven new drugs administered as monotherapy or in combination. These drugs include: 1) ipilimumab, an anti-CTLA-4 blocking antibody, 2) drugs targeting the tyrosine kinase pathways including BRAF and MEK which include vemurafenib, dabrafenib, trametinib, and cobimetinib, and 3) monoclonal antibodies that bind to the PD-1 receptor, which include the recently approved nivolumab and pembrolizumab. Though many of these therapies have demonstrated OS benefit in Phase 3 studies, there are still areas of high unmet medical need for this population. Many patients relapse within months of initiating treatment[5,6,7] or are not eligible for treatment due to tumor mutation status requirements (eg, BRAF V600 mutation is present in approximately 50% of melanoma tumors).[8,9]

Overall, despite advances in therapeutic options, patients with metastatic melanoma continue to experience poor long-term clinical outcomes, reflecting the aggressive nature and complex etiology of the disease, and highlighting the continued unmet medical need.

3.2.2 Relatlimab Mechanism of Action

Relatlimab is a fully human antibody specific for human LAG-3 that was isolated from immunized transgenic mice expressing human immunoglobulin genes. 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 (Kd, 0.25-0.5 nM) and specificity and potently blocks the interaction of LAG-3 with its ligand, MHC class II (IC50, 0.7 nM). The antibody exhibits potent in vitro functional activity in reversing LAG-3–mediated inhibition of an antigen-specific murine T cell hybridoma overexpressing human LAG-3 (IC50, 1 nM). In addition, relatlimab enhances activation of human T cells in superantigen stimulation assays when added alone or in combination with nivolumab (anti–PD-1 antibody).

See also the Investigator's Brochure (IB) for relatlimab Section 4.1 (nonclinical pharmacology studies with relatlimab) and Section 4.2 (nonclinical pharmacokinetics with relatlimab).

3.2.3 Nivolumab Mechanism of Action

Cancer immunotherapy rests on the premise that tumors can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. An effective immune

response in this setting is thought to rely on immune surveillance of tumor antigens expressed on cancer cells that ultimately results in an adaptive immune response and cancer cell death. Meanwhile, tumor progression may depend upon acquisition of traits that allow cancer cells to evade immunosurveillance and escape effective innate and adaptive immune responses.[10,11,12] Current immunotherapy efforts attempt to break the apparent tolerance of the immune system to tumor cells and antigens by either introducing cancer antigens by therapeutic vaccination or by modulating regulatory checkpoints of the immune system. T-cell stimulation is a complex process involving the integration of numerous positive as well as negative co-stimulatory signals in addition to antigen recognition by the T-cell receptor (TCR).[13] Collectively, these signals govern the balance between T-cell activation and tolerance.

PD-1 is a member of the CD28 family of T-cell co-stimulatory receptors that also includes CD28, CTLA-4, ICOS, and BTLA.[14] PD-1 signaling has been shown to inhibit CD28-mediated upregulation of IL-2, IL-10, IL-13, interferon-γ (IFN-γ) and Bcl-xL. PD-1 expression also been noted to inhibit T cell activation, and expansion of previously activated cells. Evidence for a negative regulatory role of PD-1 comes from studies of PD-1 deficient mice, which develop a variety of autoimmune phenotypes.[15] These results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self-antigens.

Nivolumab is a fully human, IgG4 (kappa) isotype, monoclonal antibody that binds PD-1. Blockade of the PD-1 pathway by nivolumab was studied using the mixed lymphocyte reaction (MLR). PD-1 blockade resulted in a reproducible enhancement of both proliferation and IFN-γ release in the MLR.[16] The effect of nivolumab on antigen-specific recall response was investigated using a CMV-re-stimulation assay with human peripheral blood mononuclear cells (PBMCs), and was evaluated by ELISA.

In vitro, nivolumab (BMS-936558) binds to PD-1 with high affinity (EC50 0.39-2.62 nM), and inhibits the binding of PD-1 to its ligands PD-L1 and PD-L2 (IC50 ± 1 nM). Nivolumab binds specifically to PD-1 and not to related members of the CD28 family such as CD28, ICOS, CTLA-4 and BTLA. Blockade of the PD-1 pathway by nivolumab results in a reproducible enhancement of both proliferation and IFN-γ release in the MLR. Using a cytomegalovirus (CMV) re-stimulation assay with human PBMC, the effect of nivolumab on antigen specific recall response indicates that nivolumab augmented IFN-γ secretion from CMV specific memory T cells in a dose-dependent manner versus isotype-matched control. In vivo blockade of PD-1 by a murine analog of nivolumab enhances the anti-tumor immune response and result in tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/N, and PAN02).[17]

3.3 Benefit/Risk Assessment

There continues to be a significant unmet need for patients with previously untreated, unresectable melanoma. BMS-986213 has the potential for increased benefit compared to nivolumab monotherapy, with an acceptable safety profile.

Study CA224020 is a Phase 1 dose escalation and cohort expansion study of the safety, tolerability, and efficacy of relatlimab administered alone and in combination with nivolumab in advanced solid tumors. As of cut-off date of 07-Apr-17, preliminary proof-of-concept efficacy has been revealed in Part C in the combination treatment expansion cohort of advanced melanoma with prior treatment with anti-PD-1/PD-L1. All subjects were treated with relatlimab 80 mg + nivolumab 240 mg every 2 weeks. The overall ORR was 11.5% (n=61 response evaluable) with a disease control rate of 49%. Biomarker analyses showed that patients whose tumor associated immune cells expressed more LAG-3 had a higher response rate, with a greater than 3-fold increase in ORR observed in patients with evidence of LAG-3 expression in at least 1% of nucleated cells within the tumor region, compared to less than 1% LAG-3 expression (ORRs of 18.2% [6/33] and 5.0% [1/20], respectively). PD-L1 expression did not appear to enrich for response.

The treatment group had the following characteristics: 1) Most patients had M1C disease (69%), 2) the cohort was heavily pretreated (76% with 2 or more prior therapies), 3) all patients had progressed while receiving anti-PD-1/PD-L1, and 4) progressive disease was the best response to prior anti-PD-1/PD-L1 in 40% of patients. Overall, relatlimab in combination with nivolumab demonstrated encouraging initial efficacy with a safety profile similar to nivolumab monotherapy.

In summary, relatlimab in combination with nivolumab has shown the capacity to induce responses in heavily treated advanced solid tumors, with the added ability to trigger responses in tumors that have demonstrated resistance to nivolumab therapy.

This study involves investigational (relatlimab) and approved (nivolumab) drugs whose effects on pregnancy are not yet known or fully defined. Contraception is therefore required for participants who are women of childbearing potential (WOCBP) or male, and for female partners of male participants who are WOCBP. These contraception guidelines (see Appendix 4) were developed for the nivolumab development program and apply to all female participants and partners of male participants who could be exposed to the drug and who could become pregnant both during treatment and during a defined period after study drug treatment.

Overall, based on preliminary data as of the clinical cutoff date of 15-Jun-2017, the safety profile of relatlimab in combination with nivolumab is manageable, with no maximum tolerated dose (MTD) reached at the tested doses up to 160 mg relatlimab and 240 mg nivolumab (flat dose, every 2 weeks [Q2W]), with evaluation of the 240 mg relatlimab/240 mg nivolumab combination dose-level ongoing. At the time of the clinical cutoff date (15-Jun-2017) one dose-limiting toxicity (DLT) of Grade 5 myocarditis was observed at the 240 mg relatlimab/240 mg nivolumab combination dose level among five evaluable subjects. There was no dose relationship between the incidence, severity, or causality of adverse events (AEs) to combination therapy. In the nine expansion cohorts, a total of 262 subjects were treated with 80 mg relatlimab and 240 mg nivolumab Q2W. Most AEs were low grade (Grade 1 to Grade 2) with a total of 26 subjects experiencing a drug-related serious adverse event (SAE). All AEs, except for one Grade 5 myocarditis and one Grade 4 drug-induced liver injury (DILI), were reversible and manageable by withholding study drug administration providing standard medical care, and/or following immune-related AE algorithms. In summary the safety profile of the combination of relatlimab and

nivolumab appears similar to nivolumab monotherapy in terms of both frequency and severity of AEs.

A pattern of immune-related adverse events has been defined for treatment with nivolumab monotherapy and nivolumab in combination with other immune-targeting agents such as relatlimab. Management algorithms have been developed for these events and are provided in Appendix 9. Most high-grade events are manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in these algorithms.

Myocarditis has been observed with nivolumab monotherapy treatment (see nivolumab IB Section 5.6.2). Given the grade 5 myocarditis event in the CA224020 study, and the known nonclinical mouse double LAG-3/PD-1 knockout myocarditis phenotype, increased cardiac surveillance with troponin measurements were instituted. As of the clinical cutoff date of 15-Jun-2017 there have been four grade 1 myocarditis cases (asymptomatic troponin elevations with imaging correlate of myocardial inflammation but without evidence of cardiac dysfunction). Treatment was delayed in all cases, and precautionary steroid treatment was given without any of the participants developing evidence of cardiac dysfunction.

Additional details on the safety profiles of relatlimab and nivolumab, including guidance regarding myocarditis and other potential risks, as well as results from other clinical studies, are available in the relatlimab and nivolumab IBs.

Evaluating the combination of relatlimab and nivolumab will provide clinical data allowing clinicians to select the appropriate treatment for each patient based on the individual risk-benefit ratio. The promising clinical activity of relatlimab combined with nivolumab in participants with advanced melanoma along with the manageable safety profile and the ongoing need for survival-prolonging agents for a large segment of the previously untreated population, supports further development of this combination and initiation of this Phase 2/3 study.

This study will employ the FDC drug product BMS-986213 in which both drugs are formulated in the same vial. However, given a theoretical risk of infusion reactions due to the new formulation, an acute toxicity safety lead-in with BMS-986213 will be completed.

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Phase 3 Primary Objective	
• The Phase 3 primary objective is to compare PFS of BMS-986213 to nivolumab monotherapy in participants with previously untreated, unresectable, or metastatic melanoma.	• PFS time as assessed by a Blinded Independent Central Review (BICR), using RECIST v1.1. PFS is defined as the time between the date of randomization and the first date of documented progression, or death due to any cause, whichever occurs first.

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Phase 3 Safety Objective:	
• To assess the overall safety and tolerability of BMS-986213 and of nivolumab monotherapy.	• Incidence of AEs, SAEs, AEs leading to discontinuation of treatment, deaths, and laboratory abnormalities.
Phase 3 Secondary Objectives	
The Phase 3 secondary objectives are: • To compare OS of BMS-986213 to nivolumab monotherapy in participants with previously untreated, unresectable or metastatic melanoma.	• OS is defined as the time between the date of randomization and the date of death due to any cause.
• To compare ORR of BMS-986213 to nivolumab monotherapy in participants with unresectable or metastatic melanoma	• ORR as assessed by a BICR. The ORR is defined as the number of subjects with a best overall response (BOR) of complete response (CR) or partial response (PR) divided by the number of randomized subjects for each treatment group. The BOR is defined as the best response designation, recorded between the date of randomization and the date of objectively documented progression per RECIST v1.1 or the date of subsequent anti-cancer therapy, whichever occurs first.
Phase 3 Tertiary/Exploratory Objective	
The Phase 3 tertiary/exploratory objectives are: • To evaluate duration of and time to objective response	• Duration of response (DOR) is defined as the time between the date of first response to the date of first documented tumor progression (per RECIST v1.1) or death due to any cause. Time to objective response (TTR) is defined as the time from randomization to the date of the first documented CR or PR.
• To evaluate PFS, ORR, DOR, and OS of BMS-986213 to nivolumab monotherapy in subgroups based on combinations of LAG-3 expression (≥ 1% expression versus < 1% expression) and PDL-1 status (≥ 1% tumor cell surface expression versus < 1% tumor cell surface expression) among participants with unresectable or metastatic melanoma	• PFS time as assessed by a BICR using RECIST v1.1. • ORR as assessed by a BICR. • DOR. • TTR. • OS.

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
treated with BMS-986213 compared to those treated with nivolumab monotherapy.	
• To evaluate the difference in symptom burden between participants with unresectable or metastatic melanoma treated with BMS-986213 and those treated with nivolumab monotherapy.	• Time to meaningful symptomatic deterioration (TTSD) as measured by the Functional Assessment of Cancer Therapy – Melanoma (FACT-M) Melanoma Subscale (MS).
• To characterize the pharmacokinetics (PK) of relatlimab and nivolumab in subjects with unresectable or metastatic melanoma treated with BMS-986213 and those treated with nivolumab monotherapy.	• PK parameters, influence of intrinsic and extrinsic covariates will be characterized using population PK models.
• To characterize immunogenicity of relatlimab and nivolumab in subjects with unresectable or metastatic melanoma treated with BMS-986213 and those treated with nivolumab monotherapy.	• Incidence of anti-drug-antibody (ADA) to relatlimab and nivolumab when administered in combination with nivolumab.
• To explore potential exposure-response relationships in subjects treated with BMS-986213.	• Potential exposure response relationship (PD effect, efficacy, and select safety) will be evaluated using integrated analysis.
• To explore potential biomarkers associated with clinical efficacy (ORR, PFS, and OS) by analyzing biomarker measures within the tumor microenvironment and periphery (eg, tumor, serum and PBMCs) as related to clinical outcomes.	• Association measures of select biomarkers and key efficacy endpoints (eg, ORR, PFS, and OS)
• To characterize changes in cancer-related symptoms and quality of life for participants with unresectable or metastatic melanoma treated with BMS-986213 and those treated with nivolumab monotherapy	• Summary measures of FACT-M total and subscale scores (and changes) following treatment.
• To characterize participant perceptions of the bothersomeness of symptomatic AEs, based on FACIT GP5 item as found in the FACT-M.	• Summary changes and frequency of responses in FACIT GP5 item measuring bother due to side effects of treatment.
• To characterize changes in overall health status and health utility for participants with unresectable or metastatic melanoma treated	• Summary measures of EQ-5D-3L visual analog scale (VAS) and utility index scores.

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
with BMS-986213 and those treated with nivolumab monotherapy.	
• To characterize changes in work productivity and activity impairment for participants with unresectable or metastatic melanoma treated with BMS-986213 and those treated with nivolumab monotherapy	• Summary measures of Work Productivity and Activity Impairment General Health (WPAI:GH) work productivity loss, activity impairment, presenteeism, and absenteeism scores.
• To evaluate PFS, PFS after next line of treatment (PFS2),ORR, and DOR of BMS-986213 to nivolumab monotherapy in participants with previously untreated, unresectable, or metastatic melanoma	• PFS and PFS2 time as assessed by investigator using RECIST v1.1. • ORR as assessed by investigator. • DOR.
• To evaluate treatment-free interval (TFI) defined as time from last dose of study treatment to the start of subsequent systemic therapy or the last known date alive (for those who never received subsequent cancer therapy)	• TFI
Phase 2 Primary Objective	
• The Phase 2 primary objective is to compare PFS of BMS-986213 to nivolumab monotherapy in participants with previously untreated, unresectable, or metastatic melanoma.	• PFS time as assessed by BICR, using RECIST v1.1. PFS time is defined as the time between the date of randomization and the first date of documented progression, or death due to any cause, whichever occurs first.
Phase 2 Safety Objective:	
• To assess safety and tolerability among participants with unresectable or metastatic melanoma treated with BMS-986213 compared to those treated with nivolumab monotherapy.	• Incidence of AEs, SAEs, AEs leading to discontinuation of treatment, deaths, and laboratory abnormalities.
Phase 2 Secondary Objectives	
The Phase 2 secondary objectives are: • To estimate the treatment effect, measured by ORR, as determined by BICR using RECIST v1.1 in all-comers and in subgroups based on combinations of LAG-3 expression (≥ 1% expression versus < 1% expression) and PDL-1 status (≥ 1% tumor cell surface	• ORR as assessed by a BICR.

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
expression versus < 1% tumor cell surface expression) among participants with unresectable or metastatic melanoma treated with BMS-986213 compared to those treated with nivolumab monotherapy.	
• To evaluate DOR and PFS rates at pre-specified time points (eg, 24 weeks) based on BICR assessments using RECIST v1.1 in the randomized population (for DOR) and in subgroups based on combinations of LAG-3 expression (≥ 1% expression versus < 1% expression and PDL-1 status (≥ 1% tumor cell surface expression versus < 1% tumor cell surface expression) among subjects with unresectable or metastatic melanoma treated with BMS-986213 and those treated with nivolumab monotherapy.	• DOR. • PFS time as assessed by a BICR using RECIST v1.1.
• To assess the 1- and 2-year OS rate in the randomized population and in subgroups based on combinations of LAG-3 expression (≥ 1% expression versus < 1% expression) and PDL-1 status (≥ 1% tumor cell surface expression versus < 1% tumor cell surface expression) among subjects with unresectable or metastatic melanoma treated with BMS-986213 and those treated with nivolumab monotherapy.	• OS is defined as the time between the date of randomization and the date of death due to any cause.
Phase 2 Exploratory Objectives	
Phase 2 exploratory objectives are: • To characterize the PK of relatlimab and nivolumab in subjects with unresectable or metastatic melanoma treated with BMS-986213 and those treated with nivolumab monotherapy.	• Summary measures of PK parameters based on population PK models including influence of intrinsic and extrinsic covariates
• To characterize the immunogenicity of relatlimab and nivolumab in subjects with unresectable or metastatic melanoma treated with BMS-986213 and those treated with nivolumab monotherapy.	• Incidence of ADA to relatlimab and ADA of nivolumab when administered in combination with relatlimab

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
• To assess the PD effects of BMS-986213 based on select biomarkers in the peripheral blood and tumor biopsy specimens.	• Summary measures of change (or % change) from baseline in various biomarkers.
• To characterize T-cell function during treatment of BMS-986213.	• Summary of pre- treatment levels and of changes in T cells levels observed on-treatment.
• To explore potential exposure-response relationships (eg, with efficacy, receptor occupancy, pharmacodynamic effects) in subjects treated with BMS-986213.	• Measures of Potential PK exposure response relationship (with pharmacodynamic effects, efficacy and select safety)
• To evaluate ORR, DOR, PFS, and PFS2 rates at pre-specified time points (eg, 24 weeks) based on investigator assessments using RECIST in the randomized population and in subgroups based on combinations of LAG-3 expression (≥ 1% expression versus < 1% expression) and PDL-1 status (≥ 1% tumor cell surface expression versus < 1% tumor cell surface expression) among subjects with unresectable or metastatic melanoma treated with BMS-986213 and those treated with nivolumab monotherapy.	• ORR. • DOR. • TTR. • PFS and PFS2 time using RECIST v1.1.

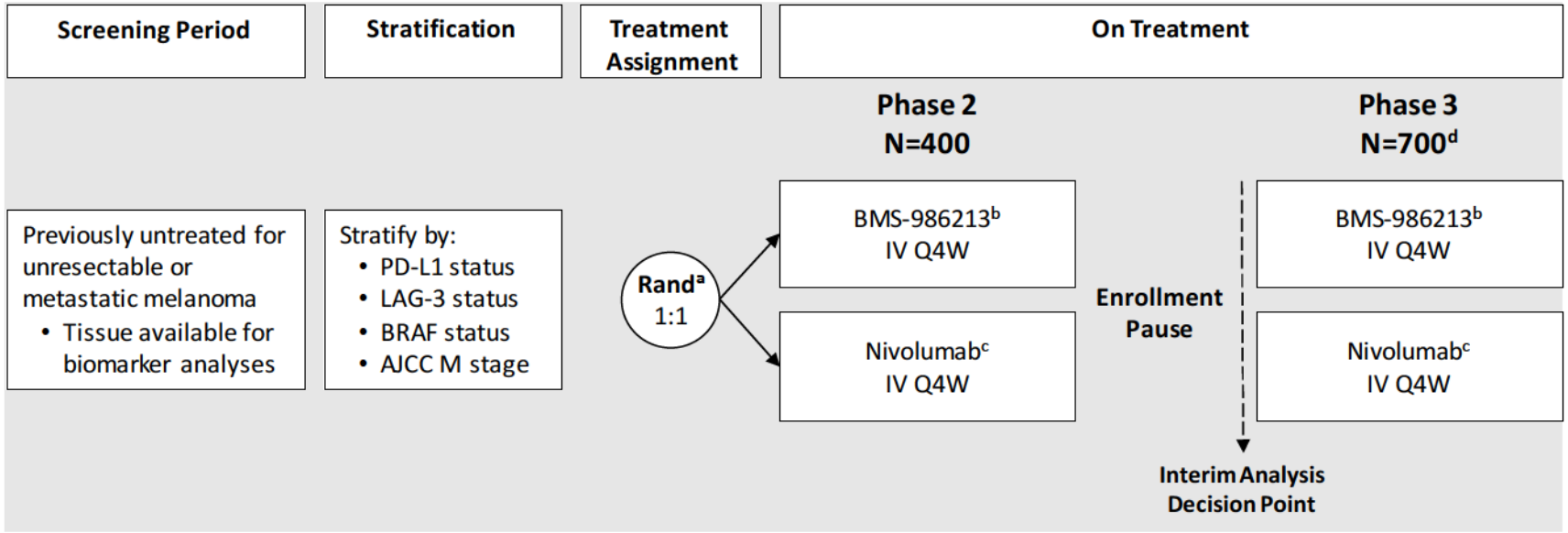
5 STUDY DESIGN

5.1 Overall Design

This is a Phase 2/3, randomized, double-blind study of BMS-986213 (FDC relatlimab/nivolumab at a 1:3 ratio) versus nivolumab monotherapy in adult and adolescent participants (≥ 12 years of age) with previously untreated, unresectable, or metastatic melanoma. Participants must have unresectable Stage III or Stage IV melanoma, per the 8th edition of the American Joint Committee on Cancer (AJCC) staging system[18] (see Appendix 7), and must not have received prior systemic therapy for the treatment of unresectable or metastatic melanoma.

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

Figure 5.1-1: Study Design Schematic



[a] A safety lead-in evaluation will be performed on the first (up to) 18 participants.

[b] BMS-986213 is the fixed-dose combination relatlimab/nivolumab at a 1:3 ratio. For adults, dosing is relatlimab 160 mg/nivolumab 480 mg. Adolescents ≥ 40 kg will receive adult dosing; for adolescents < 40 kg, dosing is relatlimab 2 mg/kg/nivolumab 6 mg/kg.

[c] Nivolumab monotherapy dosing for adults is 480 mg. Adolescents ≥40 kg will receive adult dosing; for adolescents < 40 kg, dosing is 6 mg/kg.

[d] The 700 subjects in Phase 3 will consist of the 400 from Phase 2 and an additional 300 from the Phase 3 part of the trial.

A pre-treatment tumor sample to determine PD-L1 and LAG-3 status is required to be submitted from all participants prior to randomization. The sample must be obtained within 3 months prior to enrollment from a metastatic tumor lesion or from an unresectable primary tumor lesion that has not been previously irradiated; no intervening treatment may have been administered between the time of biopsy/surgery and study entry. The tumor sample will be submitted as either a formalin-fixed paraffin-embedded (FFPE) block (preferred) or minimum of 20 slides requested, obtained from core biopsy, punch biopsy, excisional biopsy, or surgical specimen. If sufficient tissue is not available from within 3 months prior to enrollment, then a fresh biopsy will be required during the screening period. Samples will be submitted to the analytical laboratory for PD-L1 and LAG-3 testing. The analytical laboratory must provide the interactive response technology (IRT) with the related results prior to randomization.

Participants must have a documented BRAF status prior to randomization. Those participants enrolling in this study without documented results must have testing performed locally and result (wild type or mutant) be available prior to randomization.

Depending on the treatment arm, the participant will receive BMS-986213 or nivolumab until disease progression, treatment discontinuation, withdrawal of consent, or the study ends.

One cycle of treatment is defined as 4 weeks.

Dose reductions will be not be allowed.

On-study tumor assessments will begin 12 weeks from randomization and will continue every 8 weeks up to Week 52 and every 12 weeks thereafter. Tumor assessments should continue until disease progression confirmed by the BICR or treatment discontinuation, whichever occurs later.

Treatment beyond initial investigator-assessed RECIST v1.1-defined progression (see Appendix 5) is permitted if the participant has investigator-assessed clinical benefit and is tolerating study treatment (Section 8.1.2 and Section 8.1.2.2).

The decision on whether to complete the Phase 3 enrollment (N=700) or stop at the Phase 2 enrollment (N=400) will be recommended by the Data Monitoring Committee (DMC) based upon the interim analysis of PFS, which is for futility. If the Phase 2 enrollment is complete before a decision on completing the Phase 3 enrollment has been made, enrollment to the study will pause. Given estimates of accrual, this pause may be up to 5 to 6 months but could be shorter if enrollment is slower than anticipated. If the interim PFS analysis meets the pre-specified threshold and the study proceeds to Phase 3, the final PFS analysis will be performed when approximately 365 PFS events have occurred per BICR (see Section 10.2.2).

Safety Lead-In

Given a theoretical risk of infusion reactions with the administration of BMS-986213, a safety lead-in will be employed for the first (up to) 18 subjects randomized.

The lead-in will follow a 6+6+6 design to monitor for Grade 3 or 4 infusion reactions. Six subjects will be treated in each sequential set. There will be no time interval restrictions for patients to begin treatment within a set of 6.

- The infusion reaction observation period will be 48 hours. Completion of the observation period for all patients in each set must be completed prior to any randomization to the next set.
- Rules:
  - If ≤ 1 of the first 6 participants experiences a Grade 3 or 4 infusion reaction then the second set of 6 will be randomized.
    If ≥ 2 of the first 6 participants experience a Grade 3 or 4 infusion reaction then randomization will be held until further evaluations can be performed.
  - If ≤ 2 of 12 participants experience a Grade 3 or 4 infusion reaction the third set of 6 will be randomized.
    If ≥ 3 of 12 participants experience a Grade 3 or 4 infusion reaction then randomization will be held until further evaluations can be performed.
  - If ≤ 2 of 18, experience a Grade 3 or 4 reaction, randomization will be continued. If ≥ 3 of 18 subjects experience Grade 3 or 4 infusion reactions then randomization will be held until further evaluations can be performed.
- For the management of infusion reactions, please refer to the treatment guidelines outlined under Section 7.7.3.

5.1.1 Data Monitoring Committee and Other External Committees

When required, adjudicated events will be submitted to the 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 relatlimab and nivolumab. 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.

The DMC will convene to assess the results of the interim analyses (see Section 10.2.5 and provide its recommendations. Additional details concerning DMC oversight are provided in the DMC charter.

In addition, a BICR will be utilized in this study for determination of BICR-assessed endpoints. The BICR will review all available tumor assessment scans for all treated participants. Details of BICR responsibilities and procedures will be specified in the BICR charter.

5.2 Number of Participants

The Phase 2 part of the study will enroll approximately 400 participants. An interim analysis will be performed when a minimum follow-up of 12 weeks is achieved for approximately 400 randomized subjects or at least 150 PFS events have been observed using BICR. The interim PFS analysis is a futility analysis. If the interim PFS analysis is positive (based on the pre-specified threshold as defined in the Statistical Analysis Plan [SAP]), then the study will continue to Phase 3 and remain blinded. If the interim PFS analysis does not support continuing to the Phase 3 study,

the study will allow the Phase 2 data to mature and then unblind the sponsor for analysis. If the latter scenario takes place, approximately 575 participants will need to be enrolled in order to randomize 400 participants assuming a screen failure rate of 30%.

If the study does continue to Phase 3, it is expected that approximately 1000 participants will need to be enrolled to randomize at least 700 participants, assuming a screen failure rate of approximately 30%.

Participants will be randomized 1:1 to one of two parallel treatment groups:

- BMS-986213 by intravenous (IV) infusion every 4 weeks (Q4W)
- nivolumab IV Q4W

See Section 10.1 for sample size determination.

5.3 End of Study Definition

The start of the study is defined as the first visit for the first participant screened. End-of-study for the primary endpoint 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.

An interim PFS analysis will be performed when a minimum follow-up of 12 weeks is achieved for approximately 400 randomized subjects or at least 150 PFS events have been observed using BICR. If the decision from the interim analysis is not to proceed to Phase 3, the study will stop enrollment and remain blinded until the final analysis of the Phase 2 study which will be performed with a minimum of 183 PFS events.

The total duration of the study for the Phase 3 primary endpoint of PFS will be determined by accrual of events. This is estimated to occur approximately 27 months after the first participant is randomized (which includes a potential 6-month delay in enrollment at the time of the interim analysis, see Section 10.1).

Additional follow-up for OS may be conducted up to approximately 5 years after the randomization of the last participant.

5.4 Scientific Rationale for Study Design

5.4.1 Rationale for Use of Fixed-Dose Combination Product

BMS-986213, a FDC product, contains relatlimab and nivolumab in protein-mass ratio 1:3 in a single vial. The FDC will be administered via IV infusion over approximately 1 hour. 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 for medication preparation and administration error.

5.4.2 Rationale for Blinding

The study will be double-blinded in order to:

- minimize bias
- limit thresholds for classification of progression between the arms (which could subsequently affect treatment duration between the arms and have an impact on the primary endpoint of PFS)
- 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 PFS has been reached.

5.4.3 Rationale for Stratification by M-Staging, BRAF, LAG-3, and PD-L1

In order to minimize the potential for imbalances across treatment arms, there will be four stratification factors utilized in this trial: AJCC M stage (M0/M1any[0] versus M1any[1]), BRAF mutation (mutation positive versus wild type), LAG-3 status (≥ 1% expression versus < 1% expression) and PD-L1 expression (≥ 1% tumor cell surface expression versus < 1% tumor cell surface expression). Prognostic implications of M staging are well established.[19] BRAF mutations have likewise been associated with adverse clinical outcomes in melanoma patients.[20] Preliminary data from the CA224020 study have shown that LAG-3 expression may be a strong predictor of efficacy in tumors that have become resistant to anti-PD-1 therapy.[21] With regard to PD-L1 expression, previous clinical studies with nivolumab monotherapy have shown patients with PD-L1 positive tumors may have higher response rates than those with indeterminate expression.[22] Participants in the current trial will therefore be stratified by PD-L1 status as the effect of PD-L1 expression on response to PD-1 and anti-LAG-3 combination therapies is not yet known.

5.4.4 Rationale for Progression-Free Survival as a Primary Endpoint

Treatment options that are clinically active (eg, ipilimumab, vemurafenib, dabrafenib, trametinib) are increasingly available in patients with unresectable or metastatic melanoma and their use after disease progression on the current study may confound an OS endpoint. PFS is not confounded by post-study treatment therapies and has been demonstrated to correlate with overall survival in a meta-analysis of randomized, dacarbazine-controlled trials in metastatic melanoma.[23] In addition, PFS has been recognized as an acceptable regulatory endpoint. For example, dabrafenib and trametinib as monotherapy and in combination were approved by the FDA for treatment of unresectable or metastatic melanoma based on Phase 3 clinical trials where the primary endpoint was PFS.[24,25,26] Radiographic images will be collected and should be submitted on a rolling basis to an Imaging Core lab, for BICR tumor assessment.

5.4.5 Rationale for Inclusion of Adolescent Participants

Patients under 18 years of age have often been excluded from adult oncology trials because of safety or regulatory concerns; a practice that leads to delays in pediatric studies. Separate adult and pediatric cancer centers, distinct cooperative research groups, and oncologists specializing in different populations do not often conduct unified adult–pediatric clinical trials or -drug development programs.[27]

Although rare, the incidence of childhood and adolescent melanoma in the United States has been increasing in the past 35 years. This trend is most prominent in the adolescent age range, specifically those 15 to 19 years of age. Single-center and industry-sponsored trials often exclude advanced melanoma adolescent patients for historical or empiric reasons. A recent genomic analysis of pediatric melanoma demonstrates that conventional melanoma in children and adolescents shares many of the genomic features that have been described in adult melanoma, including BRAF mutations. The abstract of this genomic analysis advocated for the opportunity for pediatric patients to be enrolled in pharmaceutically sponsored trials that incorporate novel agents. Many pediatric subjects who are diagnosed with melanoma get referred to and treated by medical oncologists versus pediatric oncologists, due to divergent expertise in the field.[28] Individual countries and sites have the option of opting out of adolescent eligibility.

5.4.6 Rationale for Evaluation of Predictive Biomarkers

Despite striking advances in patient survival driven by immunotherapy, the majority of patients have not yet realized benefit from these treatments. Identification of biomarkers that predict clinical benefit or that are associated with resistance to therapy are critical needs. To date, PD-L1 expression within the tumor microenvironment has been associated with response to treatment of melanoma with nivolumab as monotherapy or in combination with ipilimumab. Similarly, preliminary data suggest that expression of LAG-3 on immune cells was associated with response to treatment of melanoma with relatlimab in combination with nivolumab. Additional biomarkers of response to immunotherapy include tumor mutation burden and gene signatures of tumor inflammation (IFNg signature). In the current trial, PD-L1 and LAG-3 levels, tumor mutation burden, and gene expression signatures will all be evaluated for predictive value of response to nivolumab monotherapy and BMS-986213. Serum, plasma, and peripheral blood immune cell analysis will be assessed in samples collected pretreatment and at time points during treatment. These analyses will allow identification of predictive biomarkers and allow discrimination between factors predictive of monotherapy versus combination therapy. Additional analysis of pretreatment versus on treatment tumor biopsies will be performed in order to identify additional pathways contributing to therapeutic resistance.

5.5 Justification for Dose

5.5.1 Justification for Fixed-Dose Combination Dosing

In this study, BMS-986213 Q4W will be administered as an IV infusion over approximately 1 hour. The dosing regimen for this study was selected after considering model predicted PK, peripheral receptor occupancy (RO), efficacy, and safety profile observed in adult population from Study CA224020, and extensive nivolumab monotherapy clinical experience.

The predicted steady-state exposure and corresponding peripheral RO of relatlimab 160 mg Q4W is expected to be similar to the 80 mg Q2W dose, that is shown to provide meaningful efficacy when administered in combination with nivolumab in various tumor types. The relatlimab steady-state average concentration and corresponding RO comparing the Q2W and Q4W regimen is provided in Table 5.5.1-1.

Table 5.5.1-1: Comparison of Relatlimab Model Predicted Steady-State Exposure and Corresponding RO between Q2W and Q4W Regimen

Parameter	80 mg Q2W (Geo.Mean)	160 mg Q4W (Geo.Mean)	% Difference
Cavg,ss (µg/mL)	19.1	19.3	1.05
RO (%)	94.4	94.4	0.00

Similarly, nivolumab 480 mg Q4W is currently under investigation in several monotherapy and combination oncology studies. The nivolumab dosing regimen was selected using population PK (PPK) and exposure-response analyses modeling and simulation approaches such that they are predicted to provide approximately equivalent exposures (Cavg,ss) following administration of nivolumab 3 mg/kg Q2W. The model predicted that following administration of nivolumab 480 mg Q4W, Cavg,ss is expected to be similar to those following nivolumab 3 mg/kg or 240 mg Q2W, though Cmin,ss is predicted to be approximately 16% lower, respectively, and are not considered to be clinically relevant. Following nivolumab 480 mg Q4W, Cmax,ss is predicted to be approximately 43% greater, relative to that following nivolumab 3 mg/kg Q2W dosing; however, the range of nivolumab exposures (median and 90% prediction intervals) following administration of 480 mg Q4W regimen across the 35 to 160 kg weight range are predicted to be maintained well below the corresponding exposures observed with the well-tolerated 10 mg/kg nivolumab Q2W dosing regimen, and are not considered to put participants at increased risk.

Relatlimab as a single agent has had an acceptable safety profile at all tested doses: 20, 80, 240, and 800 mg, flat dose. The MTD was not reached up to 800 mg relatlimab Q2W. The combination therapy of relatlimab and nivolumab when administered sequentially (nivolumab 30-minute IV infusion followed by relatlimab 1-hour IV infusion) has an acceptable safety profile of all dose combinations that have completed safety testing, up to relatlimab 160 mg/nivolumab 240 mg Q2W. In addition, safety evaluation with alternative less frequent regimen (Q4W) dose escalation cohorts are currently under investigation in Study CA224020. The less frequent dosing regimens of relatlimab are designed to afford more convenience to the target patient population and allow combination with less frequent nivolumab dosing regimens. To date, the sequential administration of relatlimab 160 mg/nivolumab 480 mg Q4W has been shown safe (1 DLT out of six evaluable subject) to move to the next cohort of relatlimab 240 mg/nivolumab 480 mg Q4W.

Robust safety data (N=304) in patients treated with sequential administration (nivolumab 240 mg IV over 30 minutes followed by relatlimab 80 mg IV over 1 hour Q2W) has shown small risk (5.9%, all Grade 1 or 2) of infusion reactions. The overall safety as well as PK profile of

BMS-986213 is not expected to be different to that of the sequential administration. The comparative safety and PK assessment between sequential, co-administration and FDC is ongoing under Part D of study CA224020. This will make possible a shorter infusion time for patients with FDC product (infusion duration of 1 hour) than sequential infusion (total infusion duration of approximately 2.5 hours).

Relatlimab 80 mg/nivolumab 240 mg Q2W has shown the capacity to induce responses in previously heavily treated advanced solid tumors, with the added ability to trigger responses in tumors that have demonstrated resistance to nivolumab therapy. As of the cutoff date of 15-Jun-2017 for Part B of Study CA224020, in subjects treated with relatlimab/nivolumab combination therapy, partial responses were seen in subjects with melanoma, cervical cancer, non-small cell lung cancer (NSCLC), and squamous cell carcinoma of the head and neck (SCCHN). There is limited data to summarize efficacy for relatlimab 160 mg/nivolumab 480 Q4W regimen. However, exposure-response profile of relatlimab 160 mg/nivolumab 480 mg Q4W is not expected to be different to the relatlimab 80 mg/nivolumab 240 mg Q2W.

5.5.2 *Justification for Nivolumab Monotherapy Dose*

The nivolumab dose of 480 mg Q4W was selected for this study based on clinical data and modeling and simulation approaches using PPK and exposure-response (ER) analyses examining relationships between nivolumab exposures and efficacy (eg, OS, OR) and safety responses, using data from studies in multiple tumor types (melanoma, NSCLC, and renal cell carcinoma [RCC]) with body weight-normalized dosing (mg/kg). A flat dose is expected to reduce prescription dosing errors, shorten pharmacy preparation time, and improve ease of administration. Extending the dosing interval to 4 weeks provides numerous benefits to patients as they would have increased flexibility between clinical visits. The PPK analyses have shown that exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered Q2W, and no clinically meaningful differences in PK across ethnicities and tumor types were observed. Nivolumab clearance and volume of distribution were found to increase as body weight increases but less than proportionally with increasing weight, indicating that milligram-per-kilogram dosing represents an over-adjustment for the effect of body weight on nivolumab PK.

Using the PPK and ER models, nivolumab exposures and probabilities of efficacy responses and risks of AEs were predicted following nivolumab 480 mg Q4W and were comparable to those following nivolumab 3 mg/kg Q2W. The overall distributions of average nivolumab steady-state exposures (Cavg,ss) were comparable following administration with either nivolumab 3 mg/kg Q2W or nivolumab 480 mg Q4W over a wide range of body weight ranges. Nivolumab 480 mg Q4W is predicted to result in approximately 43% greater steady state peak concentrations (Cmax,ss) compared to nivolumab 3 mg/kg Q2W; however, these exposures are predicted to be lower than the exposure ranges observed at doses up to nivolumab 10 mg/kg Q2W used in the nivolumab clinical program. Although the Cmax,ss of nivolumab is expected to be greater following nivolumab 480 mg Q4W compared to nivolumab 3 mg/kg Q2W, the predicted Cmax,ss following nivolumab 480 mg Q4W is well below the median Cmax,ss achieved following administration of nivolumab 10 mg/kg Q2W, a safe and tolerable dose level.

Exposure-safety analysis 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 predicted to be similar following nivolumab 480 mg Q4W relative to nivolumab 3 mg/kg Q2W across tumor types. Safety analyses using available data following nivolumab 3 mg/kg Q2W and 10 mg/kg Q2W administration indicated there were no differences in AE profiles across body weight groups. Finally, initial evidence demonstrates that, following administration of nivolumab 480 mg Q4W, nivolumab has been well tolerated.

Nivolumab 480 mg Q4W is predicted to have approximately 16% lower steady-state trough concentrations (Cmin,ss) compared to nivolumab 3 mg/kg Q2W. Though these exposures are predicted to be lower, they are on the flat part of the exposure-response curves and are not predicted to affect efficacy exposure-efficacy analyses of multiple PK measures and efficacy endpoints (eg, OS, OR) indicated that, following administration of nivolumab 480 mg Q4W, efficacy is predicted to be similar to that following administration of nivolumab 3 mg/kg Q2W across multiple tumor types. Based on these data, nivolumab 480 mg Q4W is expected to have similar efficacy and safety profiles to nivolumab 240 mg Q2W or nivolumab 3 mg/kg Q2W.

5.5.3 Dose Rationale for Adolescents

The PK of drugs and many therapeutics proteins has been shown to be similar between adolescent and adults once the effect of body size on PK is taken into consideration.[29,30] Therefore, in general, adult doses would expected to achieve similar systemic exposures in adolescents. In study CA224020, relatlimab in combination with nivolumab was administered as a 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. Adolescent participants < 40-kg body weight will be given a weight-based dose that is equivalent to the adult dose (typical subject of 80-kg body weight).

Adolescents ≥ 40 kg will be administered relatlimab 160 mg in combination with 480 mg nivolumab Q4W. Adolescents < 40 kg will be administered body weight adjusted relatlimab dose 2 mg/kg and nivolumab 6 mg/kg Q4W of relatlimab/nivolumab combination or 6 mg/kg Q4W IV infusion over approximately1 hour.

6 STUDY POPULATION

6.1 Inclusion Criteria

For entry into the study, the following criteria MUST be met.

1) Signed Written Informed Consent

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

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

2) Type of Participant and Target Disease Characteristics

a) Participants must have an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 1/Lansky Performance Score ≥ 80% for minors (ages 12-17) ONLY (for details, see Appendix 6).

b) Participants must have histologically confirmed Stage III (unresectable) or Stage IV melanoma, per the AJCC staging system (for details, see Appendix 7).

c) Participants must not have had prior systemic anticancer therapy for unresectable or metastatic melanoma.

i) Note that the following prior adjuvant or neoadjuvant melanoma therapies are allowed if all related adverse events have either returned to baseline or stabilized.

(1) Anti-PD-1 or anti-CTLA-4 therapy with at least 6 months between the last dose and date of recurrence.

(2) Interferon therapy with the last dose at least 6 weeks prior to randomization.

(3) BRAF- or MEK-inhibitor-containing regimens with at least 6 months between the last dose and date of recurrence.

d) Participants must have measurable disease by CT or MRI per RECIST v1.1 criteria (for details, see Appendix 5).

e) Tumor tissue from an unresectable or metastatic site of disease must be provided for biomarker analyses. Either a recent archival sample obtained within 3 months prior to enrollment (with no intervening treatment between time of acquisition and enrollment) or a fresh pre-treatment biopsy is to be submitted as a FFPE tissue block or unstained tumor tissue sections, to the analytical laboratory for inclusion. In order to be randomized, a participant must be classified as PD-L1 positive or PD-L1 negative, as well as LAG-3 positive or LAG-3 negative. Participants with indeterminate or unevaluable PD-L1 or LAG-3 status results will not be permitted to randomize to a treatment arm. If an insufficient amount of tumor tissue from an unresectable or metastatic site is available prior to the start of the screening phase, participants must consent to allow the acquisition of additional tumor tissue during the screening period for performance of biomarker analyses. The biopsy should be a core biopsy, a punch biopsy, an excisional biopsy, or a surgical specimen. Fine needle aspiration is unacceptable for submission. The analytical laboratory must provide IRT with the related results prior to randomization.

f) Participants must have known BRAF V600 mutation status or consent to BRAF V600 mutation testing per local institutional standards during the screening period.

g) Prior radiotherapy must have completed at least 2 weeks prior to study treatment administration.

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

3) Age and Reproductive Status

a) Male and female participants must be ≥ 12 years at the time of informed consent if local regulations and/or institutional policies allow for participants < 18 years of age (pediatric population). If pediatric population is not allowed to participate, then ≥ 18 years applies.

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

c) Women must not be pregnant or breastfeeding.

d) WOCBP must agree to follow instructions for method(s) of contraception (see Appendix 4) for the duration of treatment with study treatment(s) plus 24 weeks after the last dose of study treatment (ie, 30 days [duration of ovulatory cycle] plus the time required for nivolumab and relatlimab to undergo approximately 5 half-lives).

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception (see Appendix 4) for the duration of treatment with study treatment(s) plus 33 weeks after the last dose of the study treatment (ie, 90 days [duration of sperm turnover] plus the time required for nivolumab and relatlimab to undergo approximately 5 half-lives). In addition, male participants must be willing to refrain from sperm donation during this time.

f) WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements, and still must undergo pregnancy testing as described in this section.

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

6.2 Exclusion Criteria

1) Medical Conditions

a) Participants must not have active brain metastases or leptomeningeal metastases. Participants with brain metastases are eligible if these have been treated and there is no MRI evidence of progression for at least 4 weeks after treatment is complete and within 28 days prior to first dose of study treatment administration. There must also be no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study treatment administration. Participants with brain disease treated with whole brain radiation are not eligible.

b) Participants must not have uveal melanoma.

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

i) with type 1 diabetes mellitus

ii) hypothyroidism only requiring hormone replacement

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

iv) conditions not expected to recur in the absence of an external trigger are permitted to enroll.

d) Participants must not have a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of start of study treatment. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

e) Participants must not have a history of myocarditis.

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

g) Participants must not have had a prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast.

2) Prior/Concomitant Therapy

a) Participants must not have had prior treatment with an anti-PD-1 (except if given as adjuvant or neoadjuvant therapy for melanoma), anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody (except if given as adjuvant or neoadjuvant therapy for melanoma), or any other antibody or drug specifically targeting T-cell costimulation or immune checkpoint pathways (except for interferon given as adjuvant or neoadjuvant therapy for melanoma).

b) Participants must not have a history of life-threatening toxicity related to prior immune therapy (eg, anti-CTLA-4 or anti-PD-1/PD-L1 treatment or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways) except those that are unlikely to re-occur with standard countermeasures (eg, hormone replacement after adrenal crisis).

c) Participants must not have had prior treatment with relatlimab or any other LAG-3 targeted agent.

d) Participants must not have treatment with botanical preparations (eg, herbal supplements or traditional Chinese medicines) intended for general health support or to treat the disease under study within 2 weeks prior to randomization/treatment. Refer to Section 7.7.1 for prohibited therapies.

e) Participants must not have received a live / attenuated vaccine within 30 days of first treatment (inactivated vaccines are permitted).

3) Physical and Laboratory Test Findings

The following lab criteria must be met:

a) WBC < 2000/μL

b) Neutrophils < 1500/μL

c) Platelets < $100*10^3$/μL

d) Hemoglobin < 9.0 g/dL

e) Serum creatinine > 1.5x ULN or calculated creatinine clearance < 40 mL/min (using the Cockcroft-Gault formula):

$$\text{Female CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/dL}}$$

$$\text{Male CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/dL}}$$

f) AST/ALT > 3.0x ULN

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

h) Troponin T (TnT) or I (TnI) > 2 × institutional ULN. Between > 1 to 2 × ULN will be permitted if a repeat assessment remains ≤ 2 × ULN and patient undergoes a cardiac evaluation.

i) Participants must not have any positive test result for hepatitis B virus or hepatitis C virus indicating presence of virus, eg, Hepatitis B surface antigen (HBsAg, Australia antigen) positive, or Hepatitis C antibody (anti-HCV) positive (except if HCV-RNA negative).

j) Participants must not have a known history of a positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). NOTE: Testing for HIV must be performed at sites where mandated locally.

k) Participants must not have a positive pregnancy test at enrollment or prior to administration of study medication

4) Allergies and Adverse Drug Reaction

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

5) Other Exclusion Criteria

a) Participants must not be prisoners or involuntarily incarcerated. (Note: Under certain specific circumstances, a person who has been imprisoned may be included or permitted to continue as a participant. Strict conditions apply and BMS approval is required.)

b) Participants must not be compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness.

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

6.3 Lifestyle Restrictions

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 are not subsequently randomized. 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, 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 pre-treatment failure (ie, participant has not been randomized). If re-enrolled, the participant must re-consent.

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

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

Laboratory parameters and/or assessments that are included in Table 2-1, Screening Procedural Outline (CA224047), may be repeated in an effort to find all possible well-qualified participants. Consultation with the BMS Medical Monitor/designee may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

7 TREATMENT

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

Study treatment includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational [Medicinal] Product (Non-IP/Non-IMP) and can consist of the following:

- BMS-986213
- Nivolumab

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

Other medications used as support or escape medication for preventive, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as non-investigational products.

Investigational products used in this trial are provided in Table 7-1. There are no non-investigational products in this study.

Table 7-1: Study Treatments for CA224047

Product Description / Class and Dosage Form	Potency	Primary Packaging (Volume)/Label Type	Secondary Packaging (Qty)/Label Type	Appearance	Storage Conditions (per label)
BMS-986213 (Relatlimab 80 mg/ Nivolumab 240 mg) vial	16 mg/mL	20 mL vial/open label	2 vials/carton	Colorless to pale yellow liquid, clear to slightly opalescent, light (few) particulates (consistent in appearance to protein particulates) may be present	Refer to the label on container and/or pharmacy manual
Nivolumab 100 mg/vial	10 mg/mL	10 mL vial/open label	4 vials/carton/open label	Clear to opalescent, colorless to pale yellow liquid, light (few) particulates may be present	Refer to the label on container and/or pharmacy manual

7.1 Treatments Administered

The selection and timing of dose for each participant is presented in Table 7.1-1.

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

Table 7.1-1: Selection and Timing of Dose

Study Treatment	Patient Age/Weight	Unit dose strength(s)/Dosage level(s)	Dosage formulation/ Frequency of Administration	Route of Administration
BMS-986213	Adults and adolescents ≥ 40 kg	Relatlimab 160 mg/ Nivolumab 480 mg Total: 640 mg	Solution for injection/ every 4 weeks	IV
	Adolescents < 40 kg	Relatlimab 2 mg/kg/ Nivolumab 6 mg/kg Total: 8 mg/kg	Solution for injection/ every 4 weeks	
Nivolumab	Adults and adolescents ≥ 40 kg	480 mg	Solution for injection/ every 4 weeks	IV
	Adolescents < 40 kg	6 mg/kg	Solution for injection/ every 4 weeks	

For mg/kg dosing, the dosing calculations should be based on the body weight assessed at screening. It is not necessary to re-calculate subsequent doses if the subject weight is within 10% of the weight used to calculate the previous dose. All doses should be rounded to the nearest milligram. For an adolescent < 40 kg becoming an adult, the dose calculation should continue to be based on the body weight and not switched to flat dosing.

7.1.1 BMS-986213 or Nivolumab Dosing

BMS-986213 (prepared in normal saline for relatlimab 160 mg/nivolumab 480 mg) or nivolumab 480 mg dosing is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore-size, low-protein binding in-line filter at the protocol-specified doses. It is not to be administered as an IV push or bolus injection. Instructions for dilution and infusion of relatlimab/nivolumab or nivolumab injection will be provided in the pharmacy binder. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

Participants should receive BMS-986213 or nivolumab as a 1-hour infusion on Day 1 of each treatment cycle until progression, unacceptable toxicity, withdrawal of consent, or the study ends,

whichever occurs first. Participants should begin study treatment within 3 calendar days of randomization.

The sponsor, participants, investigator, and site staff will be blinded to the study drug administered. Each investigative site must assign an unblinded pharmacist/designee.

There will be no dose escalations or reductions of any study treatment allowed. Participants may be dosed within a ± 3 day window (ie, participants may be dosed no less than 25 days and no more than 31 days between doses). Premedication is not recommended for the first dose of either treatment.

Participants should be carefully monitored for infusion reactions during administration. If an acute infusion reaction is noted, participants should be managed according to Section 7.7.3.

Doses may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment. Dosing visits must not be skipped, only delayed.

Infusions are compatible with polyvinyl chloride (PVC) or polyolefin containers and infusion sets, and glass bottles.

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 binder.

The selection and timing of dose for each participant is provided in Table 7.1-1.

7.2 Method of Treatment Assignment

All participants will be centrally randomized using 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 informed consent form must be assigned a participant number in IRT. The investigator or designee will register the participant for enrollment by following the enrollment procedures established by BMS. The following information is required for enrollment:

- 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
- PD-L1 status (positive or negative) provided by the central lab directly to the IRT system

- LAG-3 IHC status (positive or negative) provided by the central lab directly to the IRT system
- BRAF V600 mutational status (positive or wild type)
- AJCC M stage at screening (M0/M1any[0] vs M1any[1]),

Participants will be randomized in a 1:1 ratio as described in Section 5.1 and stratified by PDL-1 status, LAG-3 status, BRAF status, and AJCC M stage as described below:

- LAG-3 status
- LAG-3 positive (≥ 1% expression) or
- LAG-3 negative (< 1% expression)
- PD-L1 Status
- PD-L1 positive (≥ 1% expression) or
- PD-L1 negative (< 1% expression)
- BRAF status
- BRAF V600 mutation positive or
- BRAF V600 wild type
- AJCC M stage at screening (see Appendix 7)
- M0/M1any(0)
- M1any(1)

The randomization procedures will be carried out via permuted blocks within each stratum, defined by combination of LAG-3 status (positive or negative), PD-L1 status (positive or negative), BRAF V600 mutational status (positive or wild type), and M Stage (M0/M1any[0] or M1any[1]). The exact procedures for using the IRT will be detailed in the IRT manual.

7.3 Blinding

The sponsor, participants, investigator, and site staff will be blinded to the study therapy administered.

Each investigative site must assign an unblinded pharmacist/designee.

Blinding of 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 investigational product 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 investigational product, the problem may be properly managed by assuming that the participant is receiving active product. It is highly desirable that the decision to unblind treatment assignment

be discussed with the BMS 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 discontinue the participant has been made.

For this study, the method of unblinding for emergency purposes is available in the IRT manual.

Any request to unblind a participant's treatment assignment for non-emergency purposes should be discussed with the BMS Medical Monitor/designee.

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

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. The procedures to be respected and the reasons for unblinding of the DMC are discussed in the DMC charter.

If the interim PFS analysis meets the pre-specified threshold and the study proceeds to Phase 3, the final PFS analysis will be performed when approximately 365 PFS events have occurred per BICR. The sponsor will be unblinded to individual treatment assignments at the time of the final PFS analysis. If the final PFS analysis is statistically significant, participants, investigator, and site staff will remain blinded to individual treatment assignments until an interim OS result is statistically significant or until final analysis of the OS endpoint, whichever comes first.

At the time of the final PFS analysis, if the results are statistically significant, there will be an interim analysis of OS (OS IA1). If the OS IA1 is not statistically significant, the second interim analysis of OS (OS IA2) will be performed when a minimum of 90% (270/300) of the expected deaths have occurred. If OS IA2 is not statistically significant, the final OS analysis will be performed when approximately 300 deaths have occurred.

Designated staff of BMS Research & Development may be unblinded prior to final PFS results to facilitate the bioanalytical analysis of pharmacokinetic, immunogenicity, and pharmacodynamic samples.

A bioanalytical scientist in the Bioanalytical Sciences department of BMS Research & Development (or a designee in the external central bioanalytical laboratory) will be unblinded to the randomized treatment assignments in order to minimize unnecessary bioanalytical analysis of samples.

To further minimize potential bias, the participants and the investigative clinical site staff are blinded to results from PD-L1 and LAG-3 analysis.

7.4 Dosage Modification

AE criteria for delaying, resuming, and discontinuing of study treatment is provided in Table 7.4-1.

Table 7.4-1: 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	In most cases of AST or ALT > 5× ULN, study treatment will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion between the investigator and the Medical Monitor/ designee must occur and approval from Medical Monitor prior to resuming therapy.

Table 7.4-1: 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
	Concurrent AST or ALT > 3× ULN and T.bili > 2× ULN, regardless of baseline value	Permanently discontinue	
Endocrinopathy			
Adrenal Insufficiency	Grade 2 adrenal insufficiency	Delay dose	Dosing may resume after adequately controlled with hormone replacement.
	Grade 3 or 4 adrenal insufficiency or adrenal crisis	Delay dose or permanently discontinue	Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If adrenal insufficiency resolves or is adequately controlled with physiologic hormone replacement, participant may not require discontinuation of study drug.
Hyperglycemia	Hyperglycemia requiring initiation or change in daily management (Grade 2 or 3)	Delay dose	Dosing may resume if hyperglycemia resolves to Grade ≤1 or baseline value, or is adequately controlled with glucose-controlling agents.
	Grade 4	Delay dose or permanently discontinue	Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If hyperglycemia resolves, or is adequately controlled with glucose-controlling agents, participant may not require discontinuation of study drug.
Hypophysitis/Hypopituitarism	Symptomatic Grade 1-3 that is also associated with corresponding abnormal lab and/or pituitary scan	Delay dose	Dosing may resume if endocrinopathy resolves to be asymptomatic, or is adequately controlled with only physiologic hormone replacement.
	Grade 4	Delay dose or permanently discontinue	Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If endocrinopathy resolves or is adequately controlled with physiologic hormone replacement, participant may not require discontinuation of study drug.

Table 7.4-1: 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
Hyperthyroidism or Hypothyroidism	Grade 2 or 3	Delay dose	Dosing may resume if endocrinopathy resolves to be asymptomatic, or is adequately controlled with only physiologic hormone replacement or other medical management.
	Grade 4	Delay dose or permanently discontinue	Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If endocrinopathy resolves or is adequately controlled with physiologic hormone replacement or other medical management, participant may not require discontinuation of study drug.
Skin			
Rash	Grade 2 rash covering > 30% body surface area or Grade 3 rash	Delay dose	Dosing may resume when rash reduces to ≤10% body surface area.
	Suspected Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or drug reaction with eosinophilia and systemic symptoms (DRESS)	Delay dose	Dosing may resume if SJS, TEN, or DRESS is ruled out and rash reduces to is ≤10% body surface area.
	Grade 4 rash or confirmed SJS,TEN, or DRESS	Permanently discontinue	
Neurological			
Guillain-Barre Syndrome (GBS)	Any Grade	Permanently discontinue	
Myasthenia Gravis (MG)	Any Grade	Permanently discontinue	
Encephalitis	Any Grade encephalitis	Delay dose	After workup for differential diagnosis, (ie, infection, tumor-related), if encephalitis is not drug related, then dosing may resume when AE resolves.

Table 7.4-1: 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
	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	
Cardiovascular			
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	
Cardiac Troponin I or Troponin T Increased	Asymptomatic	Delay dose	All troponin elevations (including asymptomatic elevations) will require a dose delay in order for the participant to undergo a cardiac evaluation (via prompt cardiology consult) and a confirmatory repeat within 24 hours. If troponin elevation is not confirmed within 24 hours in an asymptomatic participant, the dose delay may not be needed provided that the cardiac evaluation is completed and a cardiologist has made the recommendation to proceed with treatment. Otherwise, if troponin elevation is confirmed, dosing may resume when AE resolves to baseline.

Table 7.4-1: 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 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	
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.

Table 7.4-1: 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
	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	Refer to Section 7.7.3 on Treatment of Related Infusion Reactions.

7.4.1 Dose Modifications

No dose modifications for either treatment are permitted.

7.4.2 Dose Delay Criteria

Dose delay criteria apply for all drug-related AEs. Delay treatment administration if any of the delay criteria in Table 7.4-1 are met. Delay dosing for any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Study treatment must also be delayed for SARS-CoV-2 infection, either confirmed or suspected.

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

7.4.3 Criteria to Resume Treatment

Participants may resume treatment with study drug if they have completed AE management (ie, corticosteroid taper) or are on ≤ 10 mg prednisone or equivalent, and meet the requirements per Table 7.4-1.

Prior to re-initiating treatment in a participant with a dosing delay lasting > 8 weeks, the Medical Monitor (or Clinical Scientist) must be consulted. Continue tumor assessments per protocol even if dosing is delayed. Continue periodic study visits to assess safety and laboratory studies weekly or more frequently if clinically indicated during such dosing delays.

In the event of treatment delay due to SARS-CoV-2 infection (confirmed or suspected), participants with may resume treatment after all of the following: 1) at least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared or positive test result (eg, RT-PCR or viral antigen); 2) resolution of acute symptoms (including at least 24 hours has passed since last fever without fever-reducing medications); 3) evaluation by the investigator with confirmation that there are no sequelae that would place the participant at a higher risk of receiving investigational treatment; and 4) consultation by the Medical Monitor. For suspected cases, treatment may also resume if SARS-CoV-2 infection is ruled out and other criteria to resume treatment are met.

7.4.4 Management Algorithms for Immuno-Oncology Agents

Immuno-oncology (IO) agents are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Relatlimab and nivolumab are considered as immuno-oncology agents in this protocol. Early recognition and management of AEs associated with IO agents may mitigate severe toxicity. Management algorithms have been developed to assist investigators in assessing and managing the following groups of AEs:

- Gastrointestinal
- Renal
- Pulmonary (note for participants with dyspnea, CBC should be measured)
- Hepatic
- Endocrinopathy
- Skin
- Neurological
- Myocarditis

The above algorithms are found in the Appendix 9 of this protocol.

7.5 Preparation/Handling/Storage/Accountability

For nivolumab, refer to the current version of the IB and/or Pharmacy Manual for complete storage, handling, dispensing, and infusion information.

Similarly, for BMS-986213, refer to the current version of the IB and/or Pharmacy Manual for complete storage, handling, and dispensing information.

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

The product storage manager should ensure that the study treatments are 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 treatments arise, do not dispense the study treatment and contact BMS immediately.

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

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

Further guidance and information for final disposition of unused study treatments are provided in Appendix 2.

The unblinded pharmacist will obtain treatment assignment by IRT and prepare blinded drug.

7.5.1 Retained Samples for Bioavailability/Bioequivalence

Not applicable.

7.6 Treatment Compliance

Treatment compliance for all study treatments will be monitored by drug accountability, medical record, and electronic Case Report Form (eCRF). Drug accountability should be reviewed by the study-site staff at each visit to confirm treatment compliance.

7.7 Concomitant Therapy

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

7.7.1 Prohibited and/or Restricted Treatments

Prohibited and/or restricted medications taken prior to and during study treatment administration in the study are described below. Medications taken within 2 weeks prior to study treatment administration must be recorded on the CRF.

7.7.1.1 Prohibited Treatments

The following medications are prohibited during the study:

- LAG-3 targeting agents.

- Any botanical preparation (eg, herbal supplements or traditional Chinese medicines) intended to treat the disease under study or provide supportive care. Use of marijuana and its derivatives for treatment of symptoms related to cancer or cancer treatment are permitted if obtained by medical prescription or if its use (even without a medical prescription) has been legalized locally.
- Immunosuppressive agents (except used to treat a drug-related AE).
- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 7.7.2).
- Any concurrent anti-neoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents for treatment of malignancy)
- Any live / attenuated vaccine (eg, varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella [MMR]) during treatment and until 100 days after last dose. Inactivated vaccines are permitted.

7.7.1.2 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 for each participant. Imaging contraindications and contrast risks should be considered in this assessment. Participants with renal insufficiency should be assessed as to whether or not they should receive contrast and if so, what type and dose of contrast is appropriate. Specific to MRI, participants with severe renal insufficiency (ie, estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2) are at increased risk of nephrogenic systemic fibrosis. MRI contrast should not be given to this participant population. In addition, participants are excluded from MRI if they have tattoos, metallic implants, pacemakers, etc.

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

7.7.2 Permitted Therapy

Participants are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Adrenal replacement steroid doses > 10 mg daily prednisone equivalent are permitted. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.

7.7.2.1 Palliative Therapy

Palliative (limited-field) radiation therapy and palliative surgical resection are permitted if the following criteria are met:

- The participant is considered to have progressed at the time of palliative therapy and meets criteria to continue with treatment beyond progression (Section 8.1.2.2).
- The case is discussed with the BMS Medical Monitor/designee. Palliative therapy must be clearly documented as such in the study record.

Participants should not receive study treatment during radiation as the potential for overlapping toxicities with radiotherapy and BMS-986213 or with radiotherapy and nivolumab is currently not known. Anecdotal data suggest that radiotherapy administered to participants while receiving nivolumab therapy is tolerable. However, because concurrent radiotherapy and immunotherapies in cancer have not been formally evaluated, in cases where palliative radiotherapy is required for a tumor lesion, then all study treatments should be withheld for at least 1 week before, during, and 1 week after radiation. Participants should be closely monitored for any potential toxicity during and after receiving radiotherapy, and AEs related to radiotherapy should resolve to Grade 1 prior to resuming study treatment.

7.7.2.2 Surgical Resection Following Initial Response

Investigators may choose to resect solitary lesions in participants with unresectable or metastatic melanoma and render the participant free of macroscopic disease. Participants enrolled in this study may have lesions surgically resected only following consultation with the BMS Medical Monitor/designee and following the Week 20 efficacy assessments. If tumor shrinkage of the solitary lesion is noted on the re-staging assessment (eg, Week 20), it is highly encouraged that surgical resection be delayed until subsequent scans fail to demonstrate further shrinkage. Participants with a PR who go on to have surgical resection of remaining disease will be considered a PR. Tumor tissue of any resected solitary lesion should be submitted to BMS (see Section 9.8.2). Detailed instructions on the obtaining, processing, labeling, handling, storage, and shipment of these specimens will be provided in a separate procedure manual at the time of study initiation.

7.7.3 Treatment of Infusion-Related Reactions

Because both relatlimab and nivolumab contain only human immunoglobulin protein sequences, they are unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the BMS Medical Monitor/designee and reported as an SAE if it meets the criteria. Infusion reactions should be graded according to NCI CTCAE (Version 5.0) guidelines.

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

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

- Remain at bedside and monitor participant until recovery from symptoms. The following prophylactic 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 nivolumab administrations

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

- Stop the study treatment infusion, begin an IV infusion of normal saline, and treat the participant with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor participant until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. 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 treatment 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 infusion. If necessary, corticosteroids (up to 25 mg of hydrocortisone or equivalent) may be used.

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

- Immediately discontinue infusion of study treatment. Begin an IV infusion of 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 IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Participant should be monitored until the investigator is comfortable that the symptoms will not recur. Study treatment will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor participant until recovery of the symptoms.

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

7.8 Treatment After the End of the Study

At the conclusion of the study, participants who continue to demonstrate clinical benefit will be eligible to receive BMS-supplied study treatment for the maximum treatment duration specified in Section 5.3. Study treatment will be provided via an extension of the study, a rollover study requiring approval by responsible health authority and ethics committee, or through another mechanism at the discretion of BMS. BMS reserves the right to terminate access to BMS supplied study treatment if any of the following occur: a) the study is terminated due to safety concerns; b)

the development of relatlimab is terminated for other reasons, including but not limited to lack of efficacy and/or not meeting the study objectives; c) the participant can obtain medication from a government-sponsored or private health program. In all cases BMS will follow local regulations.

8 DISCONTINUATION CRITERIA

8.1 Discontinuation from Study Treatment

Participants MUST discontinue investigational product (and non-investigational product at the discretion of the investigator) for any of the following reasons:

- Participant's request to stop study treatment. Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information.
- Any clinical AE, laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant
- Termination of the study by BMS
- 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, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply and BMS approval is required.)
- Additional protocol-specified reasons for discontinuation (Section 8.1.1)

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

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

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

8.1.1 Dose Discontinuation

If a participant in any of the nivolumab/relatlimab combination arms meets criteria for discontinuation in Table 7.4-1, the participant must discontinue both nivolumab and relatlimab and be taken off the treatment phase of the study.

Nivolumab and relatlimab treatment must be permanently discontinued per criteria in Table 7.4-1 in Section 7.4 (Dosage Modification). Discontinue from study treatment for any AE, laboratory abnormality, or intercurrent illness that, in the judgment of the investigator, presents a substantial clinical risk to the participant with continued nivolumab or relatlimab dosing.

Study treatment must also be permanently discontinued for the following:

- Any event that leads to delay in dosing lasting > 8 weeks from the previous dose requires discontinuation, with the following exceptions:
- Dosing delays to allow for prolonged steroid tapers to manage drug-related AEs are allowed.
- Dosing delays lasting > 8 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS Medical Monitor (or Clinical Scientist).
- Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.

8.1.2 Treatment Beyond Progression

8.1.2.1 Rationale

Accumulating clinical evidence indicates some participants treated with immune system stimulating agents may develop progression of disease (by conventional response criteria) before demonstrating clinical objective responses and/or stable disease.[31] This phenomenon was observed in approximately 10% of participants in the Phase 1 study of nivolumab and also with ipilimumab monotherapy. Two hypotheses have been put forth to explain this phenomenon. First, enhanced inflammation within tumors could lead to an increase in tumor size which would appear as enlarged index lesions and as newly visible small non-index lesions. Over time, both the malignant and inflammatory portions of the mass may then decrease leading to overt signs of clinical improvement. Alternatively, in some individuals, the kinetics of tumor growth may initially outpace anti-tumor immune activity. With sufficient time, the anti-tumor activity will dominate and become clinically apparent. Therefore, participants will be allowed to continue study therapy after initial investigator-assessed RECIST v1.1 defined progression (See Appendix 5) if they are assessed to be deriving clinical benefit and tolerating study treatment (Section 8.1.2.2). Such participants must discontinue study therapy upon evidence of further progression.

8.1.2.2 Criteria Required for Treatment Beyond Progression

Participants will be permitted to continue study treatment beyond initial RECIST v1.1 defined PD (see Appendix 5), assessed by the investigator, as long as they meet the following criteria:

- Investigator-assessed clinical benefit

- Tolerance of study treatment
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases)
- Participant provides written informed consent prior to receiving additional study treatment. All other elements of the main consent including description of reasonably foreseeable risks or discomforts, or other alternative treatment options will still apply.

A follow-up scan should be performed at the next scheduled imaging evaluation 8 weeks later (but no sooner than 4 weeks) of initial investigator-assessed progression to determine whether there has been a decrease in the tumor size or continued PD. The assessment of clinical benefit should be balanced by clinical judgment as to whether the participant is clinically deteriorating and unlikely to receive any benefit from continued study treatment.

If the investigator feels that the participant continues to achieve clinical benefit by continuing treatment, the participant should remain on the trial and continue to receive monitoring according to the Schedule of Activities (Section 2).

For the participants who continue study therapy beyond progression, further progression is defined as an additional 10% increase in tumor burden with a minimum 5 mm absolute increase from time of initial PD. This includes an increase in the sum of diameters of all target lesions and/ or the diameters of new measurable lesions compared to the time of initial PD. All study treatment should be discontinued permanently upon documentation of further progression.

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

8.1.3 Post-Study Treatment Study Follow-Up

In this study, overall survival is a key endpoint. 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 treatment must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with Section 2 until death or the conclusion of the study.

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

8.2 Discontinuation from the Study

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

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

8.3 Lost to Follow-Up

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

9 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the Schedule of Activities.
- Protocol waivers or exemptions are not allowed.

- All immediate safety concerns must be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.
- Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Schedule of Activities.

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

If a participant shows pulmonary-related signs (hypoxia, fever) or symptoms (eg. dyspnea, cough, and fever) consistent with possible pulmonary adverse events, the participant should be immediately evaluated to rule out pulmonary toxicity, according to the suspected pulmonary toxicity management algorithm in the nivolumab IB.

For those subjects receiving on-going treatment, troponin elevations will require the subject to undergo a cardiac evaluation. Following this evaluation, determination of further treatment will be based on the discussion with the BMS Medical Monitor/designee.

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.

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

Screening Phase:

- Begins by establishing the participant's initial eligibility and signing the informed consent form (ICF).

Treatment Phase:

- Begins with the randomization call to the IRT. The participant is randomly assigned to either the BMS-986213 arm or the nivolumab monotherapy arm.
- Ends when the participant is discontinued from study therapy. For a complete list of reasons for treatment discontinuation, see Section 8.1.

Follow-Up Phase

- Begins when the decision to discontinue a participant from study therapy is made (no further treatment with study therapy) and ends when survival data have been collected for all participants (Section 8.1.3).

9.1 Efficacy Assessments

Study evaluations will take place in accordance with the Schedule of Activities in Section 2. Baseline assessments should be performed within 28 days prior to randomization by contrast enhanced CT chest, CT (or MRI with and without contrast) abdomen, pelvis, and all known or suspected sites of disease. MRI of brain (without and with contrast) should be acquired as outlined in Schedule of Activities (Section 2). CT of the Brain (without and with contrast) can be performed if MRI is contraindicated.

Subsequent assessments should include chest, abdomen, and pelvis, and all known or suspected sites of disease and should use the same imaging method as was used at baseline beginning at 12 weeks (± 1 week) after randomization and continuing every 8 weeks (± 1 week) up to Week 52 and then every 12 weeks (± 1 week). Assessments should continue until disease progression is confirmed by a BICR or treatment is discontinued, whichever occurs later. Participants with a history of brain metastasis or symptoms should have a surveillance MRI (without and with contrast) study per standard of care (approximately every 12 weeks), or sooner if clinically indicated. CT of the brain without and with contrast can be performed if MRI is contraindicated. See Table 9.1.2-1 for instructions on performance of scans in participants with contrast allergies.

Tumor imaging assessments for ongoing study treatment decisions will be completed by the investigator using RECIST v1.1 criteria, see Appendix 5.

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

9.1.1 Imaging Assessment for the Study

Images should be submitted on a rolling basis to the imaging core lab. Sites should be trained prior to scanning the first study participant. Image acquisition guidelines and submission process will be outlined in the Imaging Manual to be provided by the core lab.

9.1.2 Methods of Measurement

Acceptable imaging methods per anatomical area are detailed in Table 9.1.2-1.

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

- Should a participant have a contraindication for CT IV contrast, a non-contrast CT of the chest and a contrast-enhanced MRI of the abdomen and pelvis and other known/suspected sites of disease may be obtained.
- Should a participant have contraindication for both MR and CT IV contrasts, a non-contrast CT of the chest and a non-contrast MRI of the abdomen, pelvis, and other known/suspected sites of disease should be obtained.

PET alone will not be considered for the disease assessment. Complementary CT and/or MRI must be performed in such cases. Note: Use of CT component of a PET/CT scanner: Combined modality scanning, such as with FDG-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 FDG-PET/CT are of limited use in anatomically-based efficacy assessments, and it is, therefore, suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for anatomically-based RECIST v1.1 (see Appendix 5) measurements. However, if a site can document that the CT performed as part of a FDG PET/CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the FDG-PET/CT can be used for RECIST v1.1 measurements. Note, however, that the FDG-PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Table 9.1.2-1: Acceptable Imaging Assessment Methods for Different Anatomical Areas

Anatomic Region	Preferred Method	Alternative Methods
Chest, abdomen, and pelvis Note: Scan must cover lung apices to diaphragm, diaphragm through entire liver, and to below the pubic symphysis	CT with IV contrast	**For chest:** • CT without contrast can be used only if the participant has a clinical contraindication for iodine-based IV contrast (eg, hypersensitivity, renal insufficiency) **For abdomen and pelvis:** • MRI with gadolinium-based IV contrast is the first alternative method if the participant has a clinical contraindication for iodine-based IV contrast • CT without contrast can be used as the second alternative method only if the participant has a clinical contraindication for both contrast-enhanced CT and MRI.
Brain	MRI with IV contrast	• CT with IV contrast is the first alternative method if IV gadolinium is clinically contraindicated. • MRI without contrast can be used as a second alternative method if a participant has clinical contraindications for both contrast-enhanced CT and MRI

Notes:

- CT/MRI scans must be performed with slices thickness of ≤ 5 mm. The reconstruction interval should be equal to slice thickness to avoid gap.
- The same modality for a given anatomical coverage and the same scanning procedure (most importantly: reconstruction slice thickness, anatomic coverage, use of IV contrast) should be consistent between baseline and all subsequent follow-up scanning. If possible, the same scanner or an equivalent scanners should be used throughout the study.
- For abdomen and pelvis CT scans, oral contrast is recommended per institutional standards.
- MRI should include T1 and T2-weighted sequences with T1-weighted at both pre- and post-contrast.
- All scans generated should be exportable in electronic format (DICOM) to enable secure and rapid electronic transmission to the designated central imaging laboratory.

9.1.2.1 BICR Confirmation of Progression

Sites should submit all scans to the imaging core lab on a rolling basis, preferably within 7 days of scan acquisition throughout the duration of the study. BICR will review scans on a rolling basis and must be blinded to treatment arm and investigator assessment of submitted scans. When progression per RECIST v1.1 criteria is assessed by the investigator, the site will inform the imaging core lab, so that the BICR assessment of progression can be performed. The BICR review will be completed and the results provided to the site within approximately 5 days of receipt of the scans, provided there are no pending imaging queries to the site.

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

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

9.1.3 Patient-Reported Outcomes

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

Participants will be asked to complete the Functional Assessment of Cancer Therapy-Melanoma (FACT-M), 3-level version of the EuroQol Group's EQ-5D (EQ-5D-3L), and Work Productivity and Activity Impairment: General Health (WPAI:GH) questionnaires after randomization but prior to first dose, at on-study clinic visits while on treatment, and at Follow-Up Visits 1 and 2. Whereas

all participants will complete the EQ-5D-3L, only those ≥ 18 years of age at baseline will be asked to complete the FACT-M and WPAI:GH. All questionnaires will be provided in the participant's preferred language when available.

In addition, the EQ-5D-3L and the 16-items comprising the Melanoma Subscale (MS) of the FACT-M will be administered by telephone at designated time points during the survival follow-up phase. There exist standardized guides that can be used to facilitate telephone administration of the EQ-5D-3L though a similar guide does not exist for the MS. Participants will be provided with a hard copy of the latter questionnaire to take home and use as a visual aid during telephone interviews.

If exceptional circumstances preclude the continued administration of measures using planned modalities, then alternate administration methods may be required. Table 2-2 and Table 2-3 provide information regarding the timing of patient-reported outcomes assessments.

9.1.3.1 EQ-5D-3L

The EQ-5D-3L is a standardized instrument used to measure self-reports of health status and functioning. The instrument's descriptive system consists of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels, reflecting "no health problems," "moderate health problems," and "extreme health problems." A dimension for which there are no problems is said to be at level 1, whereas a dimension for which there are extreme problems is said to be at level 3. Thus, the vectors 11111 and 33333 represent the best health state and the worst health state, respectively, as described by the EQ-5D-3L. Altogether, the instrument describes $3^5 = 243$ health states.

Empirically-derived weights can be applied to an individual's responses to the EQ-5D-3L descriptive system to generate an index measuring the value to society of his or her current health. Such preference-weighting systems have been developed for the UK, US, Spain, Germany, and numerous other populations. Utility index values range from a 1 (full health) to 0 (dead) with negative values indicating a state considered worse than being dead. In addition, the EQ-5D-3L includes a VAS that allows respondents to rate their own current health on a 101-point scale ranging from "best imaginable" to "worst imaginable" health.

A change from baseline of 0.08 for the EQ-5D-3L utility score and of 7 for the EQ-5D-3L VAS are considered minimally important differences for the EQ-5D-3L.[32] The EQ-5D-3L uses a recall period of "today."

9.1.3.2 FACT-M

The FACT-M questionnaire will be used to assess the effects of disease symptoms on functioning and well-being. As a generic cancer-related core, the FACT-M includes the 27-item FACT General (FACT-G) to assess physical well-being (PWB; seven items), social/family well-being (SWB; seven items), emotional well-being (EWB; six items), and functional well-being (FWB; seven items). In addition, the FACT-M includes a 16-item disease-specific Melanoma Subscale (MS). A single item from the FACT-M (ie, GP5) will be used to assess the extent of perceived bother due

to symptomatic AEs. Evidence exists for the validity of this item and its usefulness as an overall summary measure of burden due to symptomatic treatment toxicities.[33]

Each FACT-M item is rated on a 5-point scale ranging from 0 (not at all) to 4 (very much). Scores for the PWB, FWB, SWB, and EWB subscales can be combined to produce a FACT-G total score, which provides an overall indicant of generic quality of life, while the FACT-G and MS scores can be combined to produce a total score for the FACT-M, which provides a composite measure of general and targeted quality of life.

A variant of the total score that is often more sensitive to physical and functional outcomes, the Trial Outcome Index (TOI), can be derived by summing the PWB, FWB, and MS scores. All scores are scaled so that higher values indicate better functioning as well as lower symptom burden.

For any given scale, the minimally important difference (MID) represents the smallest difference in score that informed patients might perceive as important and that would warrant consideration of a change in management. With regard to the MS, the minimally important difference has been estimated as a change of 2-4 points.[34] For this trial, we will use the midpoint of the range (ie, a change $\geq$ 3 points) to define a minimally important change in MS score. This interpretation has been applied in previous investigations.[35]

The FACT-M uses a 7-day recall period.

9.1.3.3 WPAI:GH

The WPAI:GH is a 6-item measure of impairment in work productivity and usual activities. Responses to the questionnaire's items are used to derive a score measuring the amount of absenteeism (work time missed), presenteeism (impairment at work/reduced on-the-job effectiveness), work productivity loss (overall work impairment/absenteeism plus presenteeism), and daily activity impairment attributable to general health. Outcomes are expressed as impairment percentages with higher numbers indicating greater impairment or less productivity.

The WPAI:GH uses a 7-day recall period.

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, surrogate, or the participant's legally authorized representative).

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

IMAEs are AEs consistent with an immune-mediated mechanism or immune-mediated component for which non-inflammatory etiologies (eg, infection or tumor progression) have been ruled out. IMAEs can include events with an alternate etiology which were exacerbated by the induction of

autoimmunity. Information supporting the assessment will be collected on the participant's case report form.

Contacts for SAE reporting are specified in Appendix 3.

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

The collection of non-serious AE information (with the exception of non-serious AEs related to SARS-CoV-2 infection) should begin at initiation of study treatment until the time points specified in the Schedule of Activities (Section 2). Non-serious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the participants.

Following the participant's written consent to participate in the study, all SAEs, whether related or not related to study treatment, must be collected, including those thought to be associated with protocol-specified procedures.

All SAEs must be collected that occur during the screening period and within 100 days of the last dose of study treatment, 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 treatment by the investigator will be reported. For participants randomized/assigned to treatment and never treated with study treatment, SAEs should be collected for 30 days from the date of randomization. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

The investigator must report any SAE that occurs after these time periods and that is believed to be related to study treatment or protocol-specified procedure.

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

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

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

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 100 days following discontinuation of dosing.

9.2.2 Method of Detecting AEs and SAEs

Adverse events 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 AE and/or SAEs. Inquiry about specific AEs should be guided by clinical judgement in the context of known adverse events, when appropriate for the program or protocol.

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

9.2.3 Follow-up of AEs and SAEs

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 9.2), and AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection 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) or for suspected cases, until SARS-CoV-2 infection is ruled out.

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

9.2.4 Regulatory Reporting Requirements for SAEs

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

Sponsor or designee will be reporting adverse events to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/EC and FDA Code of Federal Regulations 21 CFR Parts 312 and 320. A suspected, unexpected serious adverse reaction (SUSAR) is a subset of SAEs and will be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

9.2.5 Pregnancy

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

If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, or re-initiation of study treatment, a discussion between the investigator and the BMS Medical Monitor/designee must occur. If, for whatever reason, the pregnancy has ended, confirmed by negative serum pregnancy test, treatment may be resumed (at least 3 weeks and not greater than 6 weeks after the pregnancy has ended), following approvals of participant /sponsor /IRB/EC, as applicable.

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

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

In cases where a study drug can be present in seminal fluid, at exposures sufficient to potentially cause fetal toxicity, and if any sexual activity (e.g. vaginal, anal, oral) has occurred between a male participant and a pregnant WOCBP partner(s), the information should be reported to the Sponsor or designee, even if the male participant has undergone a successful vasectomy. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner(s) must sign an informed consent form for disclosure of this information. Information on the pregnancy will be collected on the Pregnancy Surveillance Form.

9.2.6 Laboratory Test Result Abnormalities

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

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

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

9.2.7 Potential Drug Induced Liver Injury (DILI)

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

Potential drug induced liver injury is defined as:

1) ALT or AST elevation > 3x ULN

AND

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

AND

3) No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, preexisting 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 noted during interim or final physical examinations, electrocardiogram, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a non-serious or serious AE, as appropriate, and reported accordingly.

9.3 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important.

All occurrences of overdose must be reported as SAEs (see Appendix 3).

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

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

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

9.4 Safety

Planned time points for all safety assessments are listed in the Schedule of Activities. Safety assessments include AEs, physical examinations, vital signs, performance status, assessment of signs and symptoms, laboratory tests, and pregnancy tests as outlined 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

Laboratory assessments are listed in Table 9.4.4-1.

- Investigators must document their review of each laboratory safety report.
- All clinical safety laboratory assessments will be performed locally per the Schedule of Activities (Section 2)

Table 9.4.4-1: Laboratory Assessment Panels

Hematology	
Hemoglobin	
Hematocrit	
Total leukocyte count, including differential	
Platelet count	
Serum Chemistry	
Aspartate aminotransferase (AST)	Albumin
Alanine aminotransferase (ALT)	Sodium
Total bilirubin	Potassium
Alkaline phosphatase	Chloride
Gamma-glutamyl transferase only when alkaline phosphatase is ≥ Grade 2	Calcium
	Phosphorus
Creatinine	Magnesium
Blood urea nitrogen (BUN) or serum urea level	TSH, free T3 and free T4 - **screening only**
Glucose	TSH, with reflexive free T3 and free T4 if TSH is abnormal - **on treatment**
Lactate dehydrogenase (LDH)	
Uric acid	Creatinine clearance (CrCl) **- screening only**
	FSH (if needed to document postmenopausal status as defined in Appendix 4) - **screening only**
Troponin (local standard to be used/allowed), Cardiac Troponin T (cTnt), or I (cTnI): For those participants receiving ongoing treatment with relatlimab, troponin elevations will require the participant to undergo a cardiac	

Table 9.4.4-1: Laboratory Assessment Panels

evaluation. Following this evaluation, determination of further treatment will be based on the discretion of the Investigator.
Urinalysis
Protein
Glucose
Blood
Leukocyte esterase or leukocyte
Specific gravity
pH
Serology (at screening)
Serum for hepatitis C antibody (if Hepatitis C antibody is positive reflex to hepatitis C RNA) or hepatitis C RNA, hepatitis B surface antigen, HIV-1 and HIV-2 antibodies. (Testing for HIV-1 and HIV-2 must be performed at sites where mandated by local requirements, see Appendix 8)
Other Analyses
Pregnancy test (WOCBP only, Section 2).

9.4.5 Imaging Safety Assessment

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

9.5 Pharmacokinetic and Immunogenicity Assessments

Serum samples for relatlimab and nivolumab PK and ADA assessments will be collected for all subjects.

9.5.1 Pharmacokinetics: Collection and Processing

A detailed schedule of PK and ADA evaluations is provided in Table 9.5.1-1. All time points are relative to the start of study drug administration. Pre-dose samples should be taken within 30 minutes before the start of dose administration. If samples are drawn but study drug(s) is not administered on the same day, samples will be retained and analyzed as planned. There is no need to collect another sample when dosing is resumed. End-of-infusion samples should be taken just prior to the end of infusion (preferably within 2 minutes). Further details of sample collection, processing, and shipment will be provided in the laboratory procedures manual. On treatment PK samples are intended to be drawn relative to actual dosing days, if a dose occurs on a different day within the cycle due to delays or minor schedule adjustments, PK samples should be adjusted accordingly.

Table 9.5.1-1: PK and ADA Sampling Schedule for Relatlimab and Nivolumab

Study Day of Sample Collection (1 Cycle = 4 Weeks)	Event (Relative to Study Treatment Dosing)	Time (hour:min) (Relative to Start of Dose Administration)	Pharmacokinetics (2 Distinct Samples)	Anti-Drug Antibodies (2 Distinct Samples)
Cycle 1 Day 1	Predose[a]		X	X
Cycle 1 Day 1	End of infusion[b]	01:00[b]	X	
Cycle 2 Day 1	Predose[a]		X	X
Cycle 6 Day 1	Predose[a]		X	X
Cycle 6 Day 1	End of infusion[b]	01:00[b]	X	
Every 4th Dose After Cycle 6				
Day 1	Predose[a]		X	X
End of Treatment and Follow-Up Period				
Follow-Up Visit 1			X	X
Follow-Up Visit 2			X	X

[a] Take all predose samples for nivolumab prior to the start of nivolumab infusion.

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

9.5.2 Pharmacokinetic Sample Analyses

The serum samples will be analyzed for relatlimab and nivolumab by a validated immunoassay. Samples collected from a participant in the nivolumab monotherapy group may not be analyzed for relatlimab concentrations. In addition, selected serum samples may be analyzed by an exploratory orthogonal method (eg, liquid chromatography [LC]-mass spectrometry [MS]/MS) that measures total relatlimab and/or nivolumab, but the generated data will not be reported. Only results generated from the validated immunoassay method will be reported. Potential results generated from any orthogonal method are intended as informational for technology exploration purposes and will not be reported.

For adolescent participants, local standards for volumes of blood based on body weight that may be drawn within a specific time period should be followed. In order to obtain the samples required for safety, PK, and PD evaluations specified at a time point, blood volumes for safety laboratory

analysis should be minimized through the use of pediatric sample tubes, if possible. If, despite the use of these measures, the blood volumes required in the Schedule of Activities for a time point will exceed those recommended for the participant, the sponsor should be contacted for instructions on which blood tests can be omitted or modified to meet volume requirements. These omitted/modified tests will likely to pharmacodynamic and/or pharmacokinetic assessments, since all required safety assessments must be performed.

9.5.3 Immunogenicity

Serum samples for analysis of development of ADAs will be collected in conjunction with analysis of relatlimab and nivolumab serum concentrations and will be collected from all participants as indicated in Table 9.5.1-1. These serum samples will be analyzed for relatlimab and nivolumab ADAs by a validated immunoassay; samples may also be analyzed for neutralizing antibodies by validated methods. Samples collected from a participant in the nivolumab monotherapy group may not be analyzed for relatlimab ADAs. Selected serum samples may be analyzed by an exploratory orthogonal method that measures anti-relatlimab or anti-nivolumab antibodies. Potential results generated from any orthogonal method are intended as informational for technology exploration purposes and will not be reported. In addition, serum samples designated for PK or biomarker assessments may also be used for immunogenicity analysis if required (eg, insufficient volume for complete immunogenicity assessment or to follow up on suspected immunogenicity related AE). Further details of blood collection and processing will be provided to the site in the procedure manual.

9.6 Pharmacodynamics

PD analysis will be performed on serum, plasma, peripheral blood RNA, and/or peripheral blood mononuclear samples collected at time points specified in Table 9.8.2.6-1. The purpose of these exploratory analyses will be to identify PD markers changing with treatment, including changes that are associated with clinical benefit.

9.7 Pharmacogenomics

Pharmacogenomics assessments include, gene expression profiling, and mutational analyses as described in further detail in Section 9.8.

9.8 Biomarkers

Peripheral blood and tumor tissue will be collected prior to therapy. Peripheral blood samples will also be collected at selected time points on treatment. If a biopsy or surgical resection is performed at the time of progression or suspected progression, tumor sample (block or slides) should be submitted for analysis. If biomarker samples are drawn but study drug(s) is not administered, samples will be retained. A detailed description of each assay system is described below and a schedule of pharmacodynamic evaluations is provided in Table 9.8.2.6-1. All biomarker sampling at time points when study drug is not administered are optional.

9.8.1 Peripheral Blood Markers

A variety of factors that may impact the immunomodulatory properties and efficacy of relatlimab in combination with nivolumab will be investigated in peripheral blood specimens taken from all

subjects prior to or during treatment. Data from these investigations will be evaluated for associations with response, survival, and/or safety (AE) data. Several analyses will be completed and are described briefly below.

9.8.1.1 Soluble Biomarkers

Soluble factors, such as cytokines, chemokines, soluble receptors, and antibodies to tumor antigens will be characterized and quantified by immunoassays in serum. Analyses may include, but not necessarily be limited to, soluble LAG-3, CXCL-9 and IL2Ralpha. Collected serum samples may also be used for the assessment of tumor antigen-specific responses elicited following treatment with monotherapy and combination therapy to explore which antitumor antibodies are most associated with clinical response. Antibody levels to cancer test antigens may be assessed by multiplex assays and enzyme-linked immunosorbent assay (ELISA).

9.8.1.2 Immunophenotyping

The proportion of specific lymphocyte subsets and expression levels of T cell co-stimulatory markers in peripheral blood mononuclear cell (PBMC) preparations will be quantified by flow cytometry. Analyses may include, but not necessarily be limited to, the proportion of T, B, and NK cells, granulocytes, the proportion of memory and effector T cell subsets, and expression levels of PD-1, PD-L1, other B7 family members, ICOS, and Ki67.

9.8.1.3 T-Cell Repertoire Analysis

Low diversity of the peripheral T-cell compartment has been shown to correlate with poor overall survival in metastatic breast cancer. A standing theory in immuno-oncology suggests a diverse and activated immune environment is better adept at eradicating tumor compared to a skewed repertoire of naïve and tolerized T cells. In order to explore whether a diverse T-cell repertoire is predictive of response to therapy, DNA/RNA sequencing will be performed on DNA/RNA isolated from peripheral blood and tumor tissue (Section 9.8.2.3) to quantitate the composition of the T-cell repertoire prior to and during therapy.

9.8.1.4 Whole Blood for Germline DNA

Whole blood will be collected from all subjects prior to treatment to generate genomic DNA for genetic analyses and to serve as a reference for tumor genomic testing. These analyses will focus on, but are not limited to, genetic variations within genes associated with PD1 and other immunoregulatory signaling pathways to determine if natural variation within those genes is associated with response to nivolumab and/or with adverse events during treatment.

9.8.1.5 Circulating Tumor DNA Analysis (Plasma) Biomarkers

The presence of cell-free DNA in circulating blood is a well-documented phenomenon. Fragments of DNA are shed into the blood stream from dividing cells during cell proliferation or cell death. In patients with cancer, a fraction of this DNA is tumor-derived and is termed circulating tumor DNA (ctDNA). Albeit small, fragments of DNA average between 180 to 200 bp and specific genomic regions can be amplified with PCR. ctDNA may be a surrogate of disease burden and/or may be used for the assessment of cancer-related gene mutations that may be associated with

response to immunotherapy. Plasma samples may also be used to assess any of the soluble factors described above.

9.8.2 Tumor Samples

Tumor biopsy specimens will be obtained from consenting subjects prior to treatment to characterize immune cell populations and expression of selected tumor markers. A fresh biopsy must be available for submission prior to randomization. Biopsies of bone lesions that do not have a soft tissue component are also unacceptable for submission. On-treatment biopsy samples are optional. Biopsied lesions should be distinct from index lesion(s) being evaluated for radiological response, if clinically feasible.

9.8.2.1 LAG-3 and PD-L1 Expression

Entry to this study is limited to subjects assessed for LAG-3 and PD-L1 expression in tumor specimens. LAG-3 and PD-L1 expression on immune cells will be measured using an analytically validated immunohistochemical assay. LAG-3 and PD-L1 status, as determined using a 1% threshold, will be stratification criteria for randomization.

9.8.2.2 Characterization of Tumor Infiltrating Lymphocytes (TILs) and Immune Biomarkers

Immunohistochemistry (IHC) or other technologies will also be used to assess the number and composition of immune infiltrates in order to define the immune cell subsets present within FFPE tumor tissue before and after exposure to therapy. These IHC analyses will include, but not necessarily be limited to, the following markers: CD8, MHC-I, MHC-II, and PD-L1.

9.8.2.3 Characterization of T-Cell Repertoire

DNA or RNA sequencing may be performed on pre-and post-treatment tumor tissue to assess the composition of the T-cell repertoire. DNA/RNA will be isolated from either the FFPE tumor block or equivalent preparations.

9.8.2.4 Gene Expression Profiling

Tumor biopsies may be examined for mRNA gene expression by RNAseq, EdgeSeq and/or equivalent technology platforms to measure the tumor transcriptome, including genes or gene signatures of interest. These include expression of LAG-3, PD1, and PD-L2 as well as inflammation gene signatures.

9.8.2.5 Tumor Genotyping, Mutational Analysis, and Tumor Antigen Profiling

DNA from tumor samples will be analyzed using whole-exome and transcriptome sequencing to determine the number of mutations found within a given sample relative to a normal host tissue, such as adjacent non-transformed cells, whole blood or PBMC. Mutations that are detected will be analyzed for their ability to bind the MHC I and MHC II proteins using prediction algorithms, such as NetMHC. Evaluating the ability of tumor mutations to bind MHC molecules will provide evidence that these mutations are serving as antigens that are recognized the immune system and are potential rejection antigens.

9.8.2.6 Tumor Sample Collection

The investigator, in consultation with the radiology staff, must determine the degree of risk associated with the procedure and find it acceptable. Biopsies may be done with local anesthesia or conscious sedation. Biopsied lesions should be distinct from index lesion(s) being evaluated for radiological response, if clinically feasible. 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 subject.

Detailed instructions of the obtaining, processing, labeling, handling, storage and shipment of specimens will be provided in a separate Procedure Manual at the time of study initiation

Table 9.8.2.6-1: CA224047 Biomarker Sampling Schedule (All subjects)[a]

Collection Timing	Serum	Plasma	Whole Blood	PBMC	Tumor
Screening	--	--	--	--	X[c]
Cycle 1 Day 1	X	X	X	X	
Cycle 2 Day 1	X	X	--	X	X[e]
Cycle 3 Day 1	X	--	--	--	--
Upon Progression[d]	X	X	--	--	X[e]

[a] Biomarker sampling occurs prior to dosing of study drug and can occur ± 5 days from the scheduled time.

[b] Original footnote b has been deleted.

[c] Tumor biopsy prior to therapy is mandatory. If a recent archived biopsy, as defined by protocol, is not available at screening, a fresh biopsy will be taken at any point prior to treatment.

[d] Samples from subjects that have confirmed progression are optional.

[e] Optional biopsies on-treatment and upon progression and may be taken at the discretion of the investigator.

9.8.2.7 Additional Research Collection

This protocol will include residual sample storage for additional research.

For All US Sites

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

For All 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.

PK, residual tumor, plasma, serum, whole blood DNA, whole blood RNA, and PBMC (see Table 9.8.2.6-1) will be retained for additional research purposes.

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

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

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

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

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

Table 9.8.2.7-1: Residual Sample Retention for Additional Research Schedule

Sample Type	Time points for which residual samples will be retained
PK	All
Tumor biopsy	All
Plasma	All
Serum	All
Whole blood DNA	All
Whole blood RNA	All
PBMC	All

9.9 Medical Resource Utilization and Health Economics

Health care resource utilization data will be collected for all randomized participants using an internal CRF developed for use in previous trials. The form, which is completed by study staff, records information about hospital admissions, including number of days spent in various wards and discharge diagnosis, as well as non-protocol specified visits related to study therapy, including

date of visit, reason for visit, and type of visit. The health care resource utilization data will be used to support subsequent economic evaluations.

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

The sample size for the study is based on a primary endpoint of PFS using BICR for either a Phase 2 or a Phase 3 study. The sample size for the Phase 2 study as justified below is approximately 400 randomized participants. The sample size for the Phase 3 study as justified below is 700 randomized participants, comprised of the Phase 2 population and an additional 300 participants.

The overall alpha for the Phase 3 study is 0.05 (two-sided) with detailed alpha-spending strategy described in Section 10.2.2.

Sample Size Justification for Phase 2 PFS Estimation

The primary objective of the Phase 2 portion of the study is to demonstrate preliminary clinical evidence of the treatment effect, measured by PFS, as determined by BICR using RECIST v1.1 in randomized participants with unresectable or metastatic melanoma treated with BMS-986213 compared to those treated with nivolumab monotherapy. The number of events is based on results from study CA209067 with a median PFS of 6.9 months for nivolumab monotherapy and 11.8 months for nivolumab with relatlimab. With 183 events, there will be approximately 80% power to detect a hazard ratio (HR) = 0.73 with a type 1 error of 0.1 (1-sided). The cure rates were assumed to be 30% in the nivolumab arm and 40% in the nivolumab with relatlimab arm. The power is also affected by non-proportional hazards, since it is driven by the number of events, not the number of study participants, and some fraction of the participants in each arm are assumed will remain event-free for the duration of the study. Approximately 400 participants will be randomized to the Phase 2 study to ensure enough power to analyze the biomarker subgroups (see section below on the secondary endpoint of ORR in subgroup).

Based on an anticipated screen failure rate of 30%, approximately 575 participants will need to be screened in order to randomize approximately 400 participants who fit the eligibility criteria.

Sample Size Justification for Phase 3 PFS Comparison

The sample size is calculated in order to compare PFS among participants randomized to receive BMS-986213 versus nivolumab. The number of events required is simulated based on results from study CA209067, with a median PFS of 6.9 months for nivolumab monotherapy and 11.8 months for nivolumab with relatlimab, incorporating 35% of subjects with durable response in the combined groups, and a piecewise hazard ratio resulting in an effective hazard ratio of approximately 0.73.

Based on these assumptions, the study requires 365 PFS events to ensure approximately 85% power to detect a hazard ratio of 0.73 with an overall type I error of 0.05. Approximately 700 participants will be randomized to the two treatment arms in a 1:1 ratio. The final PFS analysis is planned to occur when 365 participants have had a PFS event per BICR. Total enrollment will take approximately 27 months (including a potential 6-month pause due to the interim PFS analysis).

Based on an anticipated screen failure rate of 30%, approximately 1000 participants will need to be screened in order to randomize 700 participants who meet the eligibility criteria.

Sample Size Justification for Secondary Objective of Overall Survival Comparison in Phase 3 Trial

The sample size is calculated in order to compare OS among participants randomized to receive BMS-986213 versus nivolumab. The number of OS events (deaths) required is based on results from study CA209067, with a median PFS of 36.9 months for nivolumab monotherapy and 49.2 months for nivolumab with relatlimab, resulting in an effective hazard ratio of approximately 0.75. With 300 deaths the power will be approximately 69% with a type I error rate of 0.05.

Sample Size Justification for Secondary Objective of Subgroup Comparison in Phase 2 Trial

If the interim PFS analysis does not support continuing to a Phase 3 study, the study will complete as a Phase 2 trial. The primary objective of the Phase 2 study using patients with previously untreated, unresectable or metastatic melanoma is to assess preliminary clinical evidence of the treatment effect measured by PFS as determined by BICR that may represent substantial improvement over available therapies. As a secondary objective, the Phase 2 will examine ORR information in biomarker subgroups based on LAG-3 expression (≥ 1% expression versus < 1% expression) and PDL-1 status (≥ 1% tumor cell surface expression versus < 1% tumor cell surface expression). ORR information and biomarker prevalence rates (for LAG-3 positive and negative expression, and for PDL-1 positive and negative status) used in the sample size calculations were based on information from study CA209067 and interim information from study CA224020. Table 10.1-1 shows the power for varying ORRs and varying prevalence rates for subgroups, assuming a Type 1 error rate of 0.1 (one-sided) and an overall N of 400 subjects. The Benjamini-Hochberg procedure will be used to control the False Discovery Rate (FDR) when testing multiple subgroups.

Table 10.1-1: Power for Subgroups with Different N and Prevalence

Overall N for Phase 2 Study	Subgroup N	Subgroup ORR	Subgroup Prevalence	Power (one-sided alpha .1 and 20% delta)
400	200	0.7	0.5	0.991
	140	0.7	0.35	0.962
	50	0.5	0.125	0.576
	80	0.5	0.2	0.72
	50	0.33	0.125	0.57
	80	0.33	0.2	0.713
	100	0.23	0.25	0.815
	120	.23	0.3	0.865

Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled Participants	All participants who sign informed consent and were registered into IRT
Randomized	All participants who are randomized to any treatment group.
Treated	All participants who received at least one dose of double-blind study medication.

Population	Description
Safety	All randomized 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 in the following cases: • If a participant received the same incorrect treatment throughout the study, then the participant will be analyzed based on the treatment received. • If a participant received study drug from more than one treatment group, and none of the administrations were consistent with the assigned randomized treatment group, then the participant will be analyzed based on the first treatment received.
PK	All randomized participants with available serum time-concentration data.
Immunogenicity	All randomized participants with available ADA data.
Biomarker	All randomized participants with available biomarker data.

10.2 Statistical Analyses

10.2.1 Demographics and Baseline Characteristics

Frequency distributions of gender, race, ethnicity, and other categorical baseline characteristics will be tabulated. Baseline body mass index (BMI) will be derived from measurements of baseline body weight and height. Summary statistics for age, body weight, height, and BMI will be tabulated. Baseline disease characteristics will be summarized for expansion cohorts for different disease cohorts separately, as appropriate.

10.2.2 Efficacy Analyses

Below is a summary of planned statistical analyses of the primary and secondary efficacy endpoints.

Endpoint	Statistical Analysis Methods
Phase 3 Primary	
PFS time, as assessed by a BICR, using RECIST v1.1. PFS is defined as the time between the date of randomization and the first date of documented progression, or death due to any cause, whichever occurs first.	Two-sided log-rank test stratified by LAG-3 expression (≥ 1% vs < 1%), (PD-L1 status (≥ 1% vs < 1%), BRAF status, and AJCC (8th edition) M Stage in randomized participants to compare the PFS of relatlimab + nivolumab arm (BMS-986213) and the nivolumab alone arm. Hazard ratios and corresponding 2-sided 95% CI will be estimated using a Cox proportional hazards model, with

Endpoint	Statistical Analysis Methods
	treatment group as a single covariate, stratified by the above factors. PFS curves, PFS medians with 95% CIs, and PFS rates at 6 and 12 months with 95% CIs will be estimated using Kaplan-Meier methodology.
Phase 3 Secondary	
OS time is defined as the time between the date of randomization and the date of death due to any cause.	This test will only be interpreted if the primary analysis is significantly superior. Two-sided log-rank test stratified by LAG-3 expression (≥ 1% vs < 1%), PD-L1 status (≥ 1% vs < 1%), BRAF status, and AJCC (8th edition) M Stage will be used to compare the relatlimab + nivolumab arm (BMS-986213) and the nivolumab arm. Hazard ratio and corresponding two-sided 95% CI will be estimated using a Cox proportional hazards model, with treatment group as a single covariate, stratified by the above factors. Additionally, OS curves, OS medians with 95% CIs, and OS rates at 12 months with 95% CIs will be estimated using Kaplan-Meier methodology.
ORR as assessed by BICR. The ORR is defined as the number of subjects with a BOR of CR or PR divided by the number of randomized subjects for each treatment group. The BOR is defined as the best response designation, recorded between the date of randomization and the date of objectively documented progression per RECIST v1.1 or the date of subsequent anti-cancer therapy, whichever occurs first.	This test will only be interpreted if the primary (PFS) and first secondary (OS) analyses are significantly superior. Two-sided Cochran-Mantel-Haenszel (CMH) test stratified by LAG-3 expression (≥ 1% vs < 1%), (PD-L1 status (≥ 1% vs < 1%), BRAF status, and AJCC (8th edition) M Stage to compare the BMS-986213 arm and the nivolumab monotherapy arm. Associated odds ratios and 95% CIs will be calculated. Additionally, ORRs and corresponding 95% exact CIs will be calculated using the Clopper Pearson method.
Phase 3 Exploratory	Will be described in the Statistical Analysis Plan (SAP) finalized before database lock
Phase 2 Primary	
PFS time, as assessed by BICR, using RECIST v1.1. PFS time is defined as the time between the date of randomization and the first date of documented	Two-sided log-rank test stratified by LAG-3 expression (≥ 1% vs < 1%), (PD-L1 status (≥ 1% vs < 1%), BRAF status, and AJCC (8th edition) M Stage in randomized participants to compare the PFS of relatlimab + nivolumab arm (BMS-986213) and the

Endpoint	Statistical Analysis Methods
progression, or death due to any cause, whichever occurs first.	nivolumab alone arm. Hazard ratios and corresponding 2-sided 95% CI will be estimated using a Cox proportional hazards model, with treatment group as a single covariate, stratified by the above factors. PFS curves, PFS medians with 95% CIs, and PFS rates at 6 and 12 months with 95% CIs will be estimated using Kaplan-Meier methodology.
Phase 2 Secondary	
ORR as assessed by BICR.	Summary of ORR with corresponding 2-sided 95% CI in each arm and for the difference between arms, along with each category of BOR. Multiple comparisons in population subgroups will be handled using the Benjamini-Hochberg method to control the False Discovery Rate (FDR) at 0.05.
DOR is defined as the time between the date of first response to the date of first documented tumor progression (per RECIST v1.1) or death due to any cause. TTR is defined as the time from randomization to the date of the first documented CR or PR.	Summary of DOR with median (95% CI) and range (min, max) by K-M method. Summary of median Time to Response (mTTR) (95% CI)
PFS time and PFS rate as assessed by BICR, using RECIST v1.1 for subgroups	Summary of PFS with median (95% CI) by Kaplan-Meier method and PFS rate
OS is defined as the time between the date of randomization and the date of death due to any cause.	OS with median (95% CI) and range (min, max) by Kaplan-Meier method
Phase 2 Exploratory	Will be described in the SAP finalized before database lock

PFS is defined as the time between the date of randomization and the first date of documented progression, or death due to any cause, whichever occurs first. Participants who die without a reported progression will be considered to have progressed on the date of their death. Participants who did not progress or die will be censored on the date of their last evaluable tumor assessment. Participants who did not have any on study tumor assessments and did not die will be censored on their date of randomization. Participants who started anti-cancer therapy without a prior reported

progression will be censored on the date of their last evaluable tumor assessment prior to the initiation of subsequent anti-cancer therapy.

Phase 3 Testing Strategy

The Phase 2 part of the study will enroll approximately 400 participants. An interim analysis of PFS will be performed when a minimum follow-up of 12 weeks is achieved for approximately 400 randomized subjects or at least 150 PFS events have been observed using BICR.

- If the interim PFS analysis achieves the pre-specified threshold (as defined in the SAP and the DMC Charter), then the study will continue to Phase 3 and remain blinded.
- If interim PFS analysis does not achieve the pre-specified threshold (as defined in the SAP and DMC Charter) the study will not open enrollment to Phase 3. The Phase 2 data will be allowed to mature and then the sponsor will unblind for analysis. If that scenario takes place, approximately 575 participants will need to be enrolled in order to randomize 400 participants assuming a screen failure rate of 30%.

The overall alpha for the Phase 3 study is 0.05 (two-sided).

For the Phase 3 study, type I error control across endpoints will be performed hierarchically. The primary analysis is for PFS. If that analysis is significantly superior, then the secondary endpoints may be tested in the order of OS followed by ORR. That is, if the results comparing PFS between treatment groups are significant at the applicable alpha level, then results comparing OS between treatment groups will be interpreted. If the results comparing OS between treatment groups are significant, then results comparing ORR between treatment groups will be interpreted. Other endpoints will not be tested formally.

An administrative alpha penalty of 0.001 will be used for the interim PFS analysis. If the interim PFS analysis meets the pre-specified threshold and proceeds to Phase 3, the final PFS analysis will be performed when approximately 365 PFS events have occurred per BICR and will use all remaining unspent alpha. If the pre-specified efficacy boundary is achieved at PFS final analysis, all remaining alpha will be passed to OS in a hierarchical fashion as described above, and participants will continue to be followed for OS.

Assuming the PFS result is significantly superior (at the final PFS analysis), there will be interim analyses of OS. The interim OS analyses will use an O'Brien-Fleming boundary based on the actual number of deaths observed. The first interim analysis of OS (OS IA1) will take place at the same time as final PFS. If OS IA1 does not achieve statistical significance, the second interim analysis of OS (OS IA2) will be performed when a minimum of 90% (270/300) of the expected deaths have occurred. If OS IA2 is not statistically significant, the final OS analysis will be performed when approximately 300 deaths have occurred.

If PFS and OS are each significantly superior, then ORR will be formally tested.

Phase 2 Testing Strategy

If the interim PFS analysis indicates the study will stop at Phase 2 the study will not enroll any additional participants, and the study will remain blinded until the data are sufficiently mature (183 PFS events and a minimum 6 months of follow-up). The final Phase 2 analysis includes multiple subgroups of interest. The Benjamini-Hochberg method will be used to account for multiplicity by controlling the False Discovery Rate (FDR) when making comparisons in multiple subgroups.

10.2.3 Safety Analyses

All safety analyses will be performed on the Safety Population.

Endpoint	Statistical Analysis Methods
The Safety and tolerability objective (whether for Phase 2 or Phase 3) will be measured by the incidence of adverse events (AEs), serious adverse events (SAEs), adverse events leading to discontinuation, deaths, and laboratory abnormalities in each arm.	• Safety analyses will be performed in all treated participants. Descriptive statistics of safety will be presented using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 by treatment group. All on-study AEs, treatment-related AEs, SAEs, and treatment-related SAEs will be tabulated using worst grade per NCI CTCAE v 5.0 criteria by system organ class and preferred term. On-study lab parameters including hematology, chemistry, liver function, and renal function will be summarized using worst grade NCI CTCAE v 5.0 criteria.

10.2.4 Other Analyses

PK and biomarker exploratory analyses will be described in the SAP finalized before database lock.

10.2.4.1 Pharmacokinetic Analyses

Trough concentrations of relatlimab will be plotted versus study day and cycle. Nivolumab end-of-infusion and trough (Ctrough) concentrations will be tabulated using summary statistics. These data may also be pooled with other datasets for population PK analysis which will be presented in a separate report.

10.2.4.2 Immunogenicity Analyses

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

the frequency and type of AEs of special interest may be explored by immunogenicity status. In addition, potential relationships between immunogenicity and efficacy and/or PK may also be explored.

10.2.4.3 Outcomes Research

Analyses of EQ-5D-3L, FACT-M (and GP5 item alone), and WPAI:GH scores will be performed in all randomized participants who have an assessment at baseline (Day 1, assessment prior to administration of drug on day of first dose) and at least 1 subsequent assessment while on treatment. Questionnaire completion rate, defined as the proportion of questionnaires actually received out of the expected number, will be calculated and summarized at each assessment point.

EQ-5D-3L data collected during on-study clinic visits, at Follow-up Visits 1 and 2, and during the survival follow-up phase, will be described by treatment group as randomized in the following ways:

- EQ-5D-3L index scores and post-baseline changes in scores will be summarized at each assessment time point using descriptive statistics (ie, N, mean with SD and 95% CI, median, first and third quartiles, minimum, maximum). In the base case, scores will be calculated using the UK preference-weighting algorithm.
- EQ-5D-3L VAS scores and post-baseline changes in scores will be summarized at each assessment time point using descriptive statistics (ie, N, mean with SD and 95% CI, median, first and third quartiles, minimum, maximum).
- The proportion (N) of participants reporting no, moderate, or extreme problems will be presented for each of the 5 EQ-5D-3L dimensions at each assessment time point.
- A by-participant listing of the level of problems in each dimension, corresponding EQ-5D-3L health state (ie, 5-digit vector), EQ-5D-3L index score, and EQ-5D-3L VAS score will be provided.

FACT-M data collected during on-study clinic visits, at Follow-up Visits 1 and 2, and during the survival follow-up phase will be described by treatment group as randomized in the following ways:

- Scores and post-baseline changes in scores for the FACT-M total scale and subscales, and the GP5 will be summarized at each assessment time point using descriptive statistics (ie, N, mean with SD and 95% CI, median, first and third quartiles, minimum, maximum, and frequency of responses for GP5 item).
- The proportion (N) of participants with symptomatic deterioration, defined as a clinically meaningful decline in FACT-M MS score (worsening from baseline $\geq$ 34 points) or death, will be summarized at each assessment time point (on-study visits only).

WPAI:GH data collected at baseline, on-treatment visits, and at follow-up Visits 1 and 2 will be described by treatment group as randomized in the following ways:

- Employment status (Q1, Yes/No) will be summarized at each assessment time point using frequency counts and percentages.

- Hours actually worked during the past 7 days (Q4) will be summarized at each assessment time point as a categorical variable (> 0 hour/0 hour) using frequency counts and percentages.
- Absenteeism, presenteeism, work productivity loss, and activity impairment scores and post-baseline changes in scores will be summarized at each assessment time point using descriptive statistics (ie, N, mean with SD and 95% CI, median, first and third quartiles, minimum, maximum). Absenteeism and work productivity loss scores will be summarized for participants who were employed (Q1=Yes). Presenteeism will be summarized for participants who actually worked during the past 7 days (Q4 > 0 hour). Activity impairment will be summarized for all participants.

10.2.5 Interim Analyses

The DMC will perform 1 interim analysis of PFS, and up to 2 interim analyses of OS (See Section 10.2.2).

The DMC Statistical Analysis Plan will further describe the planned interim analyses.

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12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
ADA	anti-drug antibody
AEs	adverse events
AIDS	acquired immunodeficiency syndrome
AJCC	American Joint Committee on Cancer
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BICR	Blinded Independent Central Review
BMI	body mass index
BOR	best overall response
CBC	complete blood count
CD279	cluster of differentiation 279
CI	confidence interval
CMV	cytomegalovirus
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CR	complete response
CrCl	creatinine clearance
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
EQ-5D-3L	3-level version of the EuroQol Group's EQ-5D
ER	exposure-response
EWB	emotional well-being
FACT-M	Functional Assessment of Cancer Therapy – Melanoma
FACT-M MS	FACT-M Melanoma Subscale
FDC	fixed-dose combination
FDR	False Discovery Rate
FFPE	formalin-fixed paraffin-embedded
FWB	functional well-being
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	hazard ratio
IA1, IA2	interim analysis 1, interim analysis 2

Term	Definition
IB	Investigator's Brochure
ICF	informed consent form
Ig	immunoglobulin
IHC	Immunohistochemistry
IMAEs	immune-mediated AEs
IO	immuno-oncology
IP	investigational product
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IRT	interactive response technology
IV	intravenous
LAG-3	lymphocyte activation gene 3
LC	liquid chromatography
mAbs	monoclonal antibodies
MHC	major histocompatibility complex
MID	minimally important difference
MLR	mixed lymphocyte reaction
MRI	magnetic resonance imaging
MS	mass spectrometry
MTD	maximum tolerated dose
mTTR	median Time to Response
NCI	National Cancer Institute
NSCLC	non-small cell lung cancer
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cells
PD	pharmacodynamics
PD-1	programmed death-1
PD-L1	programmed death-ligand 1
PD-L2	programmed death-ligand 2
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetics
PPK	population PK
PR	partial response
PVC	polyvinyl chloride
PWB	physical well-being
Q2W	every 2 weeks
Q4W	every 4 weeks
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RO	receptor occupancy
SAE	serious adverse event
SAP	statistical analysis plan
SCCHN	squamous cell carcinoma of the head and neck

Term	Definition
SD	stable disease
SUSAR	suspected, unexpected serious adverse reaction
SWB	social/family well-being
TCR	T-cell receptor
TnI	troponin I
TnT	troponin T
TOI	Trial Outcome Index
TTR	Time to objective response
TTSD	Time to meaningful symptomatic deterioration
ULN	upper limit of normal
US	United States
VAS	visual analog scale
WBC	white blood cells
WOCBP	women of childbearing potential
WPAI:GH	Work Productivity and Activity Impairment: General Health

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

The term 'Participant' is used in the protocol to refer to a person who has consented to participate in the clinical research study. The term 'Subject' used in the eCRF is intended to refer to a person (Participant) who has consented to participate in the clinical research study.

REGULATORY AND ETHICAL CONSIDERATIONS

GOOD CLINICAL PRACTICE

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 Good Clinical Practice (GCP),
- as defined by the International Council on Harmonisation (ICH)
- in accordance with the ethical principles underlying European Union Directive 2001/20/EC
- United States Code of Federal Regulations, Title 21, Part 50 (21CFR50)
- applicable local requirements.

The study will be conducted in compliance with the protocol. The protocol and any amendments and the participant informed consent will receive approval/favorable opinion by Institutional Review Board/Independent Ethics Committee (IRB/IEC), and regulatory authorities according to applicable local 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, etc) that is likely to affect, to a significant degree one or more of the following: (1) the physical, safety or mental integrity of one or more subjects/participants; (2) the scientific value of the 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, consent form, participant recruitment materials (eg, advertisements), and any other written information to be provided to subjects/participants. The investigator or BMS should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to subjects/participants and any updates.

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

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 local health authority) except where necessary to eliminate an immediate hazard(s) to study subjects/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 for
- 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 local health authority must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the participant: (1) the consent form 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 subjects/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 subjects/participants prior to enrollment.

If the revision is done via an administrative letter, investigators must inform their IRB(s)/IEC(s).

FINANCIAL DISCLOSURE

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local 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 subjects/participants are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

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

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

Investigators must:

- Provide a copy of the consent form and written information about the study in the language in which the participant is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
- Allow time necessary for participant or participant's legally acceptable representative to inquire about the details of the study.
- Obtain an informed consent signed and personally dated by the participant or the participant's legally acceptable representative and by the person who conducted the informed consent discussion.
- Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects/participants, prior to the beginning of the study, and after any revisions are completed for new information.

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.

Revise the informed consent 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 the participant's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the participant's willingness to continue participation in the study. This communication should be documented.

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

The consent form must also include a statement that BMS and regulatory authorities have direct access to participant records.

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 informed consent form 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 assent.

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

SOURCE DOCUMENTS

The Investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original and attributable, whether the data are hand-written 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/health records (EMRs/EHRs), adverse event tracking/reporting, protocol required assessments, and/or drug accountability records).

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

STUDY TREATMENT RECORDS

Records for study treatments (whether supplied by BMS, its vendors, or the site) must substantiate study treatment 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 (e.g., 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 SOPs/standards of the sourcing pharmacy.

BMS or 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 tool, electronic CRFs 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 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 Sponsor or designee.

The confidentiality of records that could identify subjects/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, SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form. Subinvestigators in Japan may not be delegated the CRF approval task. For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

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

MONITORING

Sponsor or designee representatives will review data centrally to identify potential issues to determine a schedule of on-site visits for targeted review of study records.

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 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 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 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 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 designee.

RETURN OF STUDY TREATMENT

For this study, study treatments (those supplied by BMS, 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 treatments 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). 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)	It is the investigator's or designee's responsibility to dispose of all containers

It is the investigator's or designee's responsibility to arrange for disposal, 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 SOPs 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, ie, 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 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.

CLINICAL STUDY REPORT

A Signatory Investigator must be selected to sign the clinical study report.

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

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

SCIENTIFIC PUBLICATIONS

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

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 subjects 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 preexisting medical condition in a clinical investigation participant administered study treatment and that does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study treatment, whether or not considered related to the study treatment.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or results from other safety assessments (eg, ECG, 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/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae and should specify "intentional overdose" as the verbatim term

Events NOT Meeting the AE Definition

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

DEFINITION OF SAE

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

SERIOUS ADVERSE EVENTS

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 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 (e.g., 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 (e.g., 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 [e.g., 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; 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 potential drug induced liver injury (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 (IB) 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 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 Sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send a 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 preferred method for SAE data reporting collection is through the eCRF.
  - The paper SAE Report Form is only intended as a back-up option when the electronic data capture (EDC) system is unavailable/not functioning for transmission of the eCRF to BMS (or designee).
    - In this case, the paper forms are to be transmitted via email or confirmed facsimile (fax) transmission
    - When paper forms are used, the original paper forms are to remain on site

Pregnancies must be recorded on a paper Pregnancy Surveillance Form and transmitted via email or confirmed facsimile (fax) transmission

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

SAE Telephone Contact (required for SAE and pregnancy reporting): Refer to Contact Information list

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal 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.

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

One of the highly effective methods of contraception listed below is required during study duration and until the end of relevant systemic exposure, defined as 5 months after the end of study treatment.*

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal

• Progestogen-only hormonal contraception associated with inhibition of ovulation[b] – oral – injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation [b] • Intrauterine hormone-releasing system (IUS)[c] • Intrauterine device (IUD)[c] • Bilateral tubal occlusion
• Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. 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.* • 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 participants chooses to forego complete abstinence
NOTES: [a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. [b] Hormonal contraception may be susceptible to interaction with the study drug, 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. [c] Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness

Unacceptable Methods of Contraception*
• 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
- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus).
- Spermicide only
- Lactation amenorrhea method (LAM)

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

CONTRACEPTION GUIDANCE FOR MALE PARTICIPANTS WITH PARTNER(S) OF CHILD BEARING POTENTIAL.

- No contraceptive requirements for male participants.

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 the Appendix for Adverse Events and Serious Adverse Events Definitions and procedures for Evaluating, Follow-up and Reporting.

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

1 EVALUATION OF LESIONS

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

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

1.1 Measurable

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

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

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

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

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

1.2 Non-Measurable

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

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

1.3 Special considerations regarding lesion measurability

1.3.1 Bone lesions

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

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

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

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

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

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

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

2 RESPONSE CRITERIA

2.1 Evaluation of Target Lesions

- **Complete Response (CR):** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- **Partial Response (PR):** At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive Disease (PD):** At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
- **Not Evaluable (NE):** If one or more target lesions cannot be measured or adequately assessed as either fully resolved or too small to measure (due to missing or poor quality images), and the sum of diameters of the remaining measured target lesions (if any) has not increased sufficiently to meet Progressive Disease as defined above.

2.1.1 Special Notes on the Assessment of Target Lesions

2.1.1.1 Lymph nodes

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

2.1.1.2 Target lesions that become 'too small to measure'

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

small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

2.1.1.3 Lesions that split or coalesce on treatment

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

2.2 Evaluation of Non-Target Lesions

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

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

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

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

2.2.1.1 When the patient also has measurable disease

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

2.2.1.2 When the patient has only non-measurable disease

This circumstance arises in some trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable

disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include, an increase in lymphangitic disease from localized to widespread, or may be described as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore the increase must be substantial.

2.2.2 New Lesions

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

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

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

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

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

2.3 Response Assessment

2.3.1 Evaluation of Best Overall Response

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

2.3.2 Time Point Response

At each protocol specified time point, a response assessment occurs. Table 2.3.2-1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline. When patients have non-measurable (therefore non-target) disease only, Table 2.3.2-2 is to be used.

Table 2.3.2-1: Time Point Response: Patients With Target (± Non-Target) Disease

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

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

Table 2.3.2-2: Time Point Response: Patients with Non-target Disease Only		
Non-Target Lesions	**New Lesions**	**Overall Response**
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD
CR = complete response, PD = progressive disease and NE = inevaluable		

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

2.3.3 Best Overall Response

Best response determination of complete or partial response requires confirmation: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point of ≥ 4 weeks (28 days) later. In this circumstance, the best overall response can be interpreted as in Table 2.3.3-1. When SD is believed to be best response, it must meet the protocol specified minimum time from the date of first treatment or randomization date.

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

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

Table 2.3.3-1: Best Overall Response (Confirmation of CR and PR Required)		
Overall Response First Time Point	**Overall Response Subsequent Time Point**	**Best Overall Response**
CR	CR	CR
CR	PR	SD, PD OR PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD

Table 2.3.3-1: Best Overall Response (Confirmation of CR and PR Required)		
Overall Response First Time Point	**Overall Response Subsequent Time Point**	**Best Overall Response**
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE
CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable		

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

2.3.4 Confirmation Scans

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

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

REFERENCES

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

APPENDIX 6 ECOG, KARNOFSKY, AND LANSKY PERFORMANCE STATUS SCALES

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**	**Lansky Description**
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)

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

Definition of Primary Tumor (T)

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

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

APPENDIX 8 COUNTRY SPECIFIC REQUIREMENTS

Argentina, Czech Republic, Germany, Peru and Any Other Countries Where Exclusion of HIV Positive Participants Is Locally Mandated

	Country-specific language
Section 2 Flow Chart/Time and Events Schedule, Table 2-1: Screening Assessments- Laboratory Tests	Add "HIV" to the list of laboratory tests
Section 6.2 Exclusion Criteria, Exclusion criterion 3j	"Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)"to be replaced with "Positive test for HIV".

APPENDIX 9 MANAGEMENT ALGORITHMS FOR IMMUNO-ONCOLOGY AGENTS

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

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

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

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

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

GI Adverse Event Management Algorithm

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

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

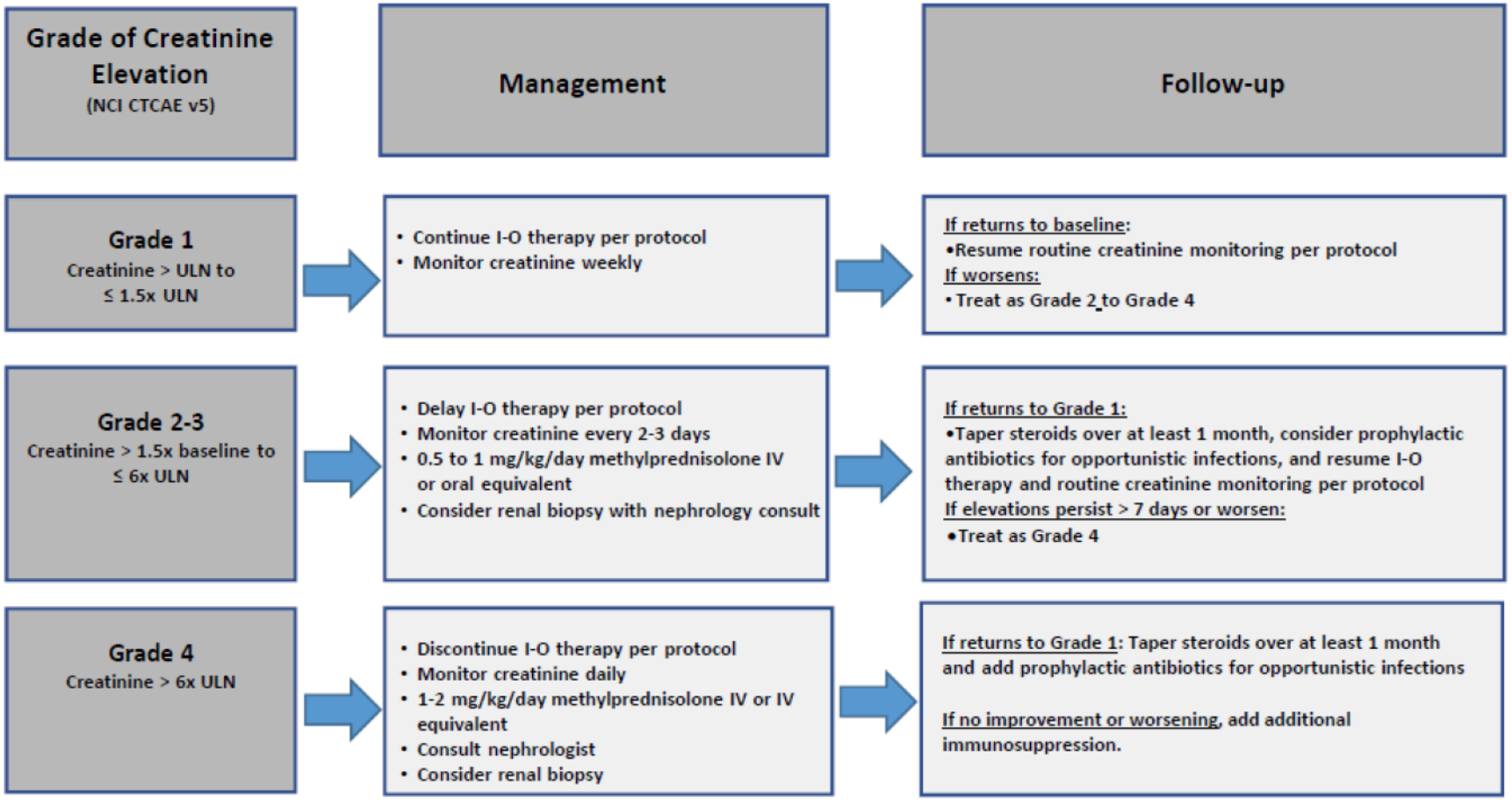
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

28-Sep-2020

Renal Adverse Event Management Algorithm

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

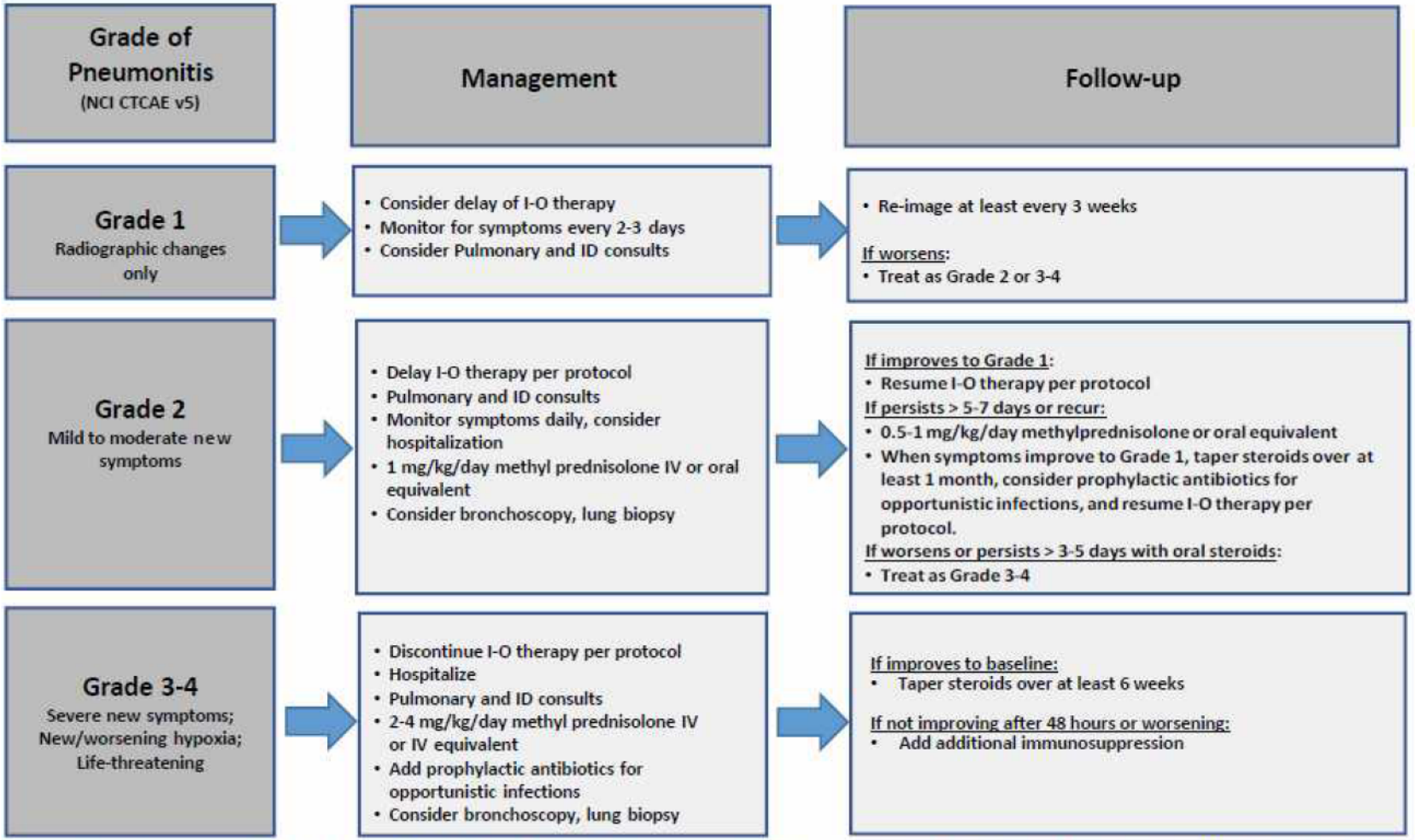


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

28-Sep-2020

Pulmonary Adverse Event Management Algorithm

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

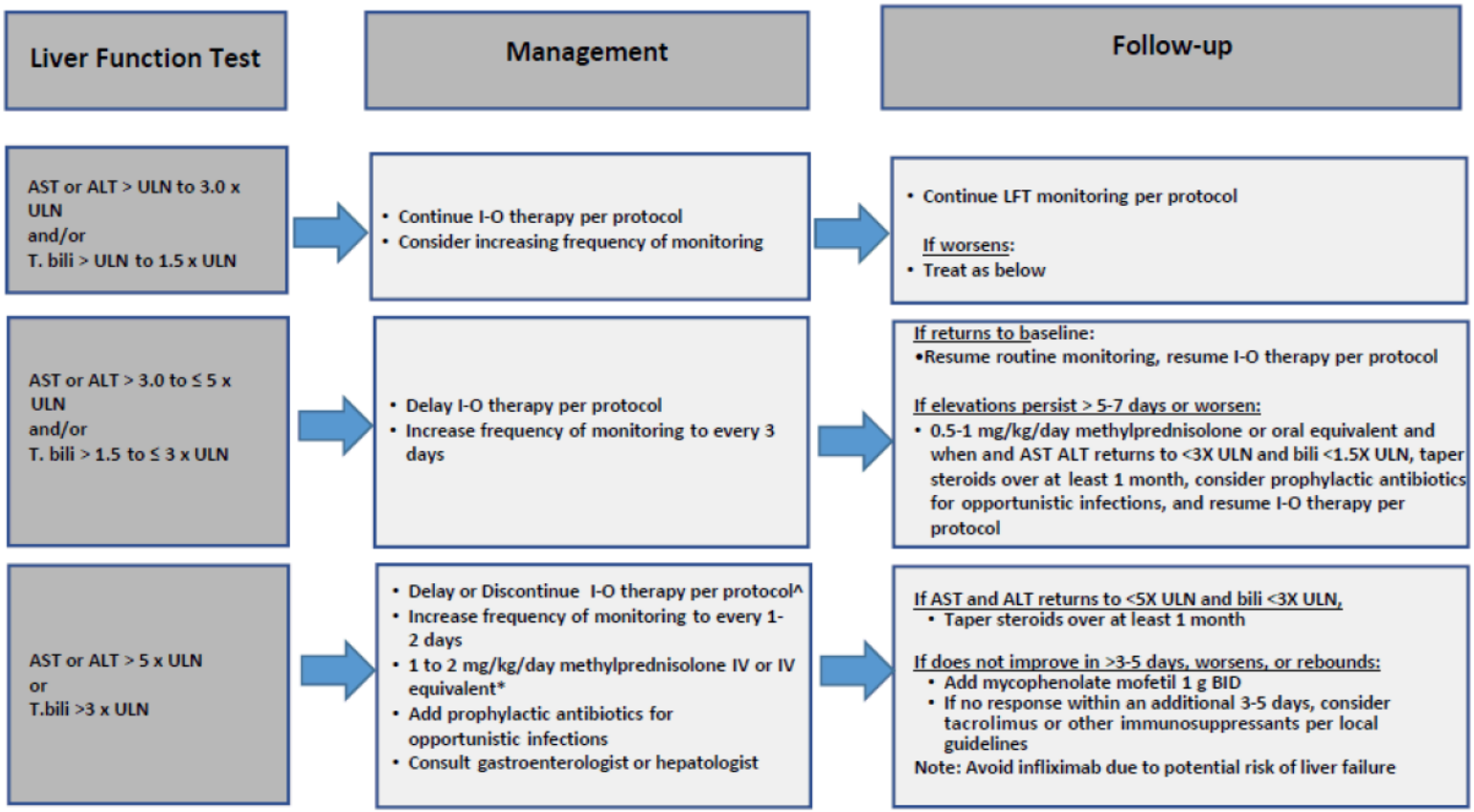


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

28-Sep-2020

Hepatic Adverse Event Management Algorithm

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



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

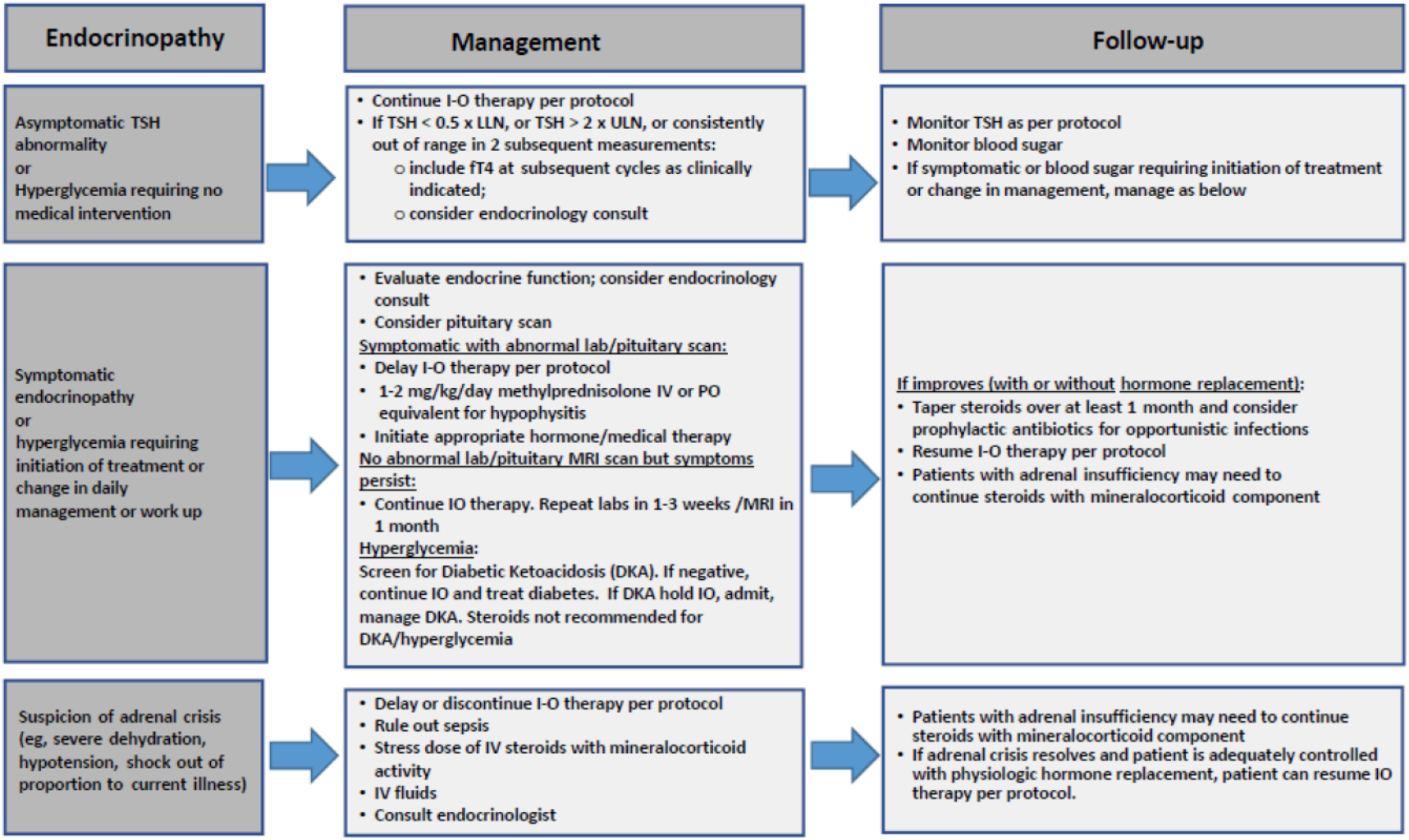
^ Please refer to protocol dose delay and discontinue criteria for specific details.

*The recommended starting dose for AST or ALT > 20 x ULN or bilirubin >10 x ULN is 2 mg/kg/day methylprednisolone IV.

28-Sep-2020

Endocrinopathy Adverse Event Management Algorithm

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

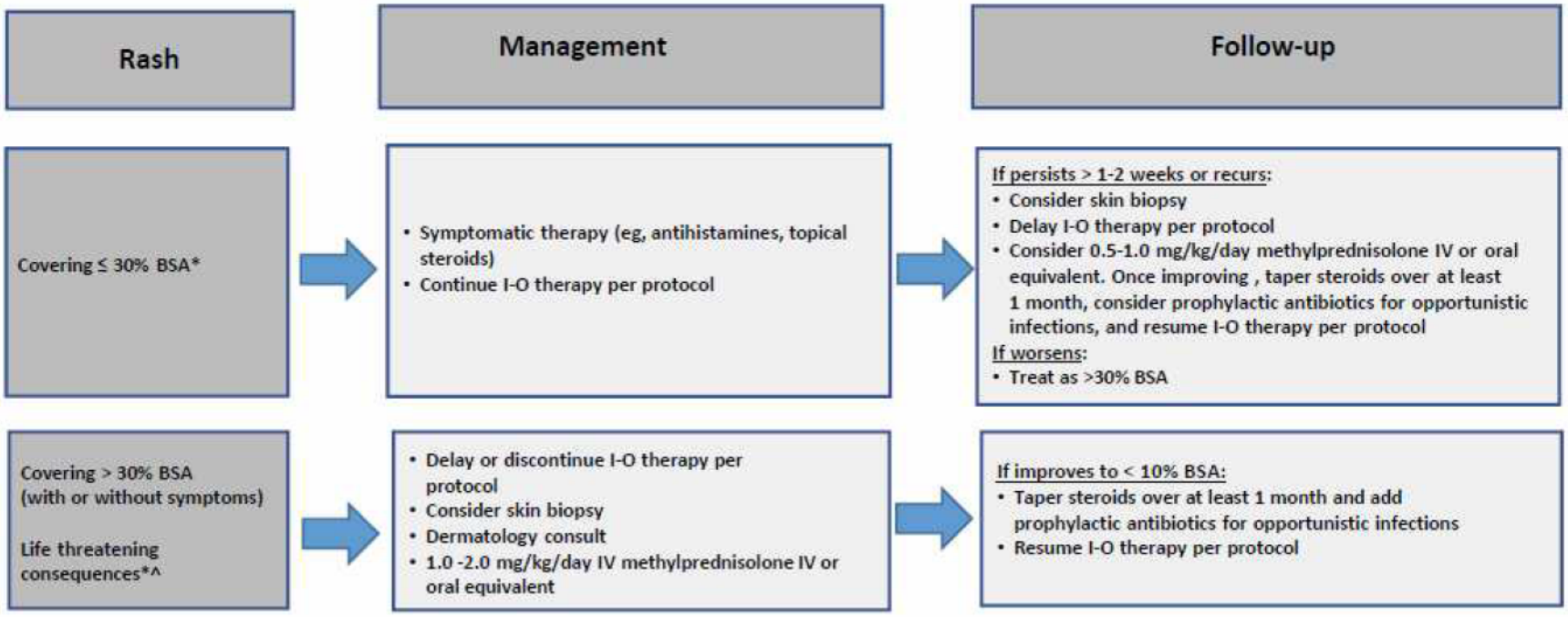


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

28-Sep-2020

Skin Adverse Event Management Algorithm

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



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

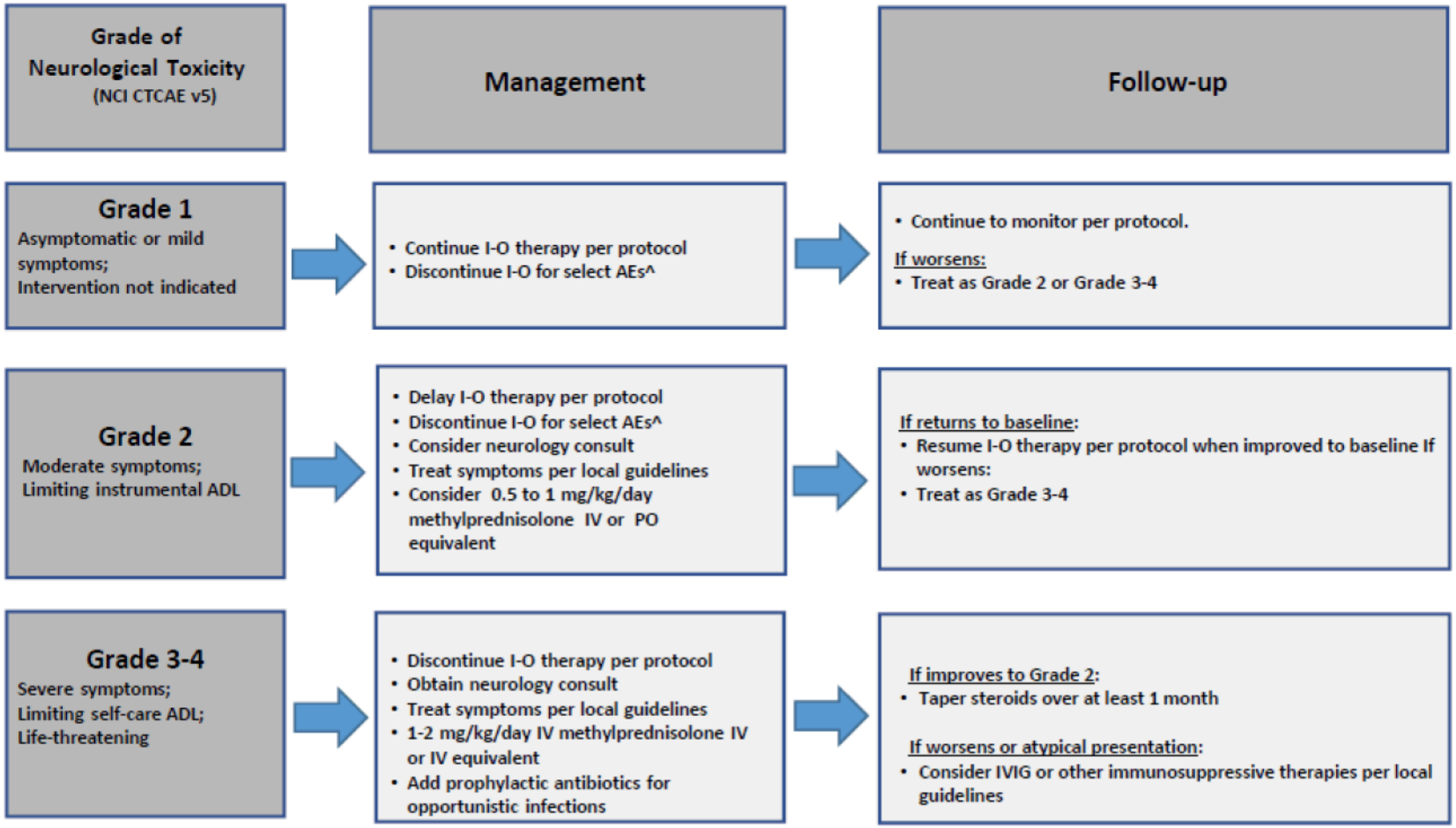
*Refer to NCI CTCAE v5 for term-specific grading criteria.

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

28-Sep-2020

Neurological Adverse Event Management Algorithm

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

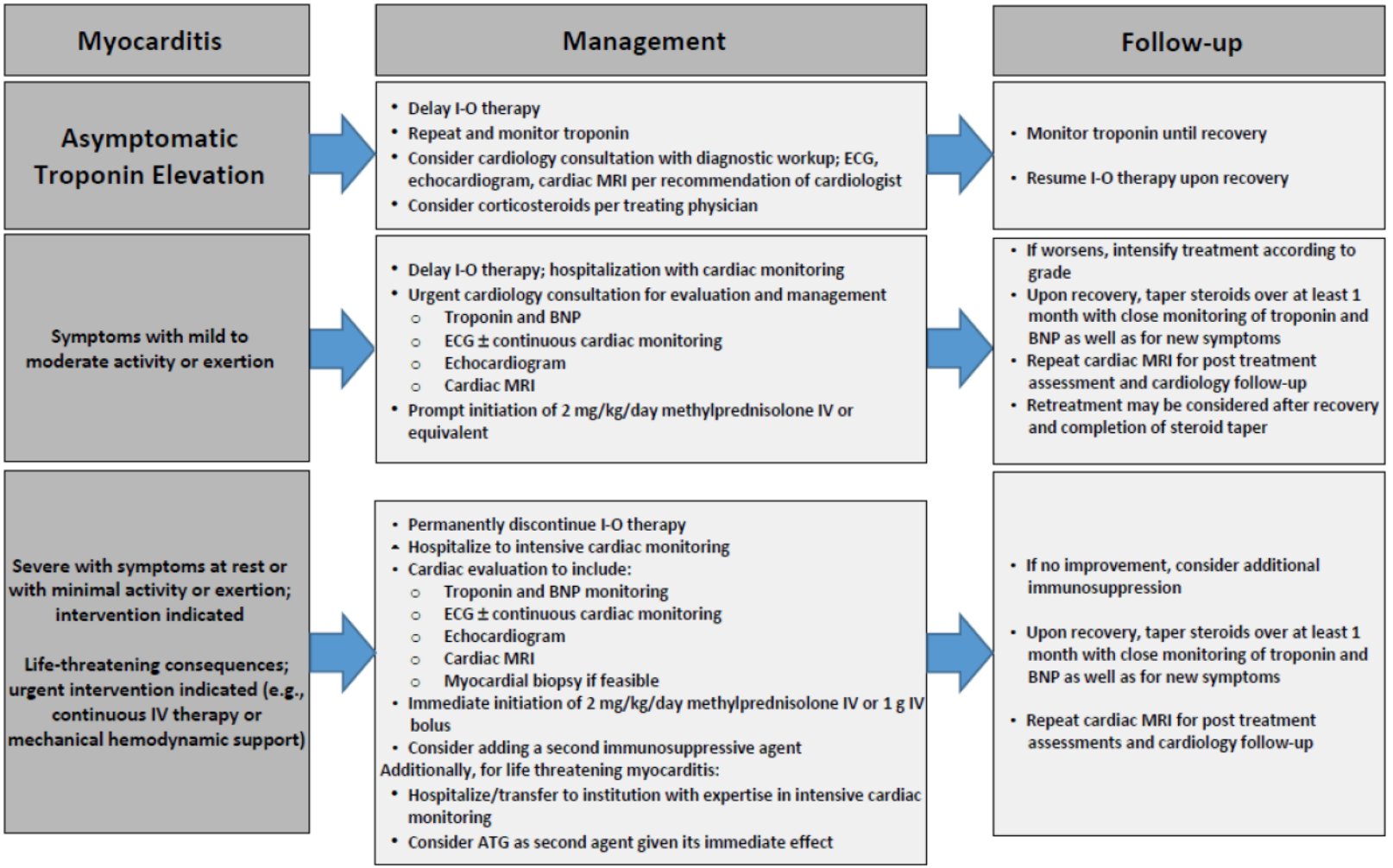


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

28-Sep-2020

Relatlimab Myocarditis Adverse Event Management Algorithm



For the protocols under CTCAE version 5.0. Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids. Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.

ATG = anti-thymocyte globulin; BNP = B-type natriuretic peptide; ECG = electrocardiogram; IV = intravenous; MRI = magnetic resonance imaging

11-Sep-2020

Approved v5.0 [redacted]

APPENDIX 10 MUCOSAL MELANOMA STAGING

Classification of Malignant Melanoma of Upper Aero-digestive Tract (7th edition of the UICC) (2009)[a]

Tumour	Characteristics		
T3	Epithelium/submucosa (mucosal disease)		
T4a	Deep soft tissue, cartilage, bone, or overlying skin		
T4b	Brain, dura, skull base, lower cranial nerves, masticator space, carotid artery, prevertebral space, mediastinal structures, cartilage, skeletal muscle, or bone		
Staging group	Tumour	Node	Metastases
III	T3	N0	M0
IVA	T3-T4a	N1	M0
IVB	T4b	Any N	M0
IVC	Any T	Any N	M1

[a] Ascierto PA, Accorona R, Botti G, et al. Mucosal melanoma of the head and neck. Crit Rev Oncol Hematol. 2017 Apr;112:136-152.

APPENDIX 11 REVISED PROTOCOL SUMMARY OF CHANGE HISTORY

Overall Rationale for the Revised Protocol 02, 22-Feb-2019

PFS2 has been added as exploratory objective.

Pregnancy tests, incorrectly removed in the revised protocol 01, have been added back during follow-up visits.

In addition, minor changes were made to clarify timing of procedures and to improve clarity as noted in the table below.

Summary of Key Changes For Revised Protocol 02

Section Number & Title	Description of Change	Brief Rationale
Synopsis, Rationale	Updated study aim from ORR and PFS to just PFS.	To correct a discrepancy and to be aligned with the body text of the protocol.
Synopsis, Objectives and Endpoints	Added Phase 2 and Phase 3 safety objectives.	To define safety objectives.
Synopsis, Overall Design	Changing on-study tumor assessments to through Week 52 instead of Week 49.	Clarified timing.
Section 2, Table 2-1: Screening Procedural Outline	Added BRAF, NRAS, and KIT mutation testing.	Added to support sites referencing Table 2-1.
Section 2, Table 2-2: On-Study Assessments	Added procedures for elevated troponin levels. Added timing window for ECG.	Added for sites guidance. Added to bring clarity.
Section 2, Table 2-3: Follow-Up Procedural Outline	Added pregnancy testing for Follow-Up Visits 1 and 2.	Were incorrectly removed in the previous revision.
Section 2, Table 2-3: Follow-Up Procedural Outline	Added PFS2 assessments.	Added to match the additional exploratory objective
Section 2, Table 2-3: Follow-Up Procedural Outline	Removed note regarding survival visit phone follow-up for FACT-M questionnaire.	This scale is not administered during survival follow-up, only Follow-Up Visits 1 and 2.
Section 2, Table 2-3: Follow-Up Procedural Outline	Clarified the FACT-M subscale is the melanoma subscale (MS).	Clarified for sites.
Section 4, Objectives and Endpoints	Moved safety and tolerability objective from exploratory to a separate "Safety" objective for both Phase 2 and Phase 3.	Clarified safety into its own objective.
Section 4, Objectives and Endpoints	Added a Phase 3 exploratory objective to include PFS, PFS2, ORR, and, DOR for combo treatment versus nivolumab monotherapy.	Added additional exploratory objectives of clinical relevance to the melanoma field.

Summary of Key Changes For Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
	Added PFS2 to the Phase 2 exploratory objectives.	
Section 6.2, Exclusion Criteria, 2), e) Section 7.7.1.1 Prohibited Treatments	Added criteria to exclude receiving live/attenuated vaccine with 30 days of study treatment, during treatment, and until 100 days after last dose.	Added to provide better guidance to the sites.
Section 5.1, Overall Design	Changed description of decision point to refer to interim analysis.	Simplified for consistency.
Section 9.1.3, Patient-Reported Outcomes	Clarified timing of the PRO items.	Clarified for sites.
Section 9.1.3.1, EQ-5D-3L	Clarified change from baseline assessment and added reference.	Clarified for sites.
Section 9.4.4, Table 9.4.4-1: Laboratory Assessment Panels	Added option for leukocyte esterase or leukocyte.	Clarified for sites.
Section 9.5.1, Pharmacokinetics: Collection and Processing	Added clarification for sampling if study drug is not administered.	Clarified for sites.
Section 10.2.2, Efficacy Analyses	Moved ORR analysis to above OS. Under Testing Strategy, changed OS to ORR.	Revised.
Section 10.2.3, Safety Analyses	Summarized safety endpoints into one.	Revised.
Section 11, References	Updated citation 21.	Updated for ease of reference.
Section 5.1.1, Data Monitoring Committee and Other External Committees Section 7, Treatment Section 7.3, Blinding Section 8.1, Discontinuation from Study Treatment Section 9.2.2, Method of Detecting AEs and SAEs Section 9.2.5, Pregnancy Section 10.2.5, Interim Analyses	Added clarifying language to bring in line with required language across all BMS protocols.	Additional required language for all BMS protocols.
Appendix 3, Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow Up and Reporting	Updated AE definitions, clarified SAE definitions, revised assessment of causality, and updated reporting requirements.	Added updated required language for AEs.

Summary of Key Changes For Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Appendix 9, Management Algorithms for Immuno-oncology Agents	Updated algorithms to include version date.	Updated per program requirements.
Appendix 10, Mucosal Melanoma Staging	Added new appendix.	To support classification of mucosal melanoma.

Overall Rationale for the Revised Protocol 01, 15-Aug-2018

Change of Endpoints

The primary endpoint for Phase 2 and the interim analysis endpoint were both changed to PFS instead of ORR. The changes were based on simulations performed by resampling data from 1L Melanoma study CA209067 with the assumption that the CA224047 study will perform similar to 067. The simulation results indicated that PFS is the better predictor of final trial success (final Phase 3 PFS p-value < 0.049 with a penalty for the interim analysis) compared to ORR, DCR (disease control rate), or a combination of ORR and DCR.

In addition, minor changes were made to clarify timing of procedures and to improve clarity as noted in the table below.

Summary of Key Changes For Revised Protocol 01

Section Number & Title	Description of Change	Brief Rationale
Section 2, Schedule of Activities Table 2-1: Screening Procedural Outline (CA224047)	• Physical Measurements and Assessments of Signs and Symptoms were updated to note they should be performed within 14 days of randomization.	• Updated to specify timing of procedures.
	• Brain Imaging note was updated.	• Clarified use of MRI with and without contrast as applicable to all participants.
Section 2, Schedule of Activities Table 2-2: On-Study Assessments (CA224047) Table 2-3: Follow-Up Procedural Outline (CA224047)	• Brain Imaging note was updated.	• Clarified use of MRI with and without contrast as applicable to all participants as well as updated timing of procedure.
	• Troponin note was update to include predose timing.	• Updated to specify timing of procedure.
Section 2, Schedule of Activities Table 2-3: Follow-Up Procedural Outline (CA224047)	• Pregnancy Testing was removed.	• No longer required during follow-up.
	• Brain Imaging note was updated.	• Clarified use of MRI with and without contrast as applicable to all participants as well as updated timing of procedure.
	• PK and Immunogenicity blood sample timing was adjust from Survival Follow-Up to Follow-Up Visits 1 and 2.	• Samples corrected to correspond with in-clinic visits.
	• FACT-M Subscale was added to Survival Follow-Up Visit.	• Added to collect more detailed outcomes data.
	• Added "Biomarker Assessments" to Tumor Tissue Biopsy.	• Added for clarity.
Section 3.1.1, Research Hypothesis	• Updated endpoints from ORR to PFS.	• PFS is the better predictor of final trial success

Summary of Key Changes For Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 4, Objectives and Endpoints Phase 3 Tertiary/Exploratory Objective	• Added parameters for LAG-3 expressions (≥ 1% expression versus < 1% expression) and PDL01 status (≥ 1% tumor cell surface expression versus < 1% tumor cell surface expression) • Revised Endpoints language throughout for clarity.	Added/revised for clarity.
Section 4, Objectives and Endpoints Phase 2 Primary Objective	• Updated endpoints from ORR to PFS and updated endpoints to PFS.	• PFS is the better predictor of final trial success
Section 4, Objectives and Endpoints Phase 2 Secondary Objectives	• Added parameters for LAG-3 expressions (≥ 1% expression versus < 1% expression) and PDL01 status (≥ 1% tumor cell surface expression versus < 1% tumor cell surface expression) throughout • Revised Endpoints language throughout for clarity.	Added/revised for clarity.
Section 4, Objectives and Endpoints Phase 2 Secondary Objectives	• Added parameters for LAG-3 expressions (≥ 1% expression versus < 1% expression) and PDL01 status (≥ 1% tumor cell surface expression versus < 1% tumor cell surface expression) throughout • Revised Endpoints language throughout for clarity. • Combined receptor occupancy objective with exposure-response objective. • Removed tumor growth dynamic survival model objective.	Added/revised for clarity.
Section 5.1, Overall Design Figure 5.1-1: Study Design Schematic	• Removed line indicating split of Phase 2 population into interim and post-interim review populations. • Updated footnotes b and c for adolescent weight lower-bound • Added footnote d to Phase 3 population.	• No longer needed. • Weight was previous > 40 kg, should be ≥ 40 kg. • Footnote clarifies that the total population combines Phase 2 participants with additional Phase 3 participants.

Summary of Key Changes For Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.1, Overall Design	• Updated tumor assessments from Week 49 to 52.	• Updated to specify timing of procedures.
Section 5.2, Number of Participants Section 5.3, End of Study Definition Section 7.3, Blinding	• Updated interim analysis to include all 400 participants from Phase 2 and clarified results of the interim analysis.	• Clarified procedures based on interim analysis results.
Section 5.4.2, Rationale for Blinding	• Updated endpoints from ORR to PFS and updated endpoints to PFS.	• PFS is the better predictor of final trial success
Section 6.1, Inclusion Criteria 2), c), (3)	• Added additional prior adjuvant or neoadjuvant therapy parameters for BRAF- or MEK-inhibitor-containing regimens with at least 6 months between the last dose and date of recurrence	• Adds clarification for possible other therapies.
Section 6.1, Inclusion Criteria 3), f)	• Removed statement exempting azoospermic males from contraceptive requirements.	• Azoospermic males are not exempt.
Section 6.2, Exclusion Criteria, 1), a)	• Changed MRI progression timing from 8 weeks to 4. • Added participants with brain disease treated with whole brain radiation are ineligible.	• Updated timing. • Excludes participants with whole brain radiation treatment.
Section 6.2, Exclusion Criteria, 1), b)	• Change ocular melanoma to uveal melanoma.	• Changed for better specificity.
Section 6.2, Exclusion Criteria, 3), h)	• Revised troponin criteria language.	• Changed to simplify testing procedure.
Section 7.1, Treatments Administered	• Added language to regarding weight-based dosing adjustments.	• Added for additional clarity on dosing.
Section 7.4.2, Dose Delay Criteria	• Removed language regarding dose delays due to extenuating circumstances	• Added to simply procedures.
Section 7.4.3, Criteria to Resume Treatment	• Added ≥ Grade 3 qualifier for adrenal insufficiency.	• Added for more specificity.
Section 7.4.4 Management Algorithms for Immuno-Oncology Agents Appendix 9	• Added myocarditis.	• Added for additional management information.
Section 7.7.1.2, Restricted Treatments	• Removed entire section.	• No longer allow for corticosteroid exception.

Summary of Key Changes For Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 7.7.2.2, Surgical Resection Following Initial Response	• Updated timing from Week 21 to Week 20.	• Corrected per study visits.
Section 9.1, Efficacy Assessments	• Updated brain imaging requirements and timing.	• Updated for clarity and timing.
Section 9.4.4, Clinical Safety Laboratory Assessments Table 9.4.4-1: Laboratory Assessment Panel	• Removed direct bilirubin and HPV status.	• Not needed.
Section 9.5.2, Pharmacokinetic Sample Analysis	• Added language clarifying blinded analyses.	• Added for clarity.
Section 9.5.3, Immunogenicity	• Moved up to be included in PK section.	• Moved for better placement in document.
Section 9.8.1.3, T-Cell Repertoire Analysis Section 9.8.1.4, Whole Blood for Germline DNA Section 9.8.1.5, Circulating Tumor DNA Analysis (Plasma) Biomarkers Section 9.8.2.3, Characterization of T-Cell Repertoire	• Clarified procedures.	• Updated for clarity.
Section 9.8.2.1, LAG-3 and PD-L1 Expression	• Updated to add PD-L1	• Added for clarity.
Section 9.8.2.6, Tumor Sample Collection Details	• Removed details regarding fresh biopsy.	• Removed to provide more flexibility for sites.
Section 9.8.2.6, Tumor Sample Collection Details Table 9.8.2.6-1: CA224047 Biomarker Sampling Schedule (All subjects)	• Removed footnote b.	• Biomarker samples are not optional.
Section 10.1, Sample Size Determination Section 10.2.2, Efficacy Analyses	• Updated endpoints and analyses from ORR to PFS.	• PFS is the better predictor of final trial success
Section 10.2.5, Interim Analysis	• Updated interim analysis to include all 400 participants from Phase 2 and clarified results of the interim analysis.	• Clarified procedures based on interim analysis results.

Summary of Key Changes For Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Appendix 4, Women of Childbearing Potential Definitions and Methods of Contraception	• Removed "hormonal methods of contraception including oral contraceptive pills containing a combination of estrogen and progesterone, vaginal ring, injectables, implants hormonal methods of contraception from "User Independent" category.	• Such methods are not user independent.
Appendix 8, Country Specific Requirements	• Removed France, Italy, and Spain.	• Requirements do not apply in those countries.
Appendix 9, Management Algorithms for Immuno-Oncology Agents	• Updated all algorithms with current data. • Added myocarditis algorithm	• Updated for current requirements. • Added for additional requirements.
NCI CTCAE	• Updated from version 4.0 to 5.0	• Updated throughout.
All	Minor formatting and typographical corrections	Minor, therefore have not been summarized