Official Title of Study:

A Randomized, Open-Label, Phase 2 Study of Nivolumab in Combination with Ipilimumab or Nivolumab Monotherapy in Participants with Advanced or Metastatic Solid Tumors of High Tumor Mutational Burden (TMB-H)

(CheckMate 848: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 848)

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Clinical Protocol CA209848

A Randomized, Open-Label, Phase 2 Study of Nivolumab in Combination with Ipilimumab or Nivolumab Monotherapy in Participants with Advanced or Metastatic Solid Tumors of High Tumor Mutational Burden (TMB-H)

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Protocol Amendment 04
Incorporates Administrative Letters 04, 05, 06, and 07

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DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Protocol Amendment 04	04-May-2021	Clarified statistical analysis populations for blood tumor mutational burden (bTMB) final analysis, tissue tumor mutational burden (tTMB) interim analysis, and tTMB final analysis. Updates made to align with current nivolumab Investigator Brochure (IB) and Bristol-Myers Squibb Company (BMS) guidelines for protocols with nivolumab using Common Terminology Criteria for Adverse Events (CTCAE) v5. Updates made to treatment management algorithms for immuno-oncology agents. Added safety reporting and dose modification related to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Incorporated Administrative Letters 04, 05, 06, and 07. Note: After Administrative Letter 07, Medical Monitor/Clinical Trial Physician responsibility transitioned from [redacted], to [redacted]. Since Protocol Amendment 04 was in development, the personnel update was not communicated in an administrative letter. This responsibility has now transitioned to [redacted].
Administrative Letter 07	28-Jul-2020	The purpose of this administrative letter is to advise of a change in study personnel and update aligning with the BMS Medical Contacts or designee referenced.
Administrative Letter 06	18-Jun-2020	The purpose of this administrative letter is to advise of a change in study personnel and title update aligning with the BMS Medical Contacts or designee referenced.
Administrative Letter 05	11-Mar-2020	The purpose of this administrative letter is to advise of a change in study personnel and title updates.
Administrative Letter 04	08-Jan-2020	This letter serves to clarify and correct the Study Design Schematic of Revised Protocol 03. In the section referencing the Study Design Schematic, Synopsis, Figure 2.1 and Section 5.1, Figure 5.1-1 (Overall Design) the sample size is referenced incorrectly as n = 159. As part of Revised Protocol 03, the number of randomized participants was updated to range from approximately 183 to 342 however was inadvertently not updated in the Study Design Schematic therefore this should be updated to n = 183.
Revised Protocol 03	14-Aug-2019	Provided clarification that pre-screening requirements on tTMB and bTMB results should be ≥ 10 mut/Mb (tTMB ≥ 10 mut or the new cutoff value of bTMB determined by the 1st interim analysis). Clarified that Belgium and the Netherlands will not enroll adolescent participants and therefore all content related to pediatric/adolescents is not applicable for sites in those countries. Added Section 3.2.5 on Nivolumab Clinical Pharmacology to Background Updated the range of participants and further clarified statistical analyses and sample size determination. Added standard language regarding use of CT component of a PET-CT scanner. Clarified biomarker tissue collection to occur during pre-screening. Also included updates per Administrative Letter 02, update to study personnel Medical Monitor and Study Director, and Administrative Letter 03, clarified and corrected a typo in Exclusion Criteria (Section 6.2).

Document	Date of Issue	Summary of Change
		Made minor editorial and grammatical corrections throughout.
Administrative Letter 03	29-May-2019	This letter serves to clarify and correct a typo in the Exclusion Criteria of Revised Protocol 02. In the section referencing Exclusion Criteria (Section 6.2), Physical and Laboratory Test Findings, (bullet number 3) regarding the calculated creatinine clearance reflecting the normal range. This exclusion criteria is intended to exclude patients with significant renal function impairment as indicated by elevated serum creatinine unless creatinine clearance is greater than the specified values for adults and adolescents, respectively.
Administrative Letter 02	07-Mar-2019	The purpose of this administrative letter is to advise of a change in study personnel.
Revised Protocol 02	11-Dec-2018	Incorporates feedback received from FDA on the study design of CA209-848 and Administrative Letter 01.
Administrative Letter 01	10-Jul-2018	Notification that a new IND number (140,266, for tissue agnostic, pan tumor in TMB-H population) will be used for CA209-848 protocol.
Revised Protocol 01	18-May-2018	This protocol is listed a “Revised protocol 1” to remain Title 21 CFR Part 11 compliant (FDA regulations on electronic records and electronic signatures). The initial protocol CA209848 was never activated as initially written. The study was fully revised and, therefore, there are no summary of changes to compare to the initial protocol.
Original Protocol	13-Oct-2016	Not applicable

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 04:

This amendment incorporates clarifications concerning the analysis populations used for the blood tumor mutational burden (bTMB) and tissue tumor mutational burden (tTMB) cohorts and the type of analysis (interim or final primary) being performed. Enrollment into the bTMB high population was closed in Dec-2019, as the required number of participants needed for final analysis was met. Enrollment into the tTMB high population remained ongoing to complete enrollment for this participant population. Because of the varying enrollment rates, the bTMB final analysis will coincide with the tTMB interim efficacy analysis, leading to the need for clarification of the primary analysis populations for both analyses. Both of these analyses will take place after study-wide randomization has completed.

- The final analysis population for the primary endpoint (overall response rate [ORR] based on blinded independent central review [BICR] assessments) for the bTMB high population will be all participants in the salvage setting randomized before the study closed enrollment to this cohort in Dec-2019; the database cutoff (last patient last visit [LPLV]) for the analysis will be at least 12 months after last patient first treatment and after completion of study-wide randomization.
- The primary analysis population for the tTMB interim analysis (ORR based on BICR assessments) is limited to tTMB high participants in the salvage setting randomized at least 12 months prior to the LPLV for the analysis to allow sufficient time to demonstrate durability of response. Study-wide randomization will complete prior to the LPLV for the analysis.
- The final analysis of the primary endpoint (ORR based on BICR assessments) for the tTMB high population in the salvage setting will be performed at least 12 months after all tTMB high participants have been randomized.

Protocol Amendment 04 incorporates changes per previous Administrative Letters 04, 05, 06, and 07, and updates to align with current Bristol Myers Squibb Company (BMS) guidelines for nivolumab studies (including current nivolumab Investigator Brochure [IB] version 19, addendum version 1) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) guidance.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 04

Section Number & Title	Description of Change	Brief Rationale
Synopsis: Data Monitoring Committee; Section 5.1.1.1: Data Monitoring Committee	Added data monitoring committee (DMC) review of the bTMB final analysis results.	The bTMB final analysis will coincide with the tTMB interim analysis, so it was decided to have the DMC review both results.
Synopsis: Figure 2: Study Design Schematic; Section 5.1: Overall Design; Figure 5.1-1: Study Design Schematic	Corrected the number of potential randomized study participants.	As part of Revised Protocol 03, the number of randomized participants was updated to approximately 183 to 342, but the Study Design Schematic had not previously been updated to reflect this change.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Synopsis: Key Inclusion Criteria	Added '(salvage setting)' to criterion 1a.	Clarified that the eligible participant disease characteristics described in Inclusion Criterion 1a (updated in Revised Protocol 02 dated 11-Dec-2018) represent salvage setting characteristics. No change to the actual criterion for eligibility.
Section 2: Schedule of Activities Tables 2-1, 2-2, 2-3, 2-4, and 2-5	Added collection of all serious adverse events (SAEs) and non-serious adverse events (AEs) associated with SARSCoV-2 infection.	Aligned with current BMS guidelines for protocol updates concerning SARS-CoV-2.
Section 2: Schedule of Activities Table 2-1; Section 5.1: Overall Design; Section 6.1: Inclusion Criteria 2c	Added "validated CLIA" to instances of acceptable bTMB results	Clarification that the Foundation Medicine bTMB assay is validated by Clinical Laboratory Improvement Amendments (CLIA).
Section 5.4.5: Rationale for Two Year Duration of Treatment	Deleted prior references to Keynote-010 and Keynote-006.	Aligned with current BMS guidelines for protocols with nivolumab, in which outdated background information on analyses of pembrolizumab progression rates has been removed.
Section 5.5.4: Clinical Pharmacology Summary	Updated current nivolumab pharmacokinetic (PK) parameters to include more details of nivolumab clearance in nivolumab monotherapy and nivolumab plus ipilimumab therapy and in specific populations, among which are those with renal/hepatic impairment.	Nivolumab clinical PK assessed using a population PK approach; updated to align with the current nivolumab IB.
Section 5.5.5: Rationale for 30-minute Infusion	Added current approval status for a 30-minute infusion for nivolumab, either as monotherapy or in combination, and for ipilimumab when combined with nivolumab.	Aligned with current United States prescribing information (USPI) for nivolumab and current USPI for ipilimumab
Section 6.1: Inclusion Criteria 2) Type of Participant and Target Disease Characteristics 3) Age and Reproductive Status; Appendix 4: Women of Childbearing	Added "(salvage setting)" to Criterion 2a. Removed male contraception language. Inclusion Criterion 3e is no longer applicable. In Appendix 4, the guidance for male participants is now designated as Not Applicable.	Clarified that the eligible participant disease characteristics described in Inclusion Criterion 2a (updated in Revised Protocol 02 dated 11-Dec-2018) represent salvage setting characteristics. There was no change to the actual criterion for eligibility. Aligned with the current nivolumab IB and BMS guidelines for

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Potential Definitions and Methods of Contraception; Appendix 4: Contraception Guidance for Male Participants with Partner(s) of Child Bearing Potential		protocols with nivolumab, which reflect the lack of nivolumab genotoxicity and no transmission of biologically relevant amounts to women of childbearing potential (WOCBP) partners.
Section 7.1.1: Arm A or Arm B Rollover – Nivolumab in Combination with Ipilimumab; Section 7.1.2: Arm B – Nivolumab Monotherapy	Added "approximately" to references of 30-minute intravenous infusions. Added optional instructions to flush the intravenous line with an appropriate amount of diluent.	Aligned with current BMS guidelines for protocols with nivolumab.
Section 7.4.1: Dose Delay Criteria	Updated to align with CTCAE v5 grading, and added new terms (ie, Guillain-Barre, myasthenia gravis, hypophysitis/hypopituitarism). Updated text to tabular format (Table 7.4.1-1) and included criteria to resume and/or discontinue treatment. Added instruction to delay dosing in participants with SARS-CoV-2 infection.	Aligned with current nivolumab IB and BMS guidelines for protocols with nivolumab using CTCAE v5 for safety assessments; changed to tabular format for greater ease of use. Aligned with current BMS guidelines for protocol updates concerning SARS-CoV-2.
Section 7.4.2: Criteria to Resume Treatment	Updated and moved criteria to resume treatment following specific AEs to Table 7.4.1-1. Clarified that participants may resume study treatment following steroid taper for AE management. Added criteria to resume treatment following SARS-CoV-2 infection.	Aligned with current nivolumab IB and BMS guidelines for protocols with nivolumab. Aligned with current BMS guidelines for protocol updates concerning SARS-CoV-2.
Section 7.4.4: Treatment of Nivolumab- and Ipilimumab-Related Infusion Reactions	Made minor updates to treatment guidelines.	Aligned with current BMS guidelines for protocols with nivolumab.
Section 7.4.5: Management Algorithms for Immuno-oncology Agents	Made minor updates to language referencing the management algorithms for immuno-oncology agents in Appendix 5.	Aligned with current BMS guidelines for protocols with nivolumab.
Section 7.7.1: Concomitant Therapy, Prohibited and/or Restricted Treatments; Section 7.7.2: Permitted Therapy	Made minor updates to prohibited therapies per nivolumab program updates. Added restrictions on administration of live (prohibited) or not live (permitted) SARS-CoV-2 vaccines.	Aligned with current BMS guidelines for protocols with nivolumab. Aligned with current BMS guidelines for protocol updates concerning SARS-CoV-2.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 8.1: Discontinuation from Study Treatment; Section 8.1.1: Dose Discontinuation in Nivolumab and Ipilimumab Combination; Section 8.1.2: Dose Discontinuation in Nivolumab Monotherapy Arm	Updated and moved criteria to discontinue treatment following specific AEs to Table 7.4.1-1.	Aligned with current nivolumab IB and BMS guidelines for protocols with nivolumab using CTCAE v5 for safety assessments.
Section 9: Study Assessments and Procedures	Updated to include recommendations for potential cardiac or pulmonary toxicity.	Aligned with current nivolumab IB and BMS guidelines for protocols with nivolumab.
Section 9.2.1: Time Period and Frequency for Collecting AE and SAE Information; Section 9.2.3: Follow-up of AEs and SAEs	Added instruction for collection and follow-up of SAEs and non-serious AEs associated with SARS-CoV-2 infection.	Aligned with current BMS guidelines for protocol updates concerning SARS-CoV-2.
Section 9.2.5: Pregnancy	Removed instruction for reporting of pregnancy occurring in a female partner of a male study participant.	Aligned with current nivolumab IB and essential protocol elements, which reflect the lack of nivolumab genotoxicity and no transmission of biologically relevant amount to WOCBP partners.
Section 9.5: Pharmacokinetics, Table 9.5-1: Pharmacokinetic and Immunogenicity Sampling Schedule – Arm A or Arm B Rollover – Nivolumab in Combination with Ipilimumab; Table 9.5-2: Pharmacokinetic and Immunogenicity Sampling Schedule Arm B – Nivolumab Monotherapy	Clarified site of blood draw and proper documentation of sample collection and the evaluation of samples for development of anti-drug antibody. Revised footnote b to clarify end of infusion-PK sampling.	Aligned with current BMS guidelines for protocols with nivolumab.
Section 9.10: Patient-Reported Outcomes	Revised text to clarify that alternate administration modalities may be used if necessary.	Aligned with current BMS guidelines for protocol updates concerning SARS-CoV-2.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 10: Statistical Considerations	Added "in the salvage setting" to descriptions of the primary analysis populations. Added "and study randomization is completed" to timing of the analyses.	Clarified that the primary analysis populations include salvage setting participants per inclusion criteria updated in Revised Protocol 02 dated 11-Dec-2018. Clarification that the tTMB interim analysis and bTMB and tTMB final analyses will take place after study randomization is completed.
Section 10.1: Sample Size Determination; Section 10.2: Populations for Analyses	Revised text to clarify that only participants in the bTMB high population enrolled prior to the closure of the bTMB high group will be included in the final primary bTMB efficacy analysis population. Added Table 10.2-1.	Enrollment into the bTMB high population was closed in Dec-2019; the primary bTMB efficacy analysis population will include all participants randomized into this group prior to its closure. Table 10.2-1 clarifies the primary analysis populations and timing of the analyses.
Section 10.3.6: Interim Analyses	Revised text to clarify that the primary analysis population for the tTMB interim efficacy analysis will be limited to study participants in the tTMB high population who were randomized at least 12 months prior to the LPLV for the analysis.	In order to achieve the necessary number of study participants in the tTMB high population for the tTMB primary endpoint final analysis, enrollment into this population continued after the date on which criteria were met for the tTMB interim analysis. The primary analysis population for the interim analysis will therefore consist of all tTMB high participants randomized at least 12 months prior to the LPLV for the analysis.
Section 11: References	Removed references to KEYNOTE-010 and KEYNOTE-006 per Section 5.4.5 update. Added references for current nivolumab USPI and current ipilimumab USPI.	Aligned with current BMS guidelines for protocols with nivolumab.
Section 12: Appendix 1: Abbreviations and Trademarks	Added abbreviations.	Aligned with updated text within the protocol body.
Section 12: Appendix 2: Study Governance Considerations: Monitoring	Added flexible language to allow for remote monitoring.	Aligned with current BMS guidelines for protocol updates concerning SARS-CoV-2.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 12: Appendix 5: Management Algorithms for Studies Under CTCAE Version 5.0	Updated treatment management algorithms for immuno-oncology agents.	Aligned with current nivolumab IB and BMS guidelines for protocols with nivolumab using CTCAE v5 for safety assessments.
All	Made minor formatting and typographical corrections.	These changes are minor and therefore have not been summarized.

TABLE OF CONTENTS

1 SYNOPSIS

Protocol Title: A Randomized, Open-Label, Phase 2 Study of Nivolumab in Combination with Ipilimumab or Nivolumab Monotherapy in Participants with Advanced or Metastatic Solid Tumors of High Tumor Mutational Burden (TMB-H)

(CheckMate 848: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 848)

Study Phase: 2

Rationale: Blockade of the PD-1 pathway has proven effective in generating robust anti-tumor immune responses. Nivolumab, an anti-PD-1 blocking antibody, has demonstrated overall survival benefit in multiple tumors including non-squamous cell lung cancer, squamous cell lung cancer, melanoma, renal cell carcinoma and head and neck cancer. Recent data across multiple tumor types support the hypothesis that patients with tumors harboring increased somatic mutations due to DNA mismatch-repair deficiencies are more likely to respond to anti-PD-1/PD-L1 and anti-CTLA-4 blockade. Tumor mutational burden (TMB) refers to the total number of somatic mutations that exist within a tumor's genome. A subset of these mutations may result in expressed proteins that are not recognized by the host's immune system as self, and therefore has the potential to be immunogenic and more susceptible to an immune-mediated anti-tumor response. The primary goal of this study is to demonstrate the clinical activity of nivolumab in combination with ipilimumab in multiple tumor types based on the status of TMB.

Tumors with a high mutational burden may have a higher number of neo-antigens which, in principle, would be expected to be more immunogenic than tumors with comparatively low mutational burden.[1] Therefore, high TMB has been hypothesized to correlate with improved efficacy in patients treated with immune-oncology (IO) therapies. This hypothesis has been supported by multiple publications across IO therapies, tumor types, and lines of treatment.

The available data suggest that, in addition to PD-L1, TMB is also an important predictive biomarker of the clinical efficacy of IO therapy. Therefore, patients of TMB-H across multiple solid tumors will be selected for participation in this clinical study

Study Population:

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

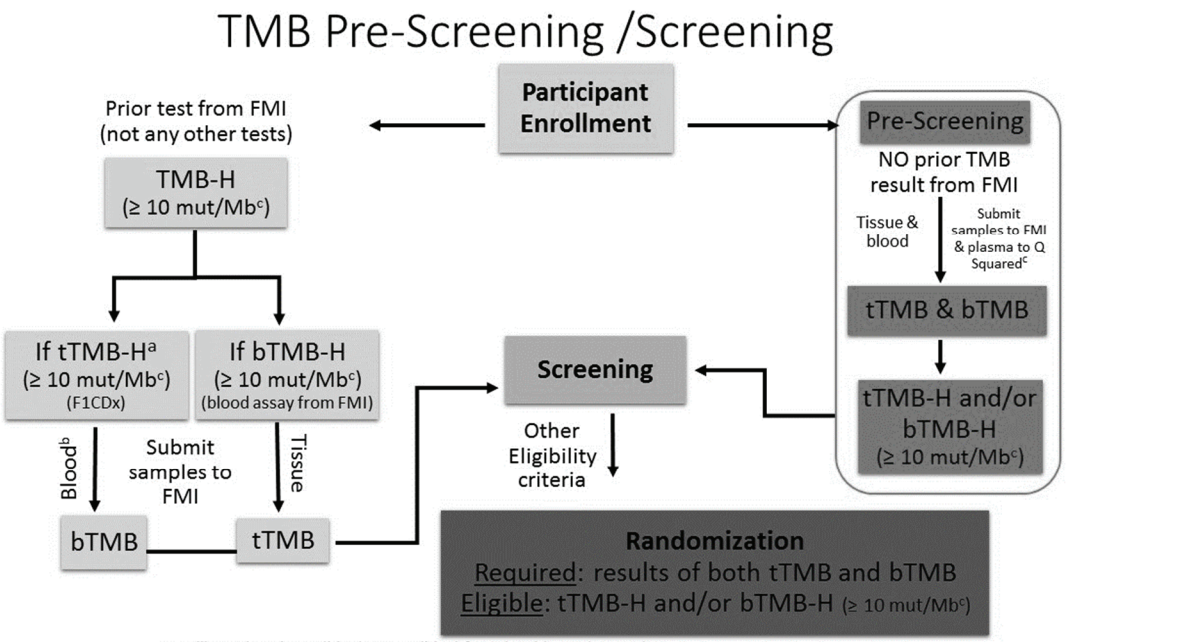
Key Inclusion Criteria (See protocol Section 6.1 for full list of criteria)

1) Type of Participant and Target Disease Characteristics

a) Participants with a refractory, metastatic, or unresectable histologically or cytologically confirmed solid malignant tumor with TMB-H who are refractory to standard local therapies per local management guidelines, or for which no standard treatment per local management guidelines is available (salvage setting).

b) The IRT must be provided with the results of both tissue and blood TMB-H testing for eligible participants prior to randomization. Both results are utilized for stratification purposes (see Figure 1).

Figure 1-1: TMB Pre-Screening/Screening



i) Participants must have either tTMB or bTMB ≥ 10 mut/Mb (tTMB ≥ 10 mut or the new cutoff value of bTMB determined by the 1st interim analysis)

ii) Prior results of TMB-H obtained with F1CDx assay (tissue) or bTMB-validated CLIA assay from Foundation Medicine (blood) are acceptable for eligibility purposes.

(1) If tTMB result is available, blood sample must be provided for central TMB testing

(2) If bTMB result is available, tissue sample must be provided for central TMB testing

(3) If neither tTMB nor bTMB result is available, both tissue and blood samples must be provided for central TMB testing

iii) TMB results obtained from any other assays are not acceptable for eligibility.

c) Participants must have measurable disease for response assessment as per RECIST 1.1 for solid tumors other than CNS, and RANO criteria for primary CNS malignancies.

2) Age and Reproductive Status

a) Males and Females, ages of 12 years and older. Sites in Belgium and the Netherlands will not include adolescents and only enroll participants 18 years or older.

Exclusion Criteria (See protocol Section 6.2 for full list of criteria)

3) Prior/Concomitant Therapy

a) Participants who received prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To estimate BICR-assessed objective response rate (ORR) in participants of tTMB-H treated with nivolumab combined with ipilimumab	• BICR-assessed ORR using RECIST 1.1, and Response Assessment for Neuro-Oncology (RANO) criteria in primary CNS tumors
• To estimate BICR-assessed ORR in participants of bTMB-H treated with nivolumab combined with ipilimumab	• BICR-assessed ORR using RECIST 1.1, and RANO criteria in primary CNS tumors
Secondary	
• To estimate the BICR-assessed duration of response (DOR) and time to response (TTR) in participants of tTMB-H treated with nivolumab combined with ipilimumab	• BICR-assessed DOR • BICR-assessed TTR
• To estimate the BICR-assessed DOR and TTR in participants of bTMB-H treated with nivolumab combined with ipilimumab	• BICR-assessed DOR • BICR-assessed TTR
• To evaluate the BICR-assessed ORR, DOR and TTR in participants of tTMB-H treated with nivolumab monotherapy	• BICR-assessed ORR • BICR-assessed DOR • BICR-assessed TTR
• To evaluate the BICR-assessed ORR, DOR and TTR in participants of bTMB-H treated with nivolumab monotherapy	• BICR-assessed ORR • BICR-assessed DOR • BICR-assessed TTR
• To evaluate Investigator-assessed ORR, DOR, TTR in participants of tTMB-H treated with nivolumab combined with ipilimumab and nivolumab monotherapy	• Investigator-assessed ORR • Investigator-assessed DOR • Investigator-assessed TTR
• To evaluate Investigator-assessed ORR, DOR, TTR in participants of bTMB-H treated with nivolumab combined with ipilimumab and nivolumab monotherapy	• Investigator-assessed ORR • Investigator-assessed DOR • Investigator-assessed TTR
• To evaluate BICR-assessed and investigator-assessed clinical benefit rate (CBR) in participants of tTMB-H treated with nivolumab combined with ipilimumab and nivolumab monotherapy	• BICR-assessed CBR • Investigator-assessed CBR
• To evaluate BICR-assessed and investigator-assessed CBR in participants of bTMB-H treated with nivolumab combined with ipilimumab and nivolumab monotherapy	• BICR-assessed CBR • Investigator-assessed CBR
• To evaluate BICR-assessed and investigator-assessed progression free survival (PFS) in participants of tTMB-H treated with nivolumab combined with ipilimumab and nivolumab monotherapy	• BICR-assessed PFS • Investigator-assessed PFS
• To evaluate BICR-assessed and investigator-assessed PFS in participants of bTMB-H treated with nivolumab combined with ipilimumab and nivolumab monotherapy	• BICR-assessed PFS • Investigator-assessed PFS
• To evaluate overall survival (OS) in participants of tTMB-H treated with nivolumab combined with ipilimumab and nivolumab monotherapy	• Overall survival

Objectives	Endpoints
• To evaluate OS in participants of bTMB-H treated with nivolumab combined with ipilimumab and nivolumab monotherapy	• Overall survival
• To assess overall safety and tolerability	• AEs, clinical laboratory values, or other safety biomarkers
Exploratory	
• To assess overall health status and health utility	• Mean change from baseline in the 3-level version of the EQ-5D (EQ-5D-3L) visual analog scale (VAS) and utility index, respectively
• To assess cancer-related symptoms and quality of life	• Mean change from baseline in domains and symptoms in the 30-item European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30).
• To characterize the pharmacokinetics of nivolumab/ipilimumab and explore exposure-response relationships with respect to safety and efficacy	• Population pharmacokinetic parameters
• To assess immunogenicity of nivolumab/ipilimumab	• Incidence of anti-nivolumab/anti-ipilimumab antibodies
• To characterize tumor and host biomarkers	• Analysis of genomic, molecular, and immunohistochemical profiles
• To assess OS and BICR-assessed and investigator-assessed ORR, DOR, PFS in all participants of TMB-H treated with nivolumab combined with ipilimumab and nivolumab monotherapy	• OS • BICR-assessed ORR • BICR-assessed DOR • BICR-assessed PFS • Investigator-assessed ORR • Investigator-assessed DOR • Investigator-assessed PFS

Overall Design:

The study will enroll participants diagnosed with select advanced or metastatic solid tumors with either tissue (tTMB) or blood TMB (bTMB) ≥ 10 mut/Mb (TMB-H). Both tissue and blood TMB will be assessed prior to randomization.

Participants without a prior known tTMB-H status available via F1CDx assay, or a prior known bTMB-validated CLIA result available from Foundation Medicine, will provide consent for pre-screening and TMB status determination, but consent for further screening procedures and study treatment should be deferred until TMB-H status is established. Screening process can continue when the participant's status is TMB-H.

Participants with a prior known result of **tTMB-H via F1CDx assay** or **bTMB-H from Foundation Medicine** may proceed immediately with full screening procedures. Both tissue and blood TMB will be assessed prior to randomization. Prior results of tTMB or bTMB obtained from

any other assays except the ones described above are not acceptable, including prior result of tTMB obtained via Foundation One assay.

Once the TMB-H status is determined, this study will consist of three phases: screening, treatment, and follow-up.

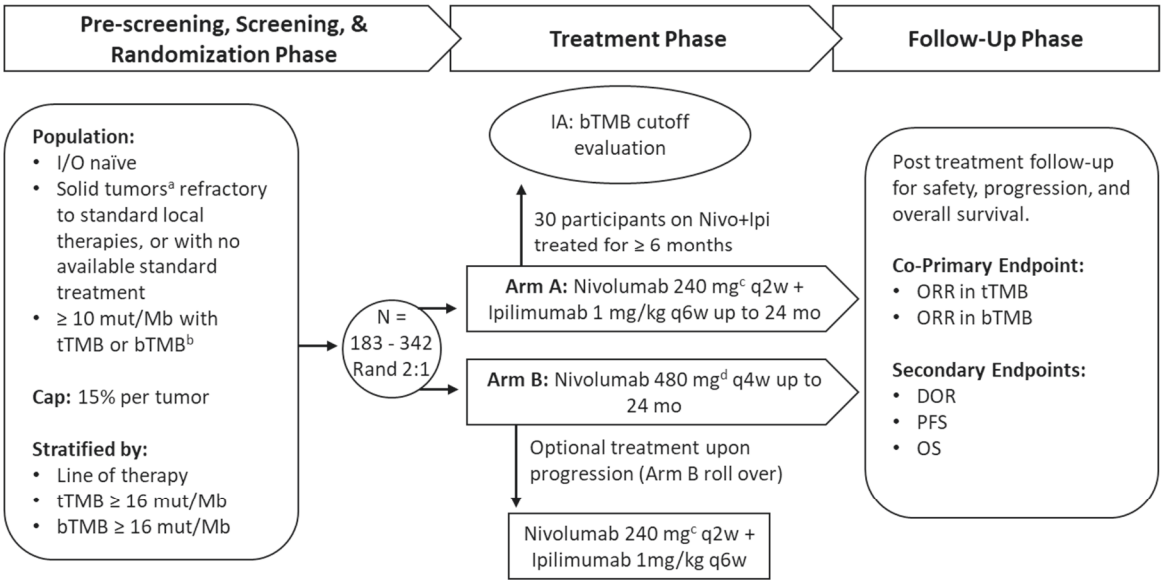
Efficacy will be evaluated using tumor specific response criteria, ie, RECIST 1.1 for solid tumors[2] and RANO criteria[3] for primary CNS tumors.

The primary analysis of BICR-assessed ORR in participants with either bTMB-H or tTMB-H will be conducted after a minimum of 12 months following LPFT. This study will end when analysis of the primary endpoint is complete. Additional survival analysis may be conducted for up to 5 years beyond the primary endpoint analysis.

Details regarding the assessments to be performed during these phases are outlined in Section 2 Schedule of Activities.

The study design schematic is presented below:

Figure 1-2: Study Design Schematic



[a] Excluding melanoma, NSCLC, RCC, and hematological malignancies.
[b] Both tTMB and bTMB results are required for randomization. tTMB ≥ 10 mut/Mb or the new cutoff value of bTMB determined by the 1st interim analysis (See Section 10.1 for further details on sample size).
[c] 3 mg/kg for adolescents with body weight < 40 kg.
[d] 6 mg/kg for adolescents with body weight < 40 kg.

Note: Mention of adolescents is not applicable for sites in Belgium or the Netherlands as adolescent participants will not be included in these countries.

Physical examinations, vital sign measurements, outcome questionnaires, biomarker collection, and clinical laboratory evaluations will be performed at selected times throughout study

participation. Participants will be closely monitored for AEs throughout the study. Blood samples will be collected for safety, pharmacokinetic (PK) and biomarker analysis.

Participants with progressive disease while on treatment with nivolumab monotherapy may be allowed to be treated beyond progression with nivolumab and ipilimumab (Arm B rollover – see Section 7.4.3).

Number of Participants:

The number of randomized participants will range from approximately 183 to 342 based on 1) the actually observed concordance between tTMB-H and bTMB-H, and 2) the new bTMB cutoff determined by the interim analysis should it occur. The per tumor type cap is approximately 15% of the total sample size.

A total of 76 TMB-evaluable subjects in the salvage setting treated with nivolumab + ipilimumab are required for each of the tTMB and bTMB populations. The sample size determination was not based on power consideration, but to provide precision on the estimation of ORR and DOR for TMB-high participants treated with nivolumab + ipilimumab. The following table summarizes the exact 95% CIs for a sample size of 76 in the nivolumab + ipilimumab arm when observed ORRs range from 25%-50%.

Sample size	Number of responses	Response rate	95% Confidence interval
76	19	0.25	(0.16, 0.36)
76	22	0.29	(0.19, 0.40)
76	24	0.32	(0.21, 0.43)
76	26	0.34	(0.24, 0.46)
76	28	0.37	(0.26, 0.49)
76	30	0.39	(0.28, 0.51)
76	32	0.42	(0.31, 0.54)
76	34	0.45	(0.33, 0.57)
76	36	0.47	(0.36, 0.59)
76	38	0.50	(0.38, 0.62)

Treatment Arms and Duration:

Study treatment:

Study Drugs for CA209848		
Medication	**Potency**	**IMP/ Non-IMP**
Nivolumab (BMS-936558-01) Solution for Injection	100 mg (10 mg/mL) and 40 mg (10 mg/mL)	IMP

Study Drugs for CA209848		
Medication	**Potency**	**IMP/ Non-IMP**
Ipilimumab (BMS-734016) Solution for Injection	200 mg (5 mg/mL)	IMP

Treatments Administered

The selection and timing of dose for each participant is as follows:

Selection and Timing of Dose

Treatment Arm	Study Treatment	Participant Age/Weight	Unit dose strength(s)/ Dosage level(s)	Frequency of Administration	Route of Administration
Arm A or Arm B rollover: nivolumab in combination with ipilimumab	Nivolumab	Adults and adolescents ≥ 40kg	240 mg	Q2 weeks up to 24 months	IV
		Adolescents < 40kg	3 mg/kg	Q2 weeks up to 24 months	IV
	Ipilimumab	All participants	1 mg/kg	Q6 weeks up to 24 months	IV
Arm B: nivolumab monotherapy	Nivolumab	Adults and adolescents ≥ 40kg	480 mg	Q4 weeks up to 24 months	IV
		Adolescents < 40kg	6 mg/kg	Q4 weeks up to 24 months	IV

Note: Mention of adolescents is not applicable for sites in Belgium or the Netherlands as adolescent participants will not be included in these countries.

Data Monitoring Committee: Yes

To provide independent oversight of safety, efficacy, and study conduct, a data monitoring committee (DMC) will be instituted. The DMC will meet regularly to ensure that participant safety is carefully monitored. The DMC will convene additional ad hoc meetings if necessary. Following each meeting, the DMC will recommend continuation, modification, or discontinuation of the study based on observed toxicities. The DMC will review the interim analysis results and determine whether the cut-off value for bTMB should be adjusted for the first interim analysis and whether criteria for superiority are met at that time for the tTMB interim analysis; the DMC will also review the bTMB final analysis results. A separate DMC charter will describe the activities of this committee in more detail.

Blinded Independent Central Review

A Blinded Independent Central Review (BICR) committee will be formed for standardized response assessment. Images will be submitted to an imaging third-party vendor for central review.

Imaging acquisition guidelines and submission process will be outlined in the CA209848 Study Imaging Manual to be provided by the vendors. For tumor types which require clinical indicators as part of the standard response assessment, the clinical indicator data will be provided to the BICR along with imaging data.

REFERENCES

1 Rizvi NA, Hellmann MD, Snyder A, et al. Cancer immunology. Mutational landscape determine sensitivity to PD-1 blockade in non-small cell lung cancer. Science. 2015; 348:124 8.

2 Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-247.

3 Wen PY, Macdonald DR, Reardon DA, et al. Updated Response Assessment Criteria for High Grade Gliomas: Response Assessment in Neuro-Oncology Working Group J Clin Oncol 28;1 3059-3067. 2010.

2 SCHEDULE OF ACTIVITIES

Table 2-1: Screening Procedural Outline (CA209848)

Procedure	Screening Visit	Notes
Pre-screening for TMB-H	Participants must have TMB-H status (tissue and/or blood) confirmed via F1CDx assay (tissue) or bTMB-validated CLIA assay from Foundation Medicine (blood) prior to signing consent for other eligibility procedures (see details in Section 6.1). Prior TMB-H results ≥ 10 mut/Mb obtained from F1CDx assay (tissue) or bTMB-validated CLIA assay from Foundation Medicine (blood) are acceptable for eligibility purposes. **Participants who do not have TMB-H status (tissue or blood) with the assays described above must sign a pre-screening informed consent form and have tissue and / or blood samples provided for central testing. See details below for Biomarkers Collection.** Both tissue and blood results obtained with these assays are required prior to randomization, and both can be done under the pre-screening, if not previously available**; as long as at least one of the results is ≥ 10 mut/Mb (tTMB ≥ 10 mut/Mb or the new cutoff value of bTMB determined by the 1st interim analysis), the participant may sign the study Informed Consent Form and proceed to additional screening procedures.**	
Biomarkers Collection		
Tumor tissue	Refer to Table 9.8-1 and Table 9.8-2: Biomarker Tissue and Blood Samples: Arm B Nivolumab Monotherapy	**If prior tTMB results are submitted, the tTMB assay must have been F1CDx.** **Foundation One or any other assays are not acceptable.** **For patients without prior tTMB results from F1CDx:** A formalin-fixed, paraffin-embedded tumor tissue (FFPET) block (preferred) or **25 unstained slides** of tumor tissue (archival tissue or fresh biopsy) is required. 10 slides are required for TMB eligibility evaluation and 15 slides are required for PD-L1 and other tumor-based biomarker evaluations. **For patients with prior tTMB results from F1CDx:** A formalin-fixed, paraffin-embedded tumor tissue (FFPET) block (preferred) or **15 unstained slides** of tumor tissue (archival tissue or fresh biopsy) is required from all participants for PD-L1 and other tumor-based biomarker evaluations. **Fresh biopsies are preferred; however, archival samples are acceptable if obtained within 9 months of signing the initial consent form ([pre-screening] and** no additional intervening therapy (excluding palliative therapy) **in between).** If a fresh biopsy is warranted, the participant must have a lesion that can be biopsied at an acceptable clinical risk as judged by the investigator in order to be eligible for the study.

Table 2-1: Screening Procedural Outline (CA209848)

Procedure	Screening Visit	Notes
		If the required number of slides are not available, the BMS Medical Monitor must be consulted **upfront**, prior to enrollment, to discuss acceptability of the tissue available.
Collection of blood sample for TMB testing	Refer to Table 9.8-1 and Table 9.8-2: Biomarker Tissue and Blood Samples: Arm B Nivolumab Monotherapy	**If prior bTMB-validated CLIA results are submitted, bTMB testing must have been done by Foundation Medicine. Any other assays are not acceptable.** A fresh blood sample must be submitted (all participants).
Eligibility Assessments		
Informed consent	X	For participants 18 years of age or older, and legal representatives of participants age between 12 and less than 18 years old
Assent form	X	For participants ages between 12 and less than 18 years old; should be obtained per local laws and regulations
Inclusion/Exclusion criteria	X	All inclusion/exclusion criteria should be assessed at screening and confirmed prior to first dose
Medical history	X	Including diagnostic pathology report, TMB level, dMMR, and MSI-High status (if previously performed), and all previous anti-cancer treatments
Safety Assessments		
Pregnancy test	X	WOCBP only: Serum or urine (minimum sensitivity 25 IU/L or equivalent units of HCG) to be done at screening visit and repeated within 24 hours of first dose of study therapy
Concomitant medications	X	Within 14 days prior to first dose
Physical examination	X	Including height and weight within 14 days prior to randomization.
Vital signs	X	Temperature, blood pressure, and heart rate within 14 days prior to randomization.
Performance Status	X	Within 14 days prior to randomization. See Appendix 6 for ECOG performance status (for participants ≥ 16 years old with solid tumors, Appendix 9 for Karnofsky (participants ≥ 16 years old with CNS as primary tumor) and Lansky (for all participants < 16 years old)

Table 2-1: Screening Procedural Outline (CA209848)

Procedure	Screening Visit	Notes
Assessment of signs and symptoms	X	Within 14 days prior to randomization.
Serious adverse events (SAE) Assessment	X	SAEs collected from time of consent. All AEs (SAEs or non-serious AEs) associated with SARS-CoV-2 infection collected from time of consent.
Electrocardiogram (ECG)	X	Within 14 days prior to randomization.
Laboratory Tests		
Hematology and chemistry	X	See Section 9.4.3 Clinical Safety Laboratory Assessments
Hepatitis B and hepatitis C testing	X	Within 28 days prior to randomization: Hepatitis B and C testing (HBsAg and anti-HCV [HCV-RNA, if needed])
HIV Testing	X	Testing for HIV must be performed at sites where mandated locally.
Thyroid function testing	X	Thyroid panel including TSH, free T3, and free T4 within 14 days prior to randomization
Efficacy Assessments		
Body Imaging	X	For Solid Tumors: Contrast enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease, within 28 days prior to date of first dose.
Brain Imaging	X	For Primary CNS Tumor: MRI of the brain without and with gadolinium-based contrast should be performed during screening period. For Solid Tumors: Participants with known or suspected brain metastases, MRI of the brain without and with contrast is required unless participant has completed an imaging study of the brain within 28 days of study drug administration. CT of the brain without and with contrast can be performed if MRI is contraindicated. See Section 9.1.1 for further details
Other: Bone Scan		As clinically indicated per local standards. See Section 9.1.1 for further details.
IRT/Clinical Drug Supplies		
Contact IRT	X	IRT contact must occur as follows: For participant number assignment at the time informed consent is obtained. Within 3 days prior to dosing for study drug vial assignment.

Note: 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.

Note: Mention of adolescents is not applicable for sites in Belgium or the Netherlands as adolescent participants will not be included in these countries.

Table 2-2: On Study Assessments Treatment Phase - Arm A - Nivolumab in Combination with Ipilimumab (CA209848)

Procedure	Day 1	Every 2 weeks (i.e., every subsequent cycle Day 1) (± 3 Days)	Every 6 weeks (i.e. every 3 cycles Day 1 (± 3 Days)	Every 12 weeks (i.e. every 6 cycles Day 1) (± 7 Days)	Notes For the purposes of this table, a cycle refers to nivolumab every 2 weeks
Safety Assessments					
Pregnancy test	X	X (see note)			WOCBP only: Serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) to be done within 24h prior to first dose of study treatment, and then every 4 weeks (± 1 week) regardless of dosing schedule.
Weight	X	X (see note)	X (see note)		Weight must be assessed within 72h prior to dosing for adolescents < 40kg, and every 6 weeks (i.e., every 3 cycles) for adults and adolescents ≥ 40kg
Physical examination and ECOG, Karnofsky or Lansky Performance Status	X				Within 72h prior to dosing. See Appendix 6 for ECOG performance status (for participants ≥ 16 years old with solid tumors), and Appendix 9 for Karnofsky (participants ≥ 16 years old with CNS as primary tumor) and Lansky (for all participants < 16 years old)
Targeted physical examination and ECOG, Karnofsky or Lansky Performance Status		X			Must be performed within 72h prior to dosing and include at a minimum the cardiovascular, gastrointestinal, and pulmonary body systems. See Appendix 6 for ECOG performance status (for participants ≥ 16 years old with solid tumors), and Appendix 9 for Karnofsky (participants ≥ 16 years old with CNS as primary tumor) and Lansky (for all participants < 16 years old)

Table 2-2: On Study Assessments Treatment Phase - Arm A - Nivolumab in Combination with Ipilimumab (CA209848)

Procedure	Day 1	Every 2 weeks (i.e., every subsequent cycle Day 1) (± 3 Days)	Every 6 weeks (i.e. every 3 cycles Day 1 (± 3 Days)	Every 12 weeks (i.e. every 6 cycles Day 1) (± 7 Days)	Notes For the purposes of this table, a cycle refers to nivolumab every 2 weeks
Vital signs	X	X			Temperature, blood pressure, and heart rate. Must be performed prior to dosing.
Concomitant medication	Continuously				
Adverse events (including serious and non-serious) assessment	Continuously				Record at each visit. All AEs (SAEs or non-serious AEs), including those associated with SARS-CoV-2 infection, must be collected continuously throughout the treatment period. Adverse events and laboratory values will be graded according to the NCI-CTCAE version 5.
Laboratory Assessments					
Hematology and chemistry	X	X			See Section 9.4.3 Clinical Safety Laboratory Assessments. Must be performed within 72h prior to dosing.
Thyroid function testing	X		X (see note)		Thyroid function testing should be done every 4 weeks (i.e., Day 1 of every other cycle) for the first 10 cycles, and then every 8 weeks until completion of study treatment. Must be performed within 72h prior to dosing.
Pharmacokinetic Assessment	See Section 9.5				
Immunogenicity Assessment	See Section 9.5				
Biomarker assessment	See Section 9.8				
Collection of tumor tissue for biomarkers upon disease progression	See Section 9.8				If a biopsy has been performed and tissue is available, participants are requested to submit fresh tumor tissue for biomarker

Table 2-2: On Study Assessments Treatment Phase - Arm A - Nivolumab in Combination with Ipilimumab (CA209848)

Procedure	Day 1	Every 2 weeks (i.e., every subsequent cycle Day 1) (± 3 Days)	Every 6 weeks (i.e. every 3 cycles Day 1 (± 3 Days)	Every 12 weeks (i.e. every 6 cycles Day 1) (± 7 Days)	Notes For the purposes of this table, a cycle refers to nivolumab every 2 weeks
					research. Tissue submission is optional and biopsy is not required by protocol.
Additional research collection	See Section 9.8.1				
Efficacy Assessments					
Body Imaging				X (see note)	For Solid Tumors: Tumor Assessments should occur every 12 weeks (± 7 days) until BICR confirmation of disease progression or treatment discontinuation(including treatment beyond progression), whichever comes later. See Section 9.1.1 for further details.
Brain Imaging				X (see note)	For Primary CNS neoplasms: MRI without and with contrast; should have MRI of the brain approximately every 12 weeks (± 7 days) until BICR confirmation of disease progression or treatment discontinuation(including treatment beyond progression), whichever comes later. For Solid Tumors: Participants with a history of brain metastasis or symptoms should have a surveillance brain MRI per standard of care (approximately 12 weeks) or sooner if clinically indicated. See Section 9.1.1 for further details.

Table 2-2: On Study Assessments Treatment Phase - Arm A - Nivolumab in Combination with Ipilimumab (CA209848)

Procedure	Day 1	Every 2 weeks (i.e., every subsequent cycle Day 1) (± 3 Days)	Every 6 weeks (i.e. every 3 cycles Day 1 (± 3 Days)	Every 12 weeks (i.e. every 6 cycles Day 1) (± 7 Days)	Notes For the purposes of this table, a cycle refers to nivolumab every 2 weeks
Other: Bone Scan				X (see note)	As clinically indicated per local standards. See Section 9.1.1 for further details.
Outcomes Research					
EORTC QLQ-C30 and EQ-5D questionnaires	X		X		Each assessment should be completed **at the start of the clinic visit** prior to dosing or any study-related procedures. Only applies to participants ≥ 18 years of age at baseline. If the dose is delayed, then PRO completion should also be delayed and synchronized with the delayed dosing. See Section 9.10 for more details.
Study Treatment					
Contact IRT	X	X			Within 3 days prior to dosing for study drug vial assignment
Nivolumab 240 mg Q2W (adults and adolescents ≥ 40kg)	X	X			Participants should be dosed within 3 days from the scheduled dose. Participants may be dosed no less than 12 days from the previous dose.
Nivolumab 3 mg/kg Q2W (adolescents < 40 kg)	X	X			Participants should be dosed within 3 days from the scheduled dose. Participants may be dosed no less than 12 days from the previous dose.
Ipilimumab 1 mg/kg Q6W (all participants)	X		X (see note)		Ipilimumab should be administered every 6 weeks (i.e., every 3 cycles, Day 1). Participants should be dosed within 3 days from the scheduled dose

Note: Mention of adolescents is not applicable for sites in Belgium or the Netherlands as adolescent participants will not be included in these countries.

Table 2-3: On Study Assessments Treatment Phase - Arm B - Nivolumab Monotherapy (CA209848)

Procedure	Day 1	Every 4 weeks (i.e. each subsequent cycle Day 1) (± 3 Days)	Every 12 weeks (i.e. every 3 cycles Day 1) (± 7 Days)	Notes For the purposes of this table, a cycle refers to nivolumab every 4 weeks
Safety Assessments				
Pregnancy test	X	X		WOCBP only: Serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) to be done within 24h prior to first dose of study treatment, and then every 4 weeks (± 1 week) regardless of dosing schedule.
Weight	X	X		Weight must be assessed within 72h prior to dosing
Physical examination and ECOG, Karnofsky or Lansky Performance Status	X			Within 72 hours prior to dosing. See Appendix 6 for ECOG performance status (for participants ≥ 16 years old with solid tumors), and Appendix 9 for Karnofsky (participants ≥ 16 years old with CNS as primary tumor) and Lansky (for all participants < 16 years old)
Targeted physical examination and ECOG, Karnofsky or Lansky Performance Status		X		Targeted examination must be performed within 72 hours prior to dosing and include at a minimum the cardiovascular, gastrointestinal, and pulmonary body systems. See Appendix 6 for ECOG performance status (for participants ≥ 16 years old with solid tumors), and Appendix 9 for Karnofsky (participants ≥ 16 years old with CNS as primary tumor) and Lansky (for all participants < 16 years old)
Vital signs	X	X		Temperature, blood pressure, and heart rate. Must be performed prior to study drug administration.
Concomitant medication	Continuously			
Adverse events (including serious and non-serious) assessment	Continuously			Record at each visit. All AEs (SAEs or non-serious AEs), including those associated with SARS-CoV-2 infection, must be collected continuously throughout the treatment period. Adverse events and laboratory values will be graded according to the NCI-CTCAE version 5.

Table 2-3: On Study Assessments Treatment Phase - Arm B - Nivolumab Monotherapy (CA209848)

Procedure	Day 1	Every 4 weeks (i.e. each subsequent cycle Day 1) (± 3 Days)	Every 12 weeks (i.e. every 3 cycles Day 1) (± 7 Days)	Notes For the purposes of this table, a cycle refers to nivolumab every 4 weeks
Laboratory Assessments				
Hematology and chemistry	X	X		See Section 9.4.3 Clinical Safety Laboratory Assessments. Must be performed within 72h prior to study drug administration.
Thyroid function testing	X	X (see notes)		Thyroid function testing should be done every 4 weeks (i.e., Day 1 of every cycle) for the first 5 cycles, and then every 8 weeks (i.e., Day 1 of every other cycle) until completion of study treatment. Must be performed within 72h prior to study drug administration.
Pharmacokinetic Assessment	See Section 9.5			
Immunogenicity Assessment	See Section 9.5			
Biomarker assessments	See Section 9.8			
Collection of tumor tissue for biomarkers upon disease progression	See Section 9.8			If a biopsy has been performed and tissue is available, participants are requested to submit fresh tumor tissue for biomarker research. Tissue submission is optional and biopsy is not required by protocol.
Additional research collection	See Section 9.8			
Efficacy Assessments				
Body Imaging			X	For Solid Tumors: Tumor Assessments should occur every 12 weeks (± 7 days) until BICR confirmation of disease progression or treatment discontinuation(including treatment beyond progression), whichever comes later. See Section 9.1.1 for further details.

Table 2-3: On Study Assessments Treatment Phase - Arm B - Nivolumab Monotherapy (CA209848)

Procedure	Day 1	Every 4 weeks (i.e. each subsequent cycle Day 1) (± 3 Days)	Every 12 weeks (i.e. every 3 cycles Day 1) (± 7 Days)	Notes For the purposes of this table, a cycle refers to nivolumab every 4 weeks
Brain Imaging			X	For Primary CNS neoplasms: MRI without and with contrast should have MRI of the brain approximately every 12 weeks (± 7 days) until BICR confirmation of disease progression or treatment discontinuation (including treatment beyond progression), whichever comes later. For solid tumor: Participants with a history of brain metastasis or symptoms should have a surveillance brain MRI per standard of care (approximately 12 weeks) or sooner if clinically indicated. See Section 9.1.1 for further details.
Other: Bone Scan			X	As clinically indicated per local standards. See Section 9.1.1 for further details.
Outcomes Assessments				
EORTC QLQ-C30 and EQ-5D questionnaires	X	X		Each assessment should be completed **at the start of the clinic visit** prior to dosing or any study-related procedures. Only applies to participants ≥ 18 years of age at baseline. If the dose is delayed, then PRO completion should also be delayed and synchronized with the delayed dosing. See Section 9.10 for more details.
Study Treatment				
Contact IRT	X	X		Within 3 days prior to dosing for study drug vial assignment
Nivolumab 480 mg Q4W (adults and adolescents ≥ 40 kg)	X	X		Participants should be dosed within 3 days from the scheduled dose. The minimum interval between doses is 22 days.
Nivolumab 6 mg/kg Q4W (adolescents < 40 kg)	X	X		Participants should be dosed within 3 days from the scheduled dose. The minimum interval between doses is 22 days.

Note: Mention of adolescents is not applicable for sites in Belgium or the Netherlands as adolescent participants will not be included in these countries.

Table 2-4: On Study Assessments Treatment Phase – Arm B Rollover – Participants Treated with Nivolumab in Combination with Ipilimumab After Disease Progression During Nivolumab Monotherapy (CA209848)

Procedure	Day 1	Every 2 weeks (i.e. every subsequent cycle Day 1) (± 3 Days)	Every 6 weeks (i.e. every 3 cycles Day 1 (± 3 Days)	Every 12 weeks (i.e. every 6 cycles Day 1) (± 7 Days)	Notes For the purposes of this table, a cycle refers to nivolumab every 2 weeks
Safety Assessments					
Pregnancy test	X	X (see note)			WOCBP only: Serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) to be done within 24 h prior to first dose of study treatment, and then every 4 weeks (± 1 week) regardless of dosing schedule.
Weight	X	X (see note)	X (see note)		Weight must be assessed within 72h prior to dosing for adolescents < 40 kg, and every 6 weeks for adults and adolescents ≥ 40 kg
Physical examination and ECOG, Karnofsky or Lansky Performance Status	X				Within 72 hours prior to dosing. See Appendix 6 for ECOG performance status (for participants ≥ 16 years old with solid tumors), and Appendix 9 for Karnofsky (participants ≥ 16 years old with CNS as primary tumor) and Lansky (for all participants < 16 years old)
Targeted physical examination and ECOG, Karnofsky or Lansky Performance Status		X			Targeted examination must be performed within 72 hours prior to dosing and include at a minimum the cardiovascular, gastrointestinal, and pulmonary body systems. See Appendix 6 for ECOG performance status (for participants ≥ 16 years old with solid tumors), and Appendix 9 for Karnofsky (participants ≥ 16 years old with CNS as primary tumor) and Lansky (for all participants < 16 years old)

Table 2-4: On Study Assessments Treatment Phase – Arm B Rollover – Participants Treated with Nivolumab in Combination with Ipilimumab After Disease Progression During Nivolumab Monotherapy (CA209848)

Procedure	Day 1	Every 2 weeks (i.e. every subsequent cycle Day 1) (± 3 Days)	Every 6 weeks (i.e. every 3 cycles Day 1 (± 3 Days)	Every 12 weeks (i.e. every 6 cycles Day 1) (± 7 Days)	Notes For the purposes of this table, a cycle refers to nivolumab every 2 weeks
Vital signs	X	X			Temperature, blood pressure, and heart rate. Must be performed prior to dosing.
Concomitant medication	Continuously				
Adverse events (including serious and non-serious) assessment	Continuously				Record at each visit. All AEs (SAEs or non-serious AEs), including those associated with SARS-CoV-2 infection, must be collected continuously throughout the treatment period. Adverse events and laboratory values will be graded according to the NCI-CTCAE version 5.
Laboratory Assessments					
Hematology and chemistry	X	X			See Section 9.4.3 Clinical Safety Laboratory Assessments. Must be performed within 72h prior to dosing.
Thyroid function testing	X		X (see note)		Thyroid function testing should be done every 4 weeks (i.e., Day 1 of every other cycle) for the first 10 cycles, and then every 8 weeks until completion of study treatment. Must be performed within 72h prior to dosing.
Pharmacokinetic Assessment	See Section 9.5				
Immunogenicity Assessment	See Section 9.5				
Biomarker assessment	See Section 9.8				
Collection of tumor tissue for biomarkers upon disease progression	See Section 9.8				If a biopsy has been performed and tissue is available, participants are requested to submit fresh tumor tissue for biomarker

Table 2-4: On Study Assessments Treatment Phase – Arm B Rollover – Participants Treated with Nivolumab in Combination with Ipilimumab After Disease Progression During Nivolumab Monotherapy (CA209848)

Procedure	Day 1	Every 2 weeks (i.e. every subsequent cycle Day 1) (± 3 Days)	Every 6 weeks (i.e. every 3 cycles Day 1 (± 3 Days)	Every 12 weeks (i.e. every 6 cycles Day 1) (± 7 Days)	Notes For the purposes of this table, a cycle refers to nivolumab every 2 weeks
					research. Tissue submission is optional and biopsy is not required by protocol.
Additional research collection	See Section 9.8.1				
Efficacy Assessments					
Body Imaging				X (see note)	For Solid Tumors: Tumor Assessments should occur every 12 weeks (± 7 days) until BICR confirmation of disease progression or treatment discontinuation (including treatment beyond progression), whichever comes later. See Section 9.1.1 for further details.
Brain Imaging				X (see note)	For Primary CNS neoplasms: MRI without and with contrast; should have MRI of the brain approximately every 12 weeks (± 7 days) until BICR confirmation of disease progression or treatment discontinuation (including treatment beyond progression), whichever comes later. For solid tumors: Participants with a history of brain metastasis or symptoms should have a surveillance brain MRI per standard of care (approximately 12 weeks) or sooner if clinically indicated. See Section 9.1.1 for further details.
Other: Bone Scan				X (see note)	As clinically indicated per local standards. See Section 9.1.1 for further details.

Table 2-4: On Study Assessments Treatment Phase – Arm B Rollover – Participants Treated with Nivolumab in Combination with Ipilimumab After Disease Progression During Nivolumab Monotherapy (CA209848)

Procedure	Day 1	Every 2 weeks (i.e. every subsequent cycle Day 1) (± 3 Days)	Every 6 weeks (i.e. every 3 cycles Day 1 (± 3 Days)	Every 12 weeks (i.e. every 6 cycles Day 1) (± 7 Days)	Notes For the purposes of this table, a cycle refers to nivolumab every 2 weeks
Outcomes Research					
EORTC QLQ-C30 and EQ-5D questionnaires	X		X		Each assessment should be completed **at the start of the clinic visit** prior to dosing or any study-related procedures. Only applies to participants ≥ 18 years of age at baseline. If the dose is delayed, then PRO completion should also be delayed and synchronized with the delayed dosing. See Section 9.10 for more details.
Study Treatment					
Contact IRT	X	X			Within 3 days prior to dosing for study drug vial assignment
Nivolumab 240 mg Q2W (adults and adolescents ≥ 40kg)	X	X			Participants should be dosed within 3 days from the scheduled dose. Participants may be dosed no less than 12 days from the previous dose.
Nivolumab 3 mg/kg Q2W (adolescents < 40 kg)	X	X			Participants should be dosed within 3 days from the scheduled dose. Participants may be dosed no less than 12 days from the previous dose.
Ipilimumab 1mg/kg Q6W (all participants)	X		X (see note)		Ipilimumab should be administered every 6 weeks (i.e., every 3 cycles, Day 1). Participants should be dosed within 3 days from the scheduled dose

Note: Mention of adolescents is not applicable for sites in Belgium or the Netherlands as adolescent participants will not be included in these countries.

Table 2-5: Follow-up Assessments CA209848

Procedure	Follow-up Visits X01 (Day 30) (± 7 Days) and X02 (Day 100)[a] (± 7 Days) after Last Dose	Survival Follow-up Visits[b] Every 3 months (± 14 Days)	Notes
Safety Assessments			
Targeted Physical Examination	X		Targeted examination must include the cardiovascular, gastrointestinal, and pulmonary body systems and examination to specific malignancy. To assess for potential late emergent study drug related findings.
Adverse events assessment	X		Record at each visit. All AEs and SAEs must be collected continuously up to 100 days after study drug discontinuation. SAEs that relate to any later protocol specified procedure must be collected. Participants will be followed for all SAEs, non-serious AEs of special interest (as defined in Section 9), 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 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			
Hematology and chemistry	X		See Section 9.4.3 Clinical Safety Laboratory Assessments
Thyroid function testing	X		TSH with reflexive free T3 and free T4
Pharmacokinetic Assessment	See Section 9.5		
Immunogenicity Assessment	See Section 9.5		
Pregnancy test	X		WOCBP only: serum or urine
Outcome Research Assessment			
EORTC QLQ-C30 questionnaire	X		Only participants ≥ 18 years of age at baseline. See Section 9.10 for more details.

Table 2-5: Follow-up Assessments CA209848

Procedure	Follow-up Visits X01 (Day 30) (± 7 Days) and X02 (Day 100)[a] (± 7 Days) after Last Dose	Survival Follow-up Visits[b] Every 3 months (± 14 Days)	Notes
EQ-5D questionnaire	X	X	May be obtained through a telephone call or clinic visit. Only participants ≥ 18 years of age at baseline. See Section 9.10 for more details.
Efficacy Assessments			
Body Imaging	X (See note)	X (See note)	Only for solid tumor participants without progression. Tumor Assessments should occur every 12 weeks (± 7 days) from date of first dose until BICR confirmation of disease progression and treatment discontinuation (including treatment beyond progression), whichever comes later. See Section 9.1 for further details.
Brain Imaging	X (See note)	X (See note)	Primary CNS neoplasms: MRI without and with contrast should have MRI of the brain approximately every 12 weeks (± 7 days) until BICR confirmation of disease progression or treatment discontinuation (including treatment beyond progression), whichever comes later. For Solid Tumors: Participants with a history of brain metastasis or symptoms should have a surveillance brain MRI per standard of care (approximately 12 weeks) or sooner if clinically indicated. See Section 9.1 for further details.
Other: Bone Scan	X (See note)	X (See note)	As clinically indicated per local standards. See Section 9.1 for further details.
Participant status		X	Every 3 months after X02; may be accomplished by visit or phone contact, to update survival information Collect all subsequent anti-cancer treatment.

[a] Participants must be followed for at least 100 days after last dose of study treatment. Follow-up visit #1 (FU1) occurs approximately 30 days (± 7 days) after the last dose or coinciding with the date of discontinuation (± 7 days) if date of discontinuation is greater than 30 days after last dose. Follow-up visit #2 (FU2) occurs approximately 100 days (± 7 days) from last dose. Both FU1 and FU2 should be conducted in person.

[b] Survival Follow-up visits to occur every 3 months ± 14 days from Follow-up Visit 2. BMS may request that survival data be collected on all treated participants outside of the protocol 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. Survival follow-up may be conducted in person or by telephone.

3 INTRODUCTION

Blockade of the PD-1 pathway has proven effective in generating robust anti-tumor immune responses. Nivolumab, an anti-PD-1 blocking antibody, has demonstrated overall survival benefit in multiple tumors including non-squamous cell lung cancer, squamous cell lung cancer, melanoma, renal cell carcinoma and head and neck cancer. Recent data across multiple tumor types support the hypothesis that patients with tumors harboring increased somatic mutations due to DNA mismatch-repair deficiencies are more likely to respond to anti-PD-1/PD-L1 and anti-CTLA-4 blockade. Tumor mutational burden (TMB) refers to the total number of somatic mutations that exist within a tumor's genome. A subset of these mutations may result in expressed proteins that are not recognized by the host's immune system as self, and therefore has the potential to be immunogenic and more susceptible to immune-mediated anti-tumor response. The primary goal of this study is to demonstrate the clinical activity of nivolumab in combination with ipilimumab in multiple tumor types based on the status of TMB.

3.1 Study Rationale

3.1.1 Rationale for Participant Population with TMB-H Tumor

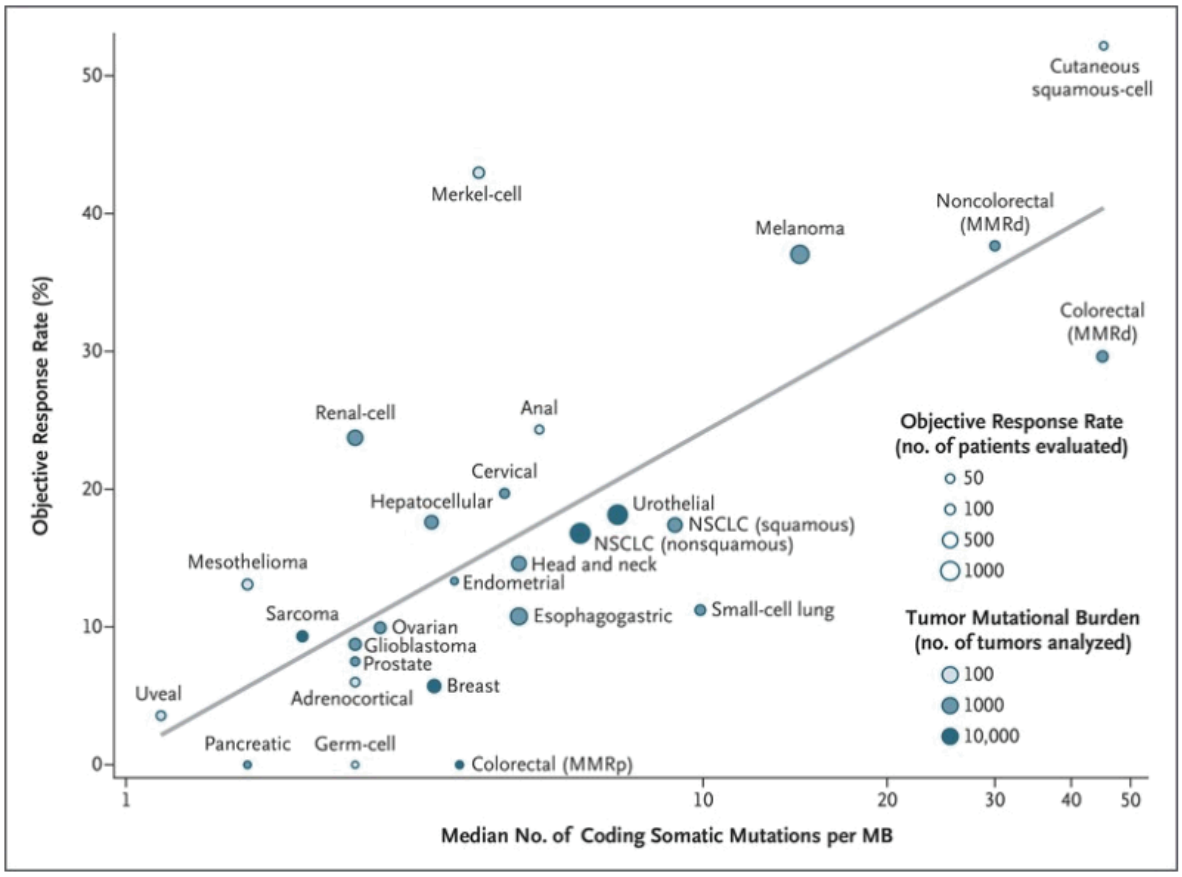
Tumors with a high mutational burden may have a higher number of neo-antigens which, in principle, would be expected to be more immunogenic than tumors with comparatively low mutational burden.[1] Therefore, high TMB has been hypothesized to correlate with improved efficacy in patients treated with immune-oncology (IO) therapies. This hypothesis has been supported by multiple publications across IO therapies, tumor types, and lines of treatment. The first published study of TMB as a biomarker of clinical outcomes was reported by Snyder et al, where high TMB (TMB-H) was found to be associated with efficacy in metastatic melanoma patients treated with anti-CTLA-4 therapy. Further studies by Rizvi et al reported TMB as a biomarker of pembrolizumab efficacy in second-line NSCLC patients.[1] Additional studies of pembrolizumab and atezolizumab in NSCLC have been generally consistent with these results.[2]

Furthermore, TMB was evaluated in an exploratory post hoc analysis in the BMS-sponsored first line NSCLC study, CheckMate 026, which represents the first phase 3 study to demonstrate the impact of TMB on efficacy of a PD-1/L1 inhibitor.[3] This analysis demonstrated that in patients with TMB-H, the ORR was numerically higher in the nivolumab arm versus the chemotherapy arm (47% vs 28%) and the median PFS was longer in the nivolumab arm compared to the chemotherapy arm (9.7 vs 5.8 mo., HR 0.62; 95% CI 0.38, 1.00). OS was notable, though similar (18.3 vs 18.8 mo. and 1 year OS rates of 64% vs 60%, respectively), between the arms in patients with TMB-H, although of note, 68% of patients in the chemotherapy arm received subsequent nivolumab.[4] Interestingly, the ORR and mPFS rates observed in the TMB-H subgroup in the nivolumab arm within CheckMate 026 were similar to those reported in the first line NSCLC study of pembrolizumab (Keynote-024), where ORR and mPFS were 45% and 10.3 months, respectively, in patients with ≥ 50% PD-L1 expression treated with pembrolizumab monotherapy.[5] Results from CA209227 showed that nivolumab combined with ipilimumab, as first line treatment in patients with metastatic NSCLC of TMB ≥10 mut/Mb, demonstrated significantly better and durable clinical response and progression-free survival benefit compared to chemotherapy,

including ORR 45.3% vs 26.9%, DOR ≥1 yr 68% vs 25%, PFS rate at 1 yr 43% vs 13%, and mPFS of 7.2 vs 5.4 months. Preliminary analysis on OS was also encouraging, and the clinical benefits are independent of PD-L1 expression. These findings further support TMB as an important, predictive and independent biomarker for clinical efficacy.

Recently, Yarchoan M, et al suggested a significant positive linear correlation between higher TMB and increased ORR after analyzing 27 tumor types/subtypes treated with anti-PD-1/PD-L1 monotherapy, which highlights the potential strong relationship between TMB and the clinical activity of anti-PD-1/PD-L1 therapies across multiple cancers.[6]

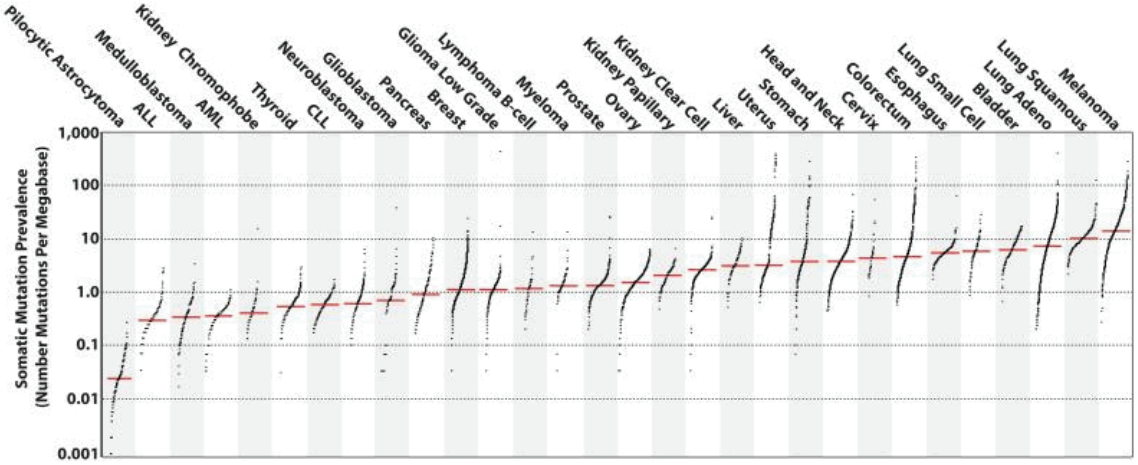
Figure 3.1.1-1: Correlation between Tumor Mutational Burden and Objective Response Rate with Anti–PD-1 or Anti–PD-L1 Therapy



Taken together, the available data suggest that, in addition to PD-L1, TMB is also an important predictive biomarker of the clinical efficacy of IO therapy. Therefore, patients of TMB-H across multiple solid tumors will be selected for participation in this clinical study.

Prevalence of TMB-H tumor: Selected tumors and their corresponding prevalence by TMB are shown in the figure below:

Figure 3.1.1-2: Tumor Mutational Burden in Various Tumor Types



Analyzed using an algorithm developed to extract mutational signatures from catalogues of somatic mutations in 7042 primary cancers. Source: adapted from Alexandrov LB, et al. Nature 2013;500:415-21[7]

3.1.2 Rationale for Study in Refractory, Metastatic, or Unresectable Setting

This trial with nivolumab in combination with ipilimumab and nivolumab monotherapy will include participants with refractory, metastatic or unresectable TMB-H malignancy who have been treated with prior non-IO therapies. In general, malignancies included in this trial are the ones that have no standard of care after first line therapy showing an improved benefit over best supportive care. The low prevalence of TMB-H in these tumor types limits the feasibility of traditional large-scale randomized trials. As a result, a high unmet medical need exists for these patients, with no less expectation for immunotherapy activity.

3.1.3 Rationale for Inclusion of Adolescent Participants

The majority of pediatric patients with cancer are enrolled in clinical trials; however, enrollment has been shown to decrease with age, and only 10% to 15% of older adolescents (ages 12 to 19) with cancer participate in clinical trials and is considered an unmet need. Much of the more than 50% decrease in overall childhood cancer mortality since 1975 has been attributed to clinical trial participation, but survival improvements for adolescents and young adults have historically lagged behind the pediatric population as a whole, and decreased participation in clinical trials may contribute to this finding.

Lack of participation in the pediatric trials may be due to differences in tumors observed in the two groups, as tumors in adolescents may mirror those observed more often in adults. For trials in adult participants with tumor types that also occur in adolescents, adolescents are often excluded due to safety or regulatory concerns. Overall, this has led to a delay in the study of new therapies in adolescents, and most problematically, a delay in new efficacious therapies reaching this population. It has been recommended that adolescents be considered for trials in adult populations

for tumor types that are observed in adolescents and that share features common to those tumors that occur in adults.[8,9] Thus, adolescents will be included in this study where locally permitted. Individual countries and sites have the option of opting out of adolescent eligibility.

This section is not applicable for sites in Belgium or the Netherlands as adolescents will not be included in these countries.

3.1.4 Rationale for Key Endpoints

Objective response rate (ORR) assessed by a blinded independent central review committee is the primary endpoint of this study. ORR is a validated clinical endpoint in many tumors, and in patients in whom a durable tumor response is achieved can be expected to derive a survival benefit from therapy.[10]

3.1.4.1 Rationale for Independent Central Review

The primary endpoint of ORR will be based on centrally-assessed radiologic tumor measurements (and additional clinical indicators, where applicable) using standard disease-specific response criteria. A centrally-assessed ORR will provide standardized assessment of progression and response using disease-specific response criteria. For this purpose, radiologic imaging from this study will be transmitted to an imaging core lab for analysis by a Blinded Independent Central Review (BICR) committee. Please see Section 9.1 and CA209848 Imaging Manual for additional information.

3.1.4.2 Rationale for Investigator Assessed Response

Investigator-assessed radiologic tumor measurements (and additional clinical indicators, where applicable) using standard disease-specific response criteria will closely reflect observed clinical practice responses, and will allow for real-time treatment decisions based on the most comprehensive, available, clinical information for the individual participant.

3.1.5 Rationale for Exploratory Biomarker Assessments

An effective anti-tumor immune response relies on a number of interactions, beginning with the immune system recognizing the tumor cell as foreign. One important means of recognition is the expression of unique tumor-specific peptides (i.e., neoantigens) that are processed, presented via the major histocompatibility complex (MHC), and subsequently recognized by T cells as immunologic targets. This triggers an immune response driven by T-cell activation, cytokine production, peripheral expansion, and infiltration of effector cells that ultimately kill the tumor cell.

A number of factors can suppress an effective anti-tumor response, including a lack of strong tumor neoantigens recognized by T cells, downregulation of the MHC on cancer cells, minimal activation or inactivation of T cells, poor infiltration of effector cells into tumors, and the actions of immune checkpoint proteins (e.g., programmed cell death protein 1 [PD-1], programmed death ligand 1 [PD-L1], cytotoxic T-lymphocyte-associated protein 4 [CTLA-4]) and tumor microenvironment modulators (e.g., regulatory T cells [TRegs] and myeloid-derived suppressor cells [MDSCs]), which limit the strength and duration of immune responses.

As described by Blank et al.,[11] requirements for T-cell-mediated tumor control (and targets for potential biomarker selection for immuno-oncology therapy) include: tumor foreignness, general immune status, immune cell infiltration, absence of checkpoints, absence of soluble inhibitors, absence of inhibitory tumor metabolism, and tumor sensitivity to immune effectors.

Tumor PD-L1 is already an established clinically validated biomarker with available complementary/companion diagnostic tests for anti-PD-1/L1 therapies in several tumor types. The utility of tumor PD-L1 as the sole predictive biomarker is limited by the lack of an optimal cut-off value for PD-L1 expression that reliably selects all patients likely to benefit from immuno-oncology therapy. For example, in SCCHN study CA209141, while improved efficacy was observed with increasing PD-L1 expression, durable responses were also observed in patients with PD-L1 non-expressing tumors.

Due to the complexity of the immune system and its response to immuno-oncology therapy, additional biomarkers beyond PD-L1 are being investigated to help clinicians to select therapy for patients most likely to benefit (e.g., those 'immune-primed' patients with one or more tumor/immune characteristics that indicate a positive response to immuno-oncology therapy) or to suggest alternative combinations beyond immuno-oncology therapy alone. Exploratory biomarkers that may be assessed in this study include but are not limited to: tumor gene expression profiling, PD-L2, CD8, and myeloid derived suppressor cells (MDSCs).

3.1.6 Rationale for Outcomes Research Assessments

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.

3.2 Background

OPDIVO® (nivolumab), is a human programmed death receptor-1 (PD-1)[12] blocking antibody approved for unresectable or metastatic melanoma, previously treated metastatic squamous non-small cell lung cancer (NSCLC), advanced renal cell carcinoma, and classical Hodgkin lymphoma in the United States and in Japan for unresectable melanoma, kidney cancer, and NSCLC, and is in clinical development for the treatment of other malignancies. Nivolumab has also demonstrated clinical activity as combination therapy with ipilimumab in melanoma, NSCLC, RCC, and Hodgkin lymphoma. The majority of responses were durable and exceeded 6 months.

The overall safety experience with nivolumab, as a monotherapy or in combination with other therapeutics, is based on experience in approximately 224,573 participants treated to date. Overall, the safety profile of nivolumab monotherapy is manageable and generally consistent across completed and ongoing clinical trials with no maximum tolerated dose (MTD) reached at any dose tested up to 10 mg/kg. There was no pattern in the incidence, severity, or causality of AEs to nivolumab dose level. Most AEs were low grade (Grade 1 - 2) with relatively few related high grade (Grade 3 - 4) AEs.

To characterize AEs of special clinical interest that are potentially associated with the use of nivolumab, Bristol-Myers Squibb (BMS) has identified select AEs based on the following principles: AEs that may differ in type, frequency, or severity from AEs caused by therapies that are not immuno-modulating; AEs that may require immunosuppression (e.g. corticosteroids) as part of their management; AEs whose early recognition and management may mitigate severe toxicity; AEs for which multiple event terms may be used to describe a single type of AE, thereby necessitating the pooling of terms for full characterization.

Based on these principles and taking into account the types of AEs already observed across studies of nivolumab monotherapy, pneumonitis, interstitial nephritis, diarrhea/colitis, hepatitis, rash, endocrinopathies, and hypersensitivity/infusion reaction events are currently considered to be select AEs. The majority of these AEs have been managed successfully with supportive care and, in more severe cases, a combination of dose delay, permanent discontinuation, and/or initiation of systemic corticosteroids.

This protocol will generate efficacy and safety data on nivolumab in combination with ipilimumab therapy and nivolumab monotherapy for refractory, metastatic and unresectable select tumor types of TMB-H (excluding melanoma, RCC, NSCLC and hematologic malignancies), some of which have not been previously examined in clinical trials.

3.2.1 Mechanism of Action of Nivolumab

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. [13,14,15]. 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).[16] 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. [17] PD-1 signaling has been shown to inhibit CD-28-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.[18] 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.

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 mixed lymphocyte reaction (MLR). Using a cytomegalovirus (CMV) re-stimulation assay with human peripheral blood mononuclear cells (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 results in tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/N, and PAN02).[19]

3.2.2 Ipilimumab Mechanism of Action

CTLA-4, an activation-induced T-cell surface molecule, is a member of the CD28:B7 immunoglobulin superfamily that competes with CD28 for B7. CTLA-4 mediated signals are inhibitory and turn off T cell-dependent immune responses.[20] Ipilimumab is a fully human monoclonal IgG1κ that binds to the CTLA-4 antigen expressed on a subset of T cells from human and nonhuman primates. The proposed mechanism of action for ipilimumab is interference of the interaction of CTLA-4 with B7 molecules on APCs, with subsequent blockade of the inhibitory modulation of T-cell activation promoted by the CTLA 4/B7 interaction.

3.2.3 Nivolumab Combined with Ipilimumab and Nivolumab Monotherapy Clinical Activity in Adults

Multiple clinical studies have evaluated nivolumab combined with ipilimumab at different doses and schedules. The following information describes the results of initial early phase clinical studies that were the basis for the nivolumab plus ipilimumab combination regimens that have been explored in late phase clinical development.

In the Phase 1 study CA209004, ascending doses of nivolumab have been studied concomitantly with ascending doses of ipilimumab in participants with unresectable or metastatic melanoma. In each arm in this multi-arm study, ipilimumab was administered once every 3 weeks for 4 doses with nivolumab administered once every 3 weeks for 8 doses. Starting at week 24, ipilimumab and nivolumab were administered once every 12 weeks for 8 doses. The three initial dose-escalation cohorts consisted of Cohort 1 (nivolumab 0.3 mg/kg + ipilimumab 3 mg/kg; n=14), Cohort 2 (nivolumab 1.0 g/kg + ipilimumab 3 mg/kg; n =17) and Cohort 3 (nivolumab 3.0 mg/kg + ipilimumab 3 mg/kg; n = 6). Later, the study was amended to include Cohort 2a which evaluated nivolumab 3 mg/kg + ipilimumab 1 mg/kg (n - 16). The primary objective was to assess safety/tolerability; the secondary objective was to assess preliminary efficacy.

Of the 52 participants evaluable for response as of the 15-Feb-2013 clinical cut-off in CA209004, 21 participants (40%) had an objective response by modified World Health Organization (mWHO) criteria. In an additional 2 participants (4%) there was an unconfirmed objective response. In Cohort 1 (0.1 mg/kg nivolumab + 3 mg/kg ipilimumab), 3 out of 14 evaluable

participants had an objective response by mWHO (21%), including 1 CR and 2 PRs. In Cohort 2 (1 mg/kg nivolumab + 3 mg/kg ipilimumab), 9 out of 17 (53%) evaluable participants had an objective response by mWHO, including 3 CRs (18%) and 6 PRs (35%). In Cohort 2a (3 mg/kg nivolumab + 1 mg/kg ipilimumab), 6 out of 15 (40%) response evaluable participants had an objective response by mWHO, including 1 CR (7%) and 5 PRs (33%). In Cohort 3 (3 mg/kg nivolumab + 3 mg/kg ipilimumab), 3 out of 6 (50%) evaluable participants had an objective response by mWHO, all 3 of which were PRs (50%).

Preliminary analysis revealed 16 of the 52 evaluable participants (31%) had > 80% reduction in the size of target tumor lesions by the week 12 evaluation. This is compared to < 2% for 3 mg/kg ipilimumab monotherapy based on CA184020 (N=540) and < 3% for nivolumab monotherapy based on CA209003 (N=94, 0.1-10 mg/kg).

The following dose limiting toxicities (DLTs) were observed: in Cohort 1, Grade 3 elevated AST/ALT (1 participant); in Cohort 2, Grade 3 uveitis (1 participant) and Grade 3 elevated AST/ALT (1 participant) and in Cohort 3, Grade 4 elevated lipase (2 participants) and Grade 3 elevated lipase (1 participant). Based on these data, Cohort 2 was identified as the maximum tolerated dose (MTD) and Cohort 3 exceeded the MTD.

A total of 53 melanoma participants were treated with nivolumab combined with ipilimumab in CA209004 across Cohorts 1, 2, 2a, and 3. At least 1 adverse event (AE) regardless of causality has been reported in 98% of participants treated. The most common (reported at 10% incidence) treatment related AEs (any Grade 93%; Grade 3-4 53%:) are rash (55%; 4%), pruritus (47%; 0%), vitiligo (11%; 0%), fatigue (38%; 0%), pyrexia (21%, 0%), diarrhea (34%; 6%), nausea (21%, 0%), vomiting (11%, 2%), ALT increased (21%; 11%), AST increased (21%; 13%), lipase increased (19%; 13%), amylase increased (15%, 6%), headache (11%, 0%), and cough (13%, 0%).

The majority of AEs leading to discontinuation (regardless of causality) were Grade 3 or 4 (reported in 11 of 53 participants, 21%). Grade 3 events included lipase increased, ALT increased, AST increased, troponin I increased, colitis, diverticular perforation, pancreatitis, tachycardia, renal failure acute, choroiditis, autoimmune disorder, and pneumonitis. One participant each discontinued due to Grade 4 events of blood creatinine increased and AST increased. No drug-related deaths were reported. [21]

The combination of nivolumab with ipilimumab has been studied in the Phase 1 study CA209016. Participants with metastatic RCC (mRCC; Karnofsky performance status (KPS) ≥ 80%; untreated or any number of prior therapies) were randomized to receive nivolumab 3 mg/kg + ipilimumab 1 mg/kg (arm N3 + I1) or nivolumab 1 mg/kg + ipilimumab 3 mg/kg (arm N1 + I3) IV Q3W for 4 doses followed by nivolumab 3 mg/kg IV Q2W until progression/toxicity. The primary objective was to assess safety/tolerability; secondary objective was to assess antitumor activity.

Participants were randomized to N3 + I1 (n = 47) and N1 + I3 (n = 47). Approximately half (n = 46; 51%) had prior systemic therapy (N3 + I1: 22; N1 + I3: 26).

After a median follow-up of 22.3 months, the confirmed ORR per RECIST 1.1 (Response Evaluation Criteria in Solid Tumors) was 40.4% (N = 47) in both Arms N3 + I1 and N1 + I3;

42.1% (n = 8) and 36.8% (n = 7) had an ongoing response, with a median DOR of 88.7 weeks (95% CI: 37.14, NA) and 85.9 weeks (95% CI: 35.14, NA), respectively. Median PFS was 7.7 months (95% CI: 3.71, 14.29) and 9.4 months (95% CI: 5.62, 18.63) in Arms N3 + I1 and N1 + I3, respectively. OS at 12 months was 80.9% and 85.0% in Arms N3 + I1 and N1 + I3, respectively, and at 24 months was 67.3% and 69.6%, respectively.

The safety of nivolumab combined with ipilimumab was assessed in study CA209016. Treatment-related AEs were seen in 88/94 pts (94%), including 43/47 (92%) in N3 + I1 and 45/47 (96%) in N1 + I3.The most frequently reported drug-related AEs in N3 + I1 included fatigue (66%), cough (53.2%), and arthralgia (51.1%); the majority were Grade 1- 2. The most frequently reported drug-related AEs in N1 + I3 included fatigue (74.5%), nausea (55.3%), and diarrhea (53.2%). The majority were Grade 1-2.

Treatment-related AEs leading to discontinuation (31.9% versus 10.6%), and treatment-related serious adverse events (SAEs) (34% versus 23.4%) occurred more commonly in participants in the N1 + I3 arm than in the N3 + I1 arm, respectively. [22]

CA209012 was a multi-arm Phase 1b trial evaluating the safety and tolerability of nivolumab in patients with chemotherapy-naïve advanced non-small cell lung cancer (NSCLC), as either a monotherapy or in combination with other agents including ipilimumab, at different doses and schedules. The primary endpoint of the study was safety with secondary endpoints of objective response rate (ORR) per RECIST 1.1 and 24-week progression-free survival (PFS). Participants were assigned to receive nivolumab 3 mg/kg Q2W + ipilimumab 1mg/kg Q12W (n=38), nivolumab 3mg/kg Q2W + ipilimumab 1 mg/kg Q6W (n = 39) and nivolumab 3 mg/kg Q2W (n=52). The confirmed ORR was 47% (N3 q2w + I1 q12w), 39% (N3 q2w + I1q6w) and 23% (N3 Q2W). The median duration of response (DOR) was not reached in any of these groups.

The rate of treatment-related adverse events (AEs) in the Q12W (82%) and Q6W (72%) arms were comparable to monotherapy (72%). In the study, Grade 3/4 adverse events were 37%, 33%, and 19% for the Q12W, Q6W and nivolumab monotherapy arms, respectively. Treatment-related Grade 3-4 AEs led to discontinuation in 5% and 8% of participants in the Q12W and Q6W cohorts, respectively, and were similar to nivolumab monotherapy. There were no treatment-related deaths. The treatment-related select AEs in patients administered the optimized dosing schedule (3 mg/kg of nivolumab Q2W plus 1 mg/kg of ipilimumab Q6W) were skin related (36%), gastrointestinal (23%), endocrine (20%), and pulmonary (5%) and there were ≤ 5% treatment related Grade 3 and Grade 4 AEs per category.[23]

CA209067 was a phase 3, randomized, double-blind study of nivolumab monotherapy or nivolumab combined with ipilimumab versus ipilimumab monotherapy in first line melanoma patients. In this study, combination of nivolumab 1 mg/kg and ipilimumab 3 mg/kg for 4 doses, followed by nivolumab 3 mg/kg, Q2W (NIVO+IPI), compared with ipilimumab 3 mg/kg, Q3W x 4 doses (IPI) demonstrated a significant improvement in OS and PFS, with mOS not reached in the NIVO+IPI group compared with 19.98 months in the IPI group, and mPFS 11.7 months in the NIVO+IPI group compared with 2.9 months in the IPI group. When NIVO+IPI group was compared to nivolumab 3 mg/kg group (NIVO), a numeric difference in OS and improved PFS

(mPFS of 11.73 vs 6.87 months) were observed in favor of the combination. The ORR in NIVO+IPI (58.9%) was significantly higher than the IPI group (19.0%) and numerically higher than NIVO group (44.6%). The overall safety profile of NIVO+IPI combination therapy and NIVO monotherapy was consistent with the mechanisms of action of nivolumab and ipilimumab. In general, the frequency of AEs was lowest across AE categories in the NIVO group and highest in the NIVO+IPI group. Treatment-related AEs of Grade 3 or 4 occurred in 59% patients of the NIVO+IPI group, 21% of the NIVO group and 34% of the IPI group. Analyses of immune-mediated AEs (IMAE) showed that most IMAEs were Grade 1-2. The majority of IMAEs in the IMAE categories of diarrhea/colitis, and hepatitis were Grade 3-4. The majority of IMAEs resolved and were manageable using the recommended treatment guidelines for early evaluation and intervention.[24]

CA209214 was a phase 3, randomized, open-label study of nivolumab combined with ipilimumab versus sunitinib monotherapy in first line patients with RCC. Among the intermediated/poor-risk participants, combination of nivolumab and ipilimumab therapy (NIVO+IPI, nivolumab 3 mg/kg and ipilimumab 1 mg/kg, Q3W for 4 doses then followed by nivolumab 3 mg/kg, Q2W) demonstrated a statistically significant higher ORR (41.6%) than sunitinib (26.5%). CR was achieved in 9.4% vs 1.2% in NIVO+IPI and sunitinib groups, respectively. Responses in the NIVO+IPI group occurred early (median TTR of 2.79 months) and were durable (median DOR not reached). In the sunitinib group, mTTR (3.04 months) was similar but responses were less durable (18.17 months). NIVO+IPI combination therapy demonstrated statistically significant and superior OS (mOS was not reached) compared with sunitinib (mOS of 25.95 months). The overall safety profile of NIVO+IPI was acceptable when compared to sunitinib monotherapy. Treatment-related AEs occurred in 93% of patients receiving NIVO+IPI, and 97% receiving sunitinib; Grade 3 or 4 AEs occurred in 46% and 63%, and treatment-related AEs leading to discontinuation occurred in 22% and 12%, respectively. Most IMAEs were Grade 1-2, and the majority of IMAEs resolved and were manageable using the recommended treatment guidelines for early evaluation and intervention.[25]

3.2.4 Nivolumab Combined with Ipilimumab and Nivolumab Monotherapy Clinical Activity in Adolescents

Relatively limited data are available for the use of checkpoint inhibitors in children. A pediatric phase 1 trial of ipilimumab monotherapy in 1, 3, 5, and 10 mg/m^2 doses concluded that ipilimumab may be safely administered to pediatric patients.[26] A multi-center phase 2 trial of ipilimumab 3 mg/kg and 10 mg/kg Q4 weeks x 4 doses in adolescents with metastatic melanoma (NCT01696045) has recently closed enrollment, and the study report is being prepared. Another phase 1 study with ipilimumab in children and adolescents with treatment-resistant cancer (NCT01445379) was reported as completed recently, and study results have not been released.

Nivolumab and nivolumab in combination with ipilimumab are being investigated in pediatric participants in an ongoing Children's Oncology Group (COG) Phase 1/2 study (ADVL 1412; CA209070; NCT02304458), including participants with relapsed refractory solid tumors and lymphoma. Good tolerability was demonstrated in safety lead-in phase for both treatment arms,

with immune-mediated AEs comparable to adult experience, and both have re-opened to expansion phase. A total of 110 participants have been studied to date (Spring 2017 COG Meeting; personal communication), of which 78 received nivolumab monotherapy and 32 received the combination. Of 58 currently evaluable in the monotherapy arm, only 3 DLTs were recorded. Clinical benefit has not been reported in solid tumors in this trial, and this study is continuing to enroll into multiple cohorts using treatment with both nivolumab monotherapy and combination therapy of nivolumab and ipilimumab. Additional BMS-sponsored clinical trials in children/adolescent are ongoing, including nivolumab in children with recurrent Hodgkin Lymphoma (CA209744), and nivolumab and nivolumab in combination with ipilimumab in pediatric participants with high grade primary CNS malignancies (CA209908). The Pediatric Brain Tumor Consortium recently opened a safety and preliminary efficacy study (PBTC-045, NCT02359565) of anti-PD1 antibody pembrolizumab in children with recurrent/refractory high-grade astrocytoma, DIPG, or hypermutated tumors; data are not yet available from this trial.

Recently, FDA has approved treatment of adolescent (≥12 yr old) participants with MSI-H CRC and MSI-H pan tumor, respectively.

This section is not applicable for sites in Belgium or the Netherlands as adolescents will not be included in these countries.

3.2.5 Nivolumab Clinical Pharmacology

Nivolumab pharmacokinetics (PK) was assessed using a population PK approach for both single-agent OPDIVO and OPDIVO with ipilimumab.

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

OPDIVO with ipilimumab: When OPDIVO 1 mg/kg was administered in combination with ipilimumab 3 mg/kg, the CL of nivolumab was increased by 29%, and the CL of ipilimumab was unchanged compared to OPDIVO administered alone. When OPDIVO 3 mg/kg was administered in combination with ipilimumab 1 mg/kg, the CL of nivolumab and ipilimumab were unchanged. When OPDIVO was administerd in combination with ipilimumab, the presence of anti-nivolumab

antibodies increased the CL of nivolumab by 20% and the CL of ipilimumab was unchanged in presence of anti-ipilimumab antibodies.

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

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

Hepatic Impairment: The effect of hepatic impairment on the clearance of nivolumab was evaluated by population PK analyses in patients with HCC and in patients with other tumors with mild hepatic impairment (total bilirubin [TB] less than or equal to the ULN and AST greater than ULN or TB greater than 1 to 1.5 times ULN and any AST) and in HCC patients with moderate hepatic impairment (TB greater than 1.5 to 3 times ULN and any AST). No clinically important differences in the clearance of nivolumab were found between patients with mild/moderate hepatic impairment.

Full details on the clinical pharmacology aspects of nivolumab can be found in the Investigator Brochure (IB).

3.3 Benefit/Risk Assessment

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

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

A pattern of immune-related adverse events has been defined, for which management algorithms have been developed; these are provided in Appendix 5. Most high-grade events were manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in these algorithms.

Additional details on the safety profile of nivolumab, including results from other clinical studies, are also available in the nivolumab IB.

3.3.1 Adult Patients

Emerging data have indicated that tumors of TMB-H are likely to may be more sensitive to IO therapies, thus eliciting improved efficacy in patients treated with IO therapies as elaborated previously. Of the tumor types included in this trial, despite of available chemotherapies for the

treatment of some of these tumors, the incremental benefit of such treatment after progression to first line regimen is small and represents an area of unmet medical need.

Overall, the safety profile of nivolumab monotherapy and nivolumab in combination with ipilimumab with the selected dose in this study are comparable. Most AEs were low-grade (Grade 1 to 2) with relatively few related high-grade (Grade 3 to 4) AEs (see Section 3.2.3. Nivolumab Combined with Ipilimumab Clinical Activity in Adults). Extensive details on the safety profile of nivolumab and the combination of nivolumab and ipilimumab are available in the nivolumab and ipilimumab Investigator Brochures and will not be repeated herein.

3.3.2 Adolescent Patients

The PK characteristics (e.g., steady-state peak and trough concentrations and terminal half-life) of many antibody-based therapeutic proteins are essentially comparable between pediatrics and adults once the effect of body size on PK is taken into consideration.[27,28] Research on immunotherapy for childhood tumors is still preliminary, but available data suggested similar PK profile of nivolumab to adult patients, and did not reveal significant safety concerns that are different from adult population (see Section 5.5.3). A report of the ongoing COG trial ADVL1412 (See Section 3.2.4) indicated good tolerability among the 78 participants treated to date with nivolumab monotherapy and 32 participants with nivolumab in combination with ipilimumab.

In summary, there is increasing clinical effort with IO therapy, including nivolumab and nivolumab in combination with ipilimumab in childhood malignancies, with the aim of delivering new effective therapies to children in a more timely fashion. This trial is being conducted to demonstrate clinical efficacy and safety in adolescent patients with TMB-H tumors. The doses and schedules of nivolumab and the combination of nivolumab with ipilimumab have been -studied and found to be well-tolerated. The potential benefit is that some or all of the TMB-H tumor types in this study will be sensitive to nivolumab alone and/or in combination with ipilimumab, thus yielding clinical benefit in these adolescent patients.

The benefit-risk information regarding adolescent participants is not applicable for sites in Belgium or the Netherlands as adolescents will not be included in these countries.

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Primary	
• To estimate BICR-assessed objective response rate (ORR) in participants of tTMB-H treated with nivolumab combined with ipilimumab	• BICR-assessed ORR using RECIST 1.1, and Response Assessment for Neuro-Oncology (RANO) criteria in primary CNS tumors
• To estimate BICR-assessed ORR in participants of bTMB-H treated with nivolumab combined with ipilimumab	• BICR-assessed ORR using RECIST 1.1, and RANO criteria in primary CNS tumors
Secondary	

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
• To estimate the BICR-assessed duration of response (DOR) and time to response (TTR) in participants of tTMB-H treated with nivolumab combined with ipilimumab	• BICR-assessed DOR • BICR-assessed TTR
• To estimate the BICR-assessed DOR and TTR in participants of bTMB-H treated with nivolumab combined with ipilimumab	• BICR-assessed DOR • BICR-assessed TTR
• To evaluate the BICR-assessed ORR, DOR and TTR in participants of tTMB-H treated with nivolumab monotherapy	• BICR-assessed ORR • BICR-assessed DOR • BICR-assessed TTR
• To evaluate the BICR-assessed ORR, DOR and TTR in participants of bTMB-H treated with nivolumab monotherapy	• BICR-assessed ORR • BICR-assessed DOR • BICR-assessed TTR
• To evaluate Investigator-assessed ORR, DOR, TTR in participants of tTMB-H treated with nivolumab combined with ipilimumab and nivolumab monotherapy	• Investigator-assessed ORR • Investigator-assessed DOR • Investigator-assessed TTR
• To evaluate Investigator-assessed ORR, DOR, TTR in participants of bTMB-H treated with nivolumab combined with ipilimumab and nivolumab monotherapy	• Investigator-assessed ORR • Investigator-assessed DOR • Investigator-assessed TTR
• To evaluate BICR-assessed and investigator-assessed clinical benefit rate (CBR) in participants of tTMB-H treated with nivolumab combined with ipilimumab and nivolumab monotherapy	• BICR-assessed CBR • Investigator-assessed CBR
• To evaluate BICR-assessed and investigator-assessed CBR in participants of bTMB-H treated with nivolumab combined with ipilimumab and nivolumab monotherapy	• BICR-assessed CBR • Investigator-assessed CBR
• To evaluate BICR-assessed and investigator-assessed progression free survival (PFS) in participants of tTMB-H treated with nivolumab combined with ipilimumab and nivolumab monotherapy	• BICR-assessed PFS • Investigator-assessed PFS
• To evaluate BICR-assessed and investigator-assessed PFS in participants of bTMB-H treated with nivolumab combined with ipilimumab and nivolumab monotherapy	• BICR-assessed PFS • Investigator-assessed PFS
• To evaluate overall survival (OS) in participants of tTMB-H treated with nivolumab combined with ipilimumab and nivolumab monotherapy	• Overall survival

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
• To evaluate OS in participants of bTMB-H treated with nivolumab combined with ipilimumab and nivolumab monotherapy	• Overall survival
• To assess overall safety and tolerability	• AEs, clinical laboratory values, or other safety biomarkers
• **Exploratory**	
• To assess overall health status and health utility	• Mean change from baseline in the 3-level version of the EQ-5D (EQ-5D-3L) visual analog scale (VAS) and utility index, respectively
• To assess cancer-related symptoms and quality of life	• Mean change from baseline in domains and symptoms in the 30-item European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30).
• To characterize the pharmacokinetics of nivolumab/ipilimumab and explore exposure-response relationships with respect to safety and efficacy	• Population pharmacokinetic parameters
• To assess immunogenicity of nivolumab/ipilimumab	• Incidence of anti-nivolumab/anti-ipilimumab antibodies
• To characterize tumor and host biomarkers	• Analysis of genomic, molecular, and immunohistochemical profiles
• To assess OS and BICR-assessed and investigator-assessed ORR, DOR, PFS in all participants of TMB-H treated with nivolumab combined with ipilimumab and nivolumab monotherapy	• OS • BICR-assessed ORR • BICR-assessed DOR • BICR-assessed PFS • Investigator-assessed ORR • Investigator-assessed DOR • Investigator-assessed PFS

5 STUDY DESIGN

5.1 Overall Design

The study will enroll participants diagnosed with select advanced or metastatic solid tumors with either tissue (tTMB) or blood TMB (bTMB) ≥ 10 mut/Mb. Both tissue and blood TMB will be assessed prior to randomization.

Participants without a prior known tTMB-H status available via F1CDx assay, or a prior known bTMB-validated CLIA result available from Foundation Medicine, will provide consent for pre-screening and TMB status determination, but consent for further screening procedures and study treatment should be deferred until TMB-H status is established. Screening process can continue when the participant is TMB-H.

Participants with a prior known result of **tTMB-H via F1CDx** assay or **bTMB-H from Foundation Medicine** may proceed immediately with full screening procedures. Both tissue and blood TMB will be assessed prior to randomization. Prior results of tTMB or bTMB obtained from any other assays except the ones described above are not acceptable, including prior result of tTMB obtained via Foundation One assay.

Once the TMB-H status is determined, this study will consist of three phases: screening, treatment, and follow-up.

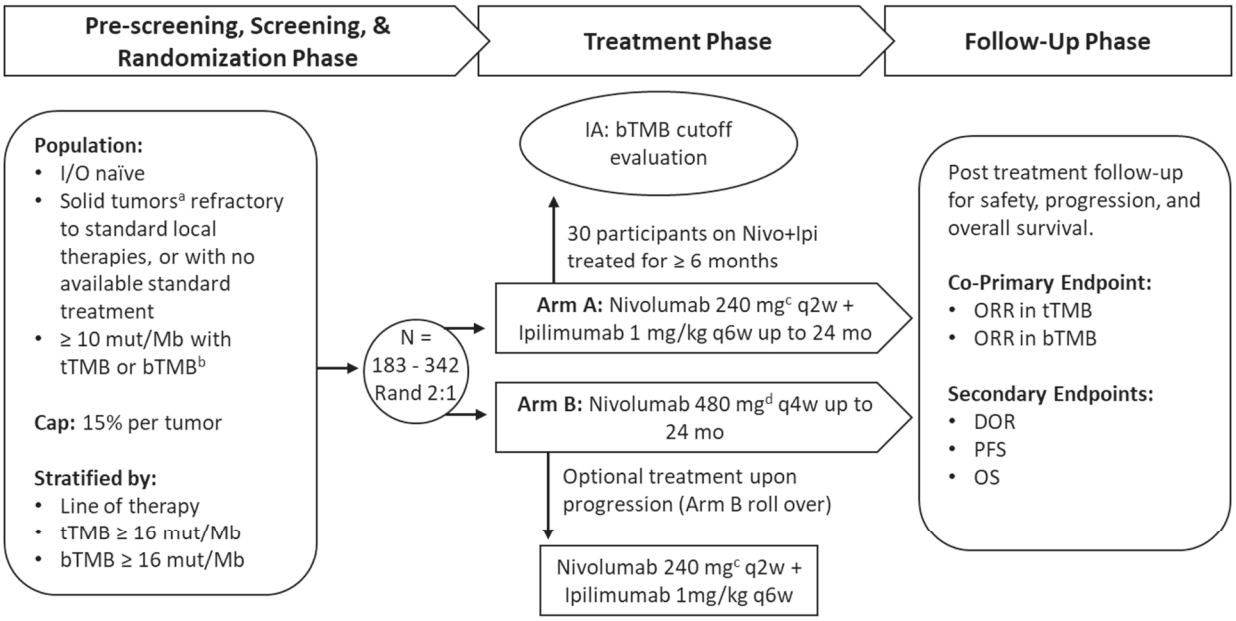
Efficacy will be evaluated using tumor specific response criteria, ie, RECIST 1.1 for solid tumors[29] and RANO criteria[30] for primary CNS tumors.

The primary analysis of BICR-assessed ORR in participants with either bTMB-H or tTMB-H will be conducted after a minimum of 12 months following LPFT. This study will end when analysis of the primary endpoint is complete. Additional survival analysis may be conducted for up to 5 years beyond the primary endpoint analysis.

Details regarding the assessments to be performed during these phases are outlined in Section 2 Schedule of Activities.

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

Figure 5.1-1: Study Design Schematic



[a] Excluding melanoma, NSCLC, RCC, and hematological malignancies.
[b] Both tTMB and bTMB results are required for randomization. tTMB ≥ 10 mut/Mb or the new cutoff value of bTMB determined by the 1st interim analysis (See Section 10.1 for further details on sample size).
[c] 3 mg/kg for adolescents with body weight < 40 kg.
[d] 6 mg/kg for adolescents with body weight < 40 kg.

Note: Mention of adolescents is not applicable for sites in Belgium or the Netherlands as adolescent participants will not be included in these countries.

Physical examinations, vital sign measurements, outcome questionnaires, biomarker collection, and clinical laboratory evaluations will be performed at selected times throughout study participation. Participants will be closely monitored for AEs throughout the study. Blood samples will be collected for safety, pharmacokinetic (PK) and biomarker analysis.

Participants with progressive disease while on treatment with nivolumab monotherapy may be allowed to be treated beyond progression with nivolumab and ipilimumab (see Section 7.4.3).

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.

5.1.1.1 Data Monitoring Committee

To provide independent oversight of safety, efficacy, and study conduct, a data monitoring committee (DMC) will be instituted. The DMC will meet regularly to ensure that participant safety is carefully monitored. The DMC will convene additional ad hoc meetings if necessary. Following each meeting, the DMC will recommend continuation, modification, or discontinuation of the study based on observed toxicities. The DMC will review the interim analysis results and determine whether the cut-off value for bTMB should be adjusted for the first interim analysis and whether criteria for superiority are met at that time for the tTMB interim analysis; the DMC will also review the bTMB final analysis results. A separate DMC charter will describe the activities of this committee in more detail.

5.1.1.2 Blinded Independent Central Review Committee

A Blinded Independent Central Review (BICR) Committee will be formed for standardized response assessment. Images will be submitted to an imaging third-party vendor for central review.

Imaging acquisition guidelines and submission process will be outlined in the CA209848 Study Imaging Manual to be provided by the vendors. For tumor types which require clinical indicators as part of the standard response assessment, the clinical indicator data will be provided to the BICR along with imaging data.

5.2 Number of Participants

The number of randomized participants will range from approximately 183 to 342 based on 1) the actually observed concordance between tTMB-H and bTMB-H, and 2) the new bTMB cutoff determined by the interim analysis should it occur (see Section 10.3.6). The per tumor type cap is approximately 15% of the total sample size.

5.3 End of Study Definition

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

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

5.4 Scientific Rationale for Study Design

The aim of this basket trial is to evaluate the efficacy of nivolumab in combination with ipilimumab in TMB-H advanced or metastatic solid tumors excluding melanoma, NSCLC and RCC. The clinical benefit of nivolumab and nivolumab in combination with ipilimumab in approved indications suggests that studying them in other cancers may identify additional clinical applications for which nivolumab in combination with ipilimumab will be safe and effective, particularly in tumors with TMB-H which are hypothesized to be more sensitive to immune checkpoint targeted therapies. CA209848 study will explore the clinical response and safety in participants with TMB-H.

5.4.1 TMB Cutoff and Stratification

High level of TMB is an emerging predictive biomarker for favorable clinical benefit in response to IO therapy, however a universal definition of "TMB high" has not been established. Most melanomas have a mutational load greater than 10 mutants/megabase (mut/Mb), and a large body of evidence demonstrated higher clinical efficacy in melanoma treated with IO therapy compared to many other tumor types which have less than 10 mut/Mb. In melanoma, nivolumab in combination with ipilimumab has convincingly demonstrated incremental efficacy than nivolumab monotherapy. In CA209568, in response to the treatment of nivolumab combined with ipilimumab in first line NSCLC patients, the ORR increased with higher TMB, and peaked at 10 mut/Mb (9% at <5 mut/Mb, 15% at ≥5-<10 mut/Mb, 44% at ≥ 10-<15 mut/Mb, and 39% at ≥15 mut/Mb). These findings suggest that TMB at 10 mut/Mb is an optimal cutoff for first line NSCLC patients. Recently, in CA209227, a phase 3 trial with first line NSCLC patients, nivolumab combined with ipilimumab demonstrated superior clinical benefit compared to chemotherapy in patients of TMB-H at a cutoff of ≥ 10 mut/Mb. Goodman A et al showed that with a TMB cut off of ≥20 mut/Mb, diverse tumor types, including melanoma, NSCLC and some rare tumors, responded well to anti-PD-1/anti-CTLA-4 with higher response rate, disease-free and overall survival[31]. In this study, we have chosen the TMB-H cut off for enrollment as ≥ 10 mut/Mb to maximize the probability of inclusion of potential responders. Participants at enrollment will also be stratified by TMB of 16 mut/Mb to ensure even distribution of participants with relatively low TMB and relatively high TMB between the 2 study arms, and allow further analysis based on TMB stratification.

5.4.2 Stratification with Line of Therapy

Patients at enrollment will be stratified by line of therapy to ensure even distribution of patients who have failed first line vs second line and beyond between the 2 arms. This is to minimize potential imbalance of differential response underlined by the different lines of therapy that the patients had received, and allow possible TMB–response analysis based on stratification of prior line of therapy.

5.4.3 Exclusion of Melanoma, NSCLC and RCC

Currently, multiple anti-PD-1/PD-L1 and/or anti-CTLA4 have been approved for Melanoma and NSCLC as first or second line treatment. Data from CA209227 highlighted superior clinical benefit of nivolumab combined with ipilimumab versus chemotherapy in first line NSCLC patients, which may provide additional effective treatment option for this population. The probability of identifying IO naïve participants with these two tumor types is considerably low. RCCs are characterized by one to two somatically acquired single nucleotide variants or small insertions and deletions per megabase pair, and have relatively low overall TMB.[32,33] Several analyses suggest that clinical response to IO therapy in RCC patients is independent of TMB, thus RCC is excluded from this study.[34,35]

5.4.4 Rationale for Treatment with Nivolumab and Ipilimumab after Disease Progression with Nivolumab Monotherapy

The combination of nivolumab with ipilimumab has demonstrated increased clinical benefit in comparison with nivolumab monotherapy in patients with melanoma and NSCLC as previously described. To maximize the potential clinical benefit for the patient, upon confirmed disease progression, patients who are initially randomized to the nivolumab monotherapy (arm B) have the option to receive nivolumab in combination ipilimumab, at the discretion of the investigator and upon discussion with the BMS Medical Monitor.

5.4.5 Rationale for Two Year Duration of Treatment

The optimal duration of immunotherapy is an important question and continues to be investigated. Clinical trials across different tumors types in the nivolumab and ipilimumab development program indicate that most of the responses occur early, with a median time to response of 2-4 months, and emerging data suggests that benefit can be maintained in the absence of continued treatment. A recent analysis in a melanoma study suggests the majority of patients who discontinue nivolumab and/or ipilimumab for toxicity maintain disease control in the absence of further treatment.[36] Furthermore, a limited duration of ipilimumab, including only 4 induction doses, resulted in long term survival in patients with metastatic melanoma, with a sustained plateau in survival starting around 2 years after the start of treatment.[37]

Accumulating data suggest that 2 years of PD-1 checkpoint inhibitor treatment may be sufficient for long term benefit. CA209003, a dose-escalation cohort expansion trial evaluating the safety and clinical activity of nivolumab in patients with previously treated advanced solid tumors (including 129 participants with NSCLC), specified a maximum treatment duration of 2 years. Among 16 participants with non-small cell lung cancer (NSCLC) who discontinued nivolumab after completing 2 years of treatment, 12 participants were alive >5 years and remained progression-free without any subsequent therapy. In the CA209003 NSCLC cohort, the overall survival (OS) curve begins to plateau after 2 years, with an OS rate of 25% at 2 years and 18% at 3 years.[38]These survival outcomes are similar to phase 3 studies in previously treated NSCLC, in which nivolumab treatment was continued until progression or unacceptable toxicity (2 year OS

rates of 23% and 29%, and 3 year OS rates of 16%-18% for squamous and non-squamous NSCLC respectively).[39]

Taken together, these data suggest that treatment beyond 2 years is unlikely to confer additional clinically meaningful benefit and that the risk of progression after discontinuing treatment at 2 years is low.

In contrast, a shorter duration of nivolumab of only 1 year was associated with increased risk of progression in previously treated patients with NSCLC, suggesting that treatment beyond 1 year is likely needed. In CA209153, patients with previously treated advanced NSCLC who completed 1 year of nivolumab therapy were randomized to either continue or stop treatment, with the option of retreatment upon progression. Among 163 patients still on treatment at 1 year and without progression, those who were randomized to continue nivolumab had significant improvement in progression-free survival (PFS) compared to those who were randomized to stop treatment, with median PFS (post-randomization) not reached vs 10.3 months, respectively; HR=0.42 (95% CI, 0.25 to 0.71). With a median follow-up of 14.9 months post-randomization, there also was a trend for patients on continued treatment to live longer (OS HR = 0.63 [95% CI: 0.33, 1.20]). Of note, the PFS curves in both groups plateau approximately 1 year after randomization (i.e., 2 years after treatment initiation), suggesting that there may be minimal benefit in extending treatment beyond a total of 2 years.[40]

Collectively, these data suggest that there is minimal if any benefit derived from continuing IO treatment beyond two years in advanced tumors. However, even though immunotherapy is well tolerated, patients will be at risk for additional toxicity with longer term treatment. Therefore, in this study, treatment will be given for a maximum of 2 years from the start of study treatment.

5.5 Justification for Dose

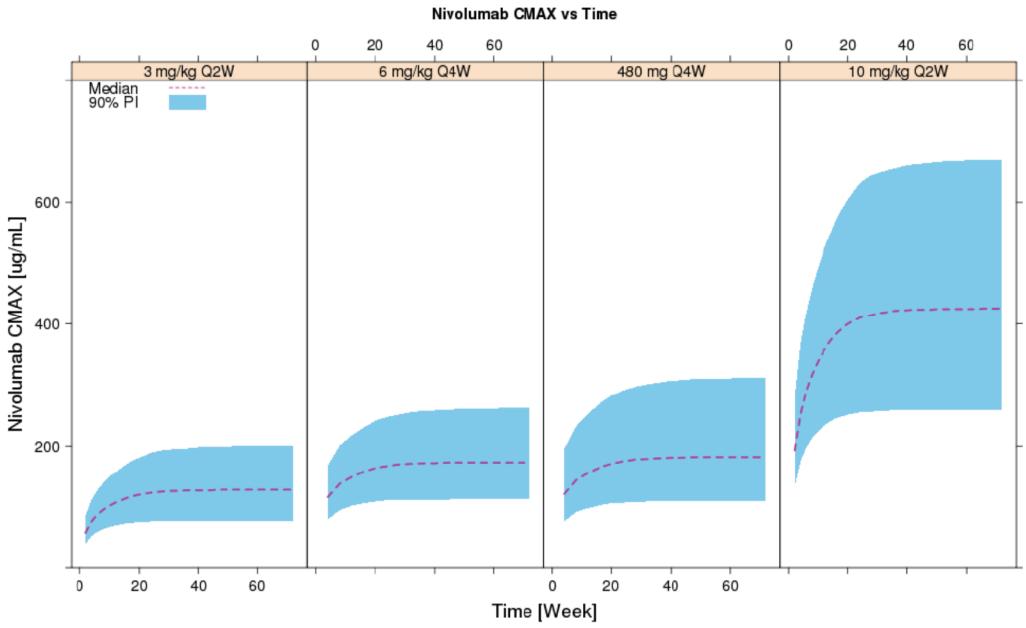
5.5.1 Rationale for Nivolumab Monotherapy Dose Selection

Nivolumab monotherapy has been extensively studied in multiple tumor types, including melanoma, NSCLC, renal cell carcinoma (RCC), classical Hodgkin's lymphoma (cHL), head and neck (H&N) and urothelial carcinoma (UC), using body weight normalized dosing (mg/kg), and has been safely administered at doses up to 10 mg/kg Q2W. Nivolumab is currently approved for the treatment of various tumors, including melanoma, NSCLC, RCC, cHL, SCCHN, and UC, using a regimen of either nivolumab 240 mg Q2W or nivolumab 480 mg Q4W.

The nivolumab 480 mg Q4W dose was selected for this study based on clinical data and modeling and simulation approaches using population pharmacokinetics (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 RCC) with body weight-normalized dosing (mg/kg).[41] 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 compared to those following nivolumab 3 mg/kg Q2W, the initially approved dose. The overall distributions of average nivolumab steady-state exposures (Cavgss) are comparable following administration with either nivolumab 3 mg/kg Q2W or nivolumab 480 mg Q4W. Nivolumab 480 mg Q4W is predicted to result in approximately 43% greater steady-state peak concentrations (Cmaxss) 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 Cmaxss of nivolumab is expected to be greater following nivolumab 480 mg Q4W compared to nivolumab 3 mg/kg Q2W, the predicted Cmaxss following nivolumab 480 mg Q4W is well below the median Cmaxss achieved following administration of nivolumab 10 mg/kg Q2W, a safe and tolerable dose level (Figure 5.5.1-1).

Figure 5.5.1-1: Predicted Nivolumab Cmax (with 90% PI) versus Time by Dosing Regimen



Exposure-safety analysis demonstrated that the exposure margins for safety are maintained following nivolumab 480 mg Q4W, and the predicted risks of AE-DC/D, AE Grade 3+, and AE-IM 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 shown to be well tolerated.[42] Nivolumab 480 mg Q4W is predicted to be approximately 16% lower steady-state trough concentrations (Cminss) compared to nivolumab 3 mg/kg Q2W. While 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.

5.5.2 Nivolumab/Ipilimumab Combination Therapy Dose Selection and Duration

The clinical pharmacology profiling of the combination of nivolumab and ipilimumab together with an overview of the results of these analyses are summarized below. In addition, the Clinical Pharmacology Section of the product labels for ipilimumab and nivolumab, as well as the Investigator Brochures, have additional details.[43,44,45,46]

5.5.2.1 Population Pharmacokinetics of Nivolumab

The PK, clinical activity, and safety of nivolumab has been assessed in completed and ongoing Phase 1, 2, and 3 studies in adult subjects with non-small cell lung cancer (NSCLC), melanoma, and renal cell carcinoma (RCC) in addition to other tumor types.[47]

The PK of nivolumab as monotherapy was characterized by PPK analysis. Nivolumab clearance increased with baseline body weight, estimated glomerular filtration (eGFR), and Eastern Cooperative Oncology Group (ECOG) performance status > 0. The PPK analysis was performed using data from 1908 subjects who received nivolumab from the following studies: nivolumab monotherapy data from studies MDX-1106-01, ONO-4538-01, ONO-4538-02, MDX-1106-03, CA209010, CA209063, and CA209037. Studies CA209004, CA209069, CA209066, and CA209067 provided PK data of nivolumab monotherapy as well as in combination with ipilimumab in the target population (advanced melanoma) who received the proposed dosing regimens. The data from these studies also allowed for an evaluation of potential drug interactions between nivolumab and ipilimumab and of the effect of immunogenicity on clearance. Thus, for this analysis, the covariates assessed included ADA status, baseline ECOG status, baseline eGFR, baseline body weight (BW), gender and co-administration of ipilimumab.

Co-administration with ipilimumab 3 mg/kg resulted in a modest increase in nivolumab CL of 35% whereas co-administration with ipilimumab 1 mg/kg did not appear to have an effect on nivolumab CL. Presence of anti-nivolumab antibodies increased nivolumab CL by 25%, consistent with prior findings. In subjects with an ECOG performance status of > 0, nivolumab CL was 22% higher (based on median values). Male subjects had a median of 12% higher volume of distribution of central compartment (VC) than females. Baseline body weight was identified as a significant covariate for both CL and VC and the magnitude of the effect of baseline eGFR on CL was not considered clinically relevant. The geometric mean CL, Vss, and terminal half-life of nivolumab were 9.83 mL/h, 7.62 L, and 24.1 days, respectively. When administered in combination, the CL of nivolumab was increased by 35%, whereas there was no effect on the clearance of ipilimumab.

5.5.2.2 Population Pharmacokinetics of Ipilimumab

The PPK of ipilimumab was evaluated using data from 1345 subjects in 4 Phase 2 studies with ipilimumab monotherapy (CA184004, CA184007, CA184008, and CA184022), as well as one Phase 1 study (CA209004), one Phase 2 study (CA209069) and one Phase 3 study (CA209067) with ipilimumab monotherapy and nivolumab in combination with ipilimumab. The ipilimumab data from CA209004, CA209069, and CA209067 are included as they provide ipilimumab PK samples that were collected in combination with nivolumab in the target population. The data from 4 ipilimumab monotherapy studies (CA184004, CA184007, CA184008, and CA184022) were included in the PPK analysis, to enable the assessment of the potential nivolumab effect on ipilimumab PK.

The co-administration of ipilimumab (3 mg/kg) with nivolumab 0.3 mg/kg and nivolumab 3.0 mg/kg resulted in minimal changes in ipilimumab CL (-7.5% and 11%, respectively); however, sample sizes at these doses were small. The CL of ipilimumab co-administered with 1 mg/kg nivolumab was estimated to be 1% higher (95% CI: 97.8 - 106) relative to the CL of ipilimumab monotherapy, demonstrating that ipilimumab CL is unaffected by co-administration of 1 mg/kg nivolumab. Ipilimumab CL was estimated to increase by 6% (95% CI: 96.5 - 115) in the presence of ipilimumab ADA, as measured by the drug tolerant (2nd generation) assay. This effect is not considered to be statistically significant (95% CI includes 1). Ipilimumab CL and VC increased with increasing baseline body weight, and ipilimumab CL increased with increasing baseline LDH.

5.5.2.3 Pharmacokinetics of Nivolumab and Ipilimumab

The PK of nivolumab and ipilimumab, when administered in combination, were characterized by summary statistics of observed data from CA209004 and by PPK analyses using serum concentration data collected in studies CA209004, CA209069 and CA209067.

A dose-related increase in nivolumab peak and trough concentrations was observed after the first dose in Study CA209004. Peak and trough concentrations after the first dose for 1 mg/kg of nivolumab in combination with 3 mg/kg of ipilimumab Q3W were in the range of 18.1 - 21.5 μg/mL and 3.2 - 4.8 μg/mL, respectively. Ipilimumab peak concentrations at 3 mg/kg in combination with 1 mg/kg nivolumab after the first dose were in the range of 63.5 - 68.5 μg/mL. Ipilimumab trough concentrations at 3 mg/kg in combination with 1 mg/kg nivolumab after the first dose were in the range of 9.8 - 11.9 μg/mL.

5.5.3 Dose 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.[27,28] Therefore, in general, adult doses would be expected to achieve similar systemic exposures in adolescents.

PK data after first dose in pediatric patients are available from CA209-908 and ADVL 1412 / CA209-070, where patients were treated with nivolumab 3 mg/kg and ipilimumab 1 mg/kg Q3W followed by nivolumab monotherapy. Serum peak and trough concentrations (geometric means [CV%]) after the first dose of nivolumab and ipilimumab, in adolescent patients are presented in Table 5.5.3-1. These values are very similar to geometric mean peak and trough concentrations in

adults who received similar dose regimen for nivolumab and ipilimumab, including NSCLC (n=501) with nivolumab (peak = 61.8 and trough = 17.5 µg/mL), and RCC (n = 497) with nivolumab (peak = 62 µg/mL, and trough = 15.3 µg/mL) and ipilimumab (peak = 19.7 µg/mL, and trough=3.93 µg/mL) (BMS internal data).

Table 5.5.3-1: Pharmacokinetics data after first dose in adolescents (12 - <18 years) patients from CA209-908 and CA209-070 (COG) study who received Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg Q3W

	CA209-908 study	CA209-070 (COG) study
Nivolumab 3 mg/kg		
Cmax 1[a] (µg/mL)	72.4 (34.5) N=6	55.3 (13) N=5
Cmin 1[b] (µg/mL)	18.3 (40.6) N=3	15.9 (23.8) N=8
Ipilimumab 1 mg/kg		
Cmax 1 (µg/mL)	20.4 (48.2) N=6	19.1 (24.1) N=16
Cmin 1 (µg/mL)	3.4 (50.1) N=3	3.53 (33.6) N=7

[a] Cmax1 = Peak concentration after first dose.

[b] Cmin1 = Trough concentration after first dose.

Population PK model based simulation has shown that exposures produced by nivolumab 480 mg Q4W and 240 mg Q2W were well below the simulated exposure range of a 10 mg/kg Q2W regimen, a previously established clinically safe dose. The body weight range for adults subjects that established the population PK model used for simulation was 34-180 kg. 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 weight-based dose that is equivalent to the adult dose (typical participant of 80-kg body weight). Adolescents with body weight ≥ 40 kg will be administered nivolumab 240 mg Q2W in nivo/ipi arm, and nivolumab 480 mg Q4W in the monotherapy arm. Adolescents < 40 kg will be administered body weight adjusted nivolumab dose of 3 mg/kg Q2W in the nivolumab in combination with ipilimumab arm, and 6 mg/kg Q4W in the monotherapy arm.

This section is not applicable for sites in Belgium or the Netherlands as adolescent participants will not be included in these countries.

5.5.4 Clinical Pharmacology Summary

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

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

Nivolumab with ipilimumab: When nivolumab 1 mg/kg was administered in combination with ipilimumab 3 mg/kg, the CL of nivolumab was increased by 29%, and the CL of ipilimumab was unchanged compared to nivolumab administered alone. When nivolumab 3 mg/kg was administered in combination with ipilimumab 1 mg/kg, the CL of nivolumab and ipilimumab were unchanged. When nivolumab was administered in combination with ipilimumab, the presence of anti-nivolumab antibodies increased the CL of nivolumab by 20%, and the CL of ipilimumab was unchanged in the presence of anti-ipilimumab antibodies.

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

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

Hepatic Impairment: The effect of hepatic impairment on the clearance of nivolumab was evaluated by population PK analyses in patients with HCC and in patients with other tumors with mild hepatic impairment (total bilirubin [TB] less than or equal to the ULN and AST greater than ULN or TB greater than 1 to 1.5 times ULN and any AST) and in patients with HCC with moderate hepatic impairment (TB greater than 1.5 to 3 times ULN and any AST). No clinically important differences in the clearance of nivolumab were found between patients with mild/moderate hepatic impairment.

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

5.5.5 Rationale for 30-minute Infusion

Long infusion times place a burden on patients and treatment centers. Establishing that nivolumab and ipilimumab can be safely administered using shorter infusion times of 30 minutes' duration will diminish the burden, provided that there is no change in the safety profile. Previous clinical studies of nivolumab and ipilimumab monotherapies and the combination of nivolumab and ipilimumab have used a 60-minute infusion duration for nivolumab and a 90-minute infusion duration for ipilimumab (1 - 3 mg/kg dosing for both). However, both nivolumab and ipilimumab have been administered at up to 10 mg/kg with the same infusion duration (ie, 60 minutes).

Establishing that nivolumab can be safely administered using a shorter infusion time (30 minutes) is under investigation. Previous clinical studies of nivolumab monotherapy have used a 60-minute infusion duration wherein, nivolumab has been safely administered up to 10 mg/kg over long treatment periods. Infusion reactions including high-grade hypersensitivity reactions have been uncommon across nivolumab clinical program. In CA209010, a dose association was observed for infusion site reactions and hypersensitivity reactions (1.7% at 0.3 mg/kg, 3.7% at 2 mg/kg and 18.5% at 10 mg/kg). All the events were Grade 1-2 and were manageable. An infusion duration of 30 minutes for 3 mg/kg nivolumab (30% of the dose provided at 10 mg/kg) is not expected to present any safety concerns compared to the prior experience at 10 mg/kg nivolumab dose infused over a 60-minute duration. The safety of nivolumab 3 mg/kg administered as a 30-min infusion was assessed in CA209153 in patients (n = 322) with previously treated advanced NSCLC. Overall, there were no clinically meaningful differences in the frequency of hypersensitivity/infusion-related reactions (of any cause or treatment-related) in patients administered nivolumab over a 30-minute infusion compared with that reported for patients with the 60-minute infusion. Thus, it was shown that nivolumab can be safely infused over 30 minutes.

Similarly, ipilimumab at 10 mg/kg has been safely administered over 90 minutes. In participants with advanced Stage II or Stage IV melanoma (CA184022 Study), where ipilimumab was administered up to a dose of 10 mg/kg, on-study drug related hypersensitivity events (Grade 1/2) were reported in 1 participant (1.4%) in the 0.3 mg/kg and in 2 participants (2.8%) in the 10 mg/kg group. There were no drug-related hypersensitivity events reported in the 3 mg/kg group. Across the 3 treatment groups, no Grade 3/4 drug-related hypersensitivity events were reported and there were no reports of infusion reactions. Ipilimumab 10 mg/kg monotherapy has also been safely administered as a 90-minute infusion in a large Phase 3 study in prostate cancer (CA184043) and as adjuvant therapy for Stage III melanoma (CA184029), with infusion reactions occurring in participants. Administering 3 mg/kg of ipilimumab represents approximately one-third of the 10 mg/kg dose.

Overall, infusion reactions including high-grade hypersensitivity reactions have been uncommon across clinical studies of nivolumab, ipilimumab, and nivolumab/ipilimumab combinations. Overall, a change in safety profile is not anticipated with 30-minute infusions of nivolumab, ipilimumab or combination.

In addition, nivolumab is approved as 30-minute infusion (as monotherapy or combination therapy) for the treatment of various tumor types.[48] Ipilimumab 1 mg/kg Q6W is approved as a

30-minute infusion when combined with nivolumab for the treatment of metastatic NSCLC and mesothelioma.[49]

6 STUDY POPULATION

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

6.1 Inclusion Criteria

1) Signed Written Informed Consent

a) Prior to study participation, written informed consent from participants, or in the case of minors, written permission (informed consent) from parents (both, if required by local law), guardians, or legally acceptable representatives must be obtained according to local laws and regulations

b) Assent from minor participants should be obtained per local laws and regulations and should be documented in accordance with local requirements.

c) Written informed consent and HIPAA authorization (applies to covered entities in the USA only) obtained from the participant/legal representative prior to performing any protocol-related procedures, including screening evaluations

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

2) Type of Participant and Target Disease Characteristics

a) Participants with a refractory, metastatic, or unresectable histologically or cytologically confirmed solid malignant tumor with TMB-H who are refractory to standard therapies per local management guidelines, or for which no standard treatment per local management guidelines is available (salvage setting).

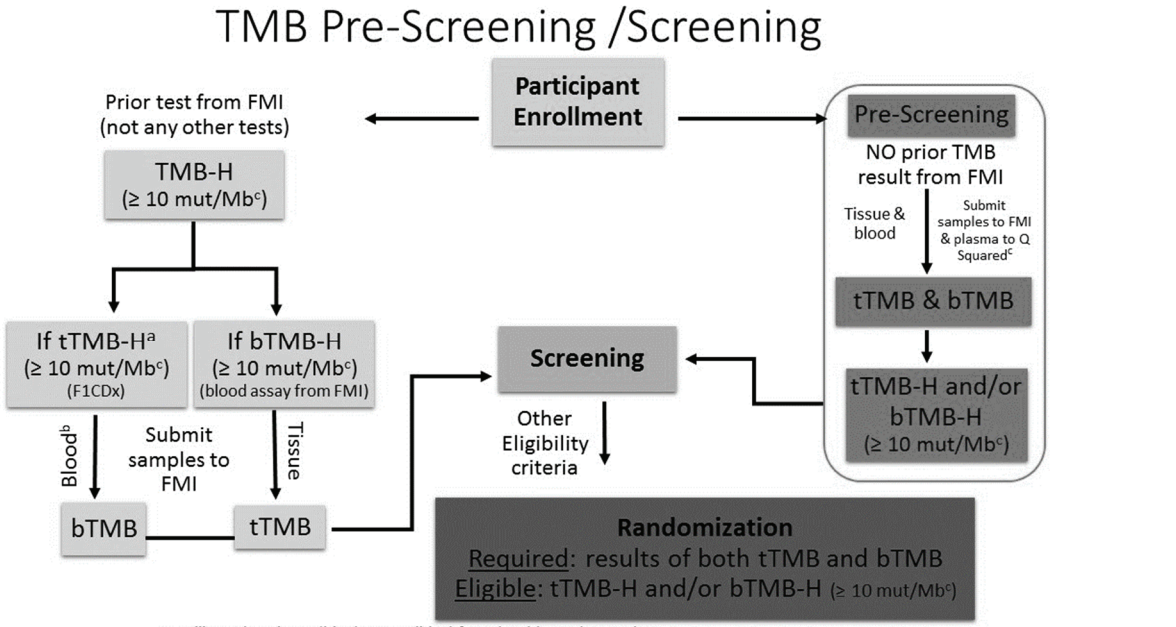
i) Treatment with botanical preparations alone (e.g. herbal supplements or traditional Chinese medicines) are not considered a line of therapy.

b) Either a formalin-fixed, paraffin-embedded (FFPE) tissue block or unstained tumor tissue sections, obtained within 9 months and no additional intervening therapy (excluding the current line of therapy and palliative local therapy) prior to enrollment, with an associated pathology report, must be submitted to the core laboratory for inclusion. Palliative local therapy includes palliative radiation therapy and palliative surgical resection to symptomatic non primary bone lesions, skin lesions, or CNS lesions (only for peripheral solid tumors, not applicable for CNS primary tumor). Radiation to the primary lesions and systemic chemotherapy are not considered palliative therapy. Biopsy should be excisional, incisional or core needle. Fine needle aspiration is unacceptable for submission

i) If a fresh biopsy is warranted, the participant must have a lesion that can be biopsied at an acceptable clinical risk as judged by the investigator in order to be eligible for the study

c) The IRT must be provided with the results of both tissue and blood TMB-H testing for eligible participants prior to randomization. Both results are utilized for stratification purposes (see Figure 6.1-1).

Figure 6.1-1: TMB Pre-Screening/Screening



i) Participants must have either tTMB or bTMB ≥ 10 mut/Mb (tTMB ≥ 10 mut/Mb or the new cutoff value of bTMB determined by the 1st interim analysis). Should one of the two populations (tTMB-H or bTMB-H) reach the targeted sample size before the other, then enrollment will continue only with participants for the other TMB-H population (bTMB-H or tTMB-H, see details in Section 10.1).

ii) Prior results of TMB-H obtained with F1CDx assay (tissue) or bTMB-validated CLIA assay from Foundation Medicine (blood) are acceptable for eligibility purposes.

(1) If tTMB result is available, blood sample must be provided for central TMB testing

(2) If bTMB result is available, tissue sample must be provided for central TMB testing

(3) If neither tTMB nor bTMB result is available, both tissue and blood samples must be provided for central TMB testing

iii) TMB results obtained from any other assays are not acceptable for eligibility.

d) Participants must have an Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 1 (participants > 16 years old with solid tumors), Karnofsky Performance Score (KPS) ≥ 80 (participants > 16 years old with primary CNS tumors) or Lansky Performance Score (LPS) ≥ 80 (participants 12 to 16 years old ONLY). For details, see Appendix 6 and 9.

e) Participants must have measurable disease for response assessment as per RECIST 1.1 for solid tumors other than CNS, and RANO criteria for primary CNS malignancies.

3) Age and Reproductive Status

a) Males and Females, ages of 12 years and older

i) If adolescents are not allowed to participate, then ≥ 18 years applies

b) Women of childbearing potential (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 breastfeeding

d) WOCBP must agree to follow instructions for method(s) of contraception for the duration of study treatment and 5 months after the last dose of study treatment (i.e., 30 days [duration of ovulatory cycle] plus the time required for the investigational drug to undergo approximately five half-lives).

e) Not Applicable per Protocol Amendment 04: Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of study treatment and 7 months after the last dose of study treatment (i.e., 90 days [duration of sperm turnover] plus the time required for the investigational drug to undergo approximately five half-lives). In addition, male participants must be willing to refrain from sperm donation during this time.

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

Investigators shall counsel 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.

The inclusion of adolescents is not applicable for sites in Belgium or the Netherlands as adolescent participants will not be included in these countries. Participants in these countries must be 18 years of age or older.

6.2 Exclusion Criteria

1) Medical Conditions

a) Women with a positive pregnancy test at enrollment or prior to administration of study medication.

b) Participants with melanoma, non-small cell lung cancer, renal cell carcinoma or hematological malignancy as primary site of disease are not eligible for this study.

c) Active brain metastases (excluding primary CNS malignancies) or leptomeningeal metastases. Participants with brain metastases are eligible if these have been treated and there is no magnetic resonance imaging (MRI) evidence of progression for at least 4 weeks after treatment is complete and within 28 days prior to first dose of study drug administration. There must also be no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalents for adults, or > 0.25 mg/kg daily prednisone equivalent for adolescents) for at least 2 weeks prior to study drug administration.

d) Prior malignancy active within the previous 2 years except for locally curable cancers that have been apparently cured or successfully resected, such as basal or squamous cell skin cancer, superficial bladder cancer, or GC, or carcinoma in situ of the prostate, cervix, or breast.

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

f) Excluding participants with serious or uncontrolled medical disorders.

2) Prior/Concomitant Therapy

a) Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents for adults, or > 0.25 mg/kg daily prednisone equivalent for adolescent) or other immunosuppressive medications within 14 days of study treatment. Inhaled or topical steroids and adrenal replacement doses > 10 mg daily prednisone equivalents for adults, or > 0.25 mg/kg daily prednisone equivalent for adolescents are permitted, in the absence of active autoimmune disease.

b) Participants who received prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways

c) All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have resolved to Grade 1 (NCI CTCAE version 5) or baseline before administration of study drug. Participants with toxicities attributed to prior anti-cancer therapy which are not expected to resolve and result in long lasting sequelae, such as neuropathy after platinum based therapy, are permitted to enroll.

d) Treatment with any chemotherapy, radiation therapy, biologics for cancer, or investigational therapy within 28 days (or, for primary CNS tumors, within 12 weeks of completion of radiation therapy) of first administration of study treatment (participants with prior cytotoxic or investigational products (IP) < 4 weeks prior to randomization might be eligible after discussion between investigator and sponsor, if toxicities from the prior treatment have been resolved to Grade 1 (NCI CTCAE version 5).

e) Treatment with botanical preparations (e.g. 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.

f) Known history of 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.

g) Participants must not have received a live / attenuated vaccine within 30 days of first treatment.

3) Physical and Laboratory Test Findings

Participants with any of the following lab criteria will be excluded from the study:

a) WBC < 2000/μL

b) Neutrophils < 1500/μL

c) Platelets < $100x10^3$/μL

d) Hemoglobin < 9.0 g/dL

e) Serum creatinine:

– For participants ≥ 18 years old: Serum creatinine > 1.5 x ULN unless creatinine clearance ≥ 40 mL/min (measured or calculated using the Cockcroft Gault formula):

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

Male CrCl = ([140 - age in years] x weight in kg x 1.00)/ (72 x serum creatinine in mg/dL)

– For participants ≥ 12 years old and < 18 years old, consider a serum creatinine based the table below, unless creatinine clearance ≥ 70 ml/min/1.73 m^2 calculated using the Schwartz formula:

Ped CrCl = (k x Ht)/Cr

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
12 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
16 to < 18 years	1.7	1.4

Note: the threshold values in this table were derived from the Schwartz formula for estimating GFR,[50] utilizing child length and stature data published by the US Centers for Disease Control and Prevention

f) AST or ALT > 3.0 x ULN

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

h) 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).

4) Allergies and Adverse Drug Reaction

a) History of severe hypersensitivity reactions to other monoclonal antibodies

b) History of allergy or hypersensitivity to study drug components

5) Other Exclusion Criteria

a) Prisoners or participants who are 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 Bristol-Myers Squibb approval is required.

b) Participants who are compulsorily detained for treatment of either a psychiatric or physical (e.g. 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.

The mention of adolescents is not applicable for sites in Belgium or the Netherlands as adolescent participants will not be included in these countries. Participants in these countries must be 18 years of age or older.

6.3 Lifestyle Restrictions

Not applicable. No restrictions are required

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but who are not subsequently entered in the study/included in the analysis population. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, as applicable, and to respond to queries from regulatory authorities. Minimal information includes date of consent, demography, screen failure details, eligibility criteria, and any serious AEs.

6.4.1 Retesting During Screening Period

Participant Re-enrollment: This study permits the re-enrollment of a participant that has discontinued the study as a pre-treatment failure (i.e. participant has not been randomized / has not been treated). If re-enrolled, the participant must be re-consented.

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 may be repeated in an effort to find all possible well-qualified participants. Consultation with the Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

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:

An IP, also known as investigational medicinal product in some regions, is defined a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently 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 preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as non-IP.

IPs used in this trial are provided in Table 7-1. There are no non-IPs in this study.

For body weight-based dosing, the dosing calculations should be based on the body weight assessed at baseline. It is not necessary to re-calculate subsequent doses if the participant weight is within 10% of the weight used to calculate the previous dose. All doses should be rounded up or to the nearest milligram per institutional standard.

Table 7-1: Study treatments for CA209848					
Product Description / Class and Dosage Form	**Potency**	**IMP/ Non-IMP**	**Blinded or Open Label**	**Packaging / Appearance**	**Storage Conditions (per label)**
Nivolumab (BMS-936558-01) Solution for Injection	100 mg (10 mg/mL) and 40 mg (10 mg/mL)	IMP	Open label	Vial or various packaging configurations	Refer to the label on container and/or pharmacy manual
Ipilimumab (BMS-734016) Solution for Injection	200 mg (5 mg/mL)	IMP	Open label	Vial or various packaging configurations	Refer to the label on container and/or pharmacy manual

7.1 Treatments Administered

The selection and timing of dose for each participant is as follows:

Table 7.1-1: Selection and Timing of Dose

Treatment Arm	Study Treatment	Participant Age/Weight	Unit dose strength(s)/ Dosage level(s)	Frequency of Administration	Route of Administration
Arm A or Arm B Rollover: nivolumab in combination with ipilimumab	Nivolumab	Adults and adolescents ≥ 40kg	240 mg	Q2 weeks up to 24 months	IV
		Adolescents < 40kg	3 mg/kg	Q2 weeks up to 24 months	IV
	Ipilimumab	All participants	1 mg/kg	Q6 weeks up to 24 months	IV
Arm B: nivolumab monotherapy	Nivolumab	Adults and adolescents ≥ 40kg	480 mg	Q4 weeks up to 24 months	IV
		Adolescents < 40kg	6 mg/kg	Q4 weeks up to 24 months	IV

Note: The mention of adolescents is not applicable for sites in Belgium or the Netherlands as adolescent participants will not be included in these countries.

7.1.1 Arm A or Arm B Rollover – Nivolumab in Combination with Ipilimumab

Nivolumab will be administered every 2 weeks. Adult participants and adolescents ≥ 40kg will receive nivolumab at a dose of 240 mg, and adolescents < 40kg will receive nivolumab at a dose of 3mg/kg; in both cases, nivolumab will be administered as an approximately 30-minute infusion on Day 1 of each treatment cycle. Ipilimumab will be administered every 6 weeks; all participants will receive ipilimumab at a dose of 1mg/kg. If needed, flush the intravenous line with an appropriate amount of diluent (e.g. 0.9% sodium chloride or 5% dextrose in water) to ensure that the complete dose is administered over approximately 30 minutes. Participants should begin study treatment within 3 calendar days of randomization.

When study treatments (nivolumab and ipilimumab) are to be administered on the same day, nivolumab is to be administered first. Nivolumab infusion must be promptly followed by a flush of diluent to clear the line of nivolumab before starting the ipilimumab infusion. The second infusion will always be the ipilimumab study treatment and will start after the infusion line has been flushed, filters changed and patient has been observed to ensure no infusion reaction has occurred.

Nivolumab and ipilimumab treatment will continue until disease progression, discontinuation due to unacceptable toxicity, withdrawal of consent, or study closure. Participants will be treated up to 24 months in the absence of disease progression or unacceptable toxicity. Maximum 24 months of treatment also applies to treatment beyond progression.

Ipilimumab is not permitted to continue on study after nivolumab is discontinued. The assessment for discontinuation of nivolumab should be made separately from the assessment made for discontinuation of ipilimumab. Although there is overlap among the discontinuation criteria, if discontinuation criteria are met for ipilimumab but not for nivolumab, treatment with nivolumab may continue at the same dose and schedule if ipilimumab is discontinued. If a participant meets criteria for discontinuation and investigator is unable to determine whether the event is related to all or any one study drug, the participant should discontinue all study drugs and be taken off the treatment phase of the study.

For ipilimumab preparation and storage instructions, refer to ipilimumab IB[51] and/or pharmacy manual.

Separate infusion bags and filters should be used when administering nivolumab and ipilimumab on the same day.

Ipilimumab is to be administered as an approximately 30-minute IV infusion and may be infused using a volumetric pump with a 0.2 to 1.2 micron low-protein binding in-line filter at the protocol-specified dose. It is not to be administered as an IV push or bolus injection. Care must be taken to assure sterility of the prepared solutions, since the drug product does not contain any antimicrobial preservatives or bacteriostatic agents. At the end of the infusion, flush the line with a sufficient quantity of diluent.

The mention of adolescents is not applicable for sites in Belgium or the Netherlands as adolescent participants will not be included in these countries.

7.1.2 Arm B – Nivolumab Monotherapy

Adult participants and adolescents ≥ 40kg will receive nivolumab at a dose of 480 mg. Adolescents < 40kg will receive nivolumab at a dose of 6mg/kg. In both cases, nivolumab will be administered as an approximately 30-minute infusion on Day 1 of each treatment cycle until progression, unacceptable toxicity, withdrawal of consent, completion of 24 months of treatment, or the study ends, whichever occurs first. If needed, flush the intravenous line with an appropriate amount of diluent (e.g. 0.9% sodium chloride or 5% dextrose in water) to ensure that the complete dose is administered over approximately 30 minutes. Participants should begin study treatment within 3 calendar days of randomization.

For nivolumab preparation and storage instructions, please refer to the nivolumab IB and/or pharmacy manual.

All participants will be monitored continuously for AEs while on study treatment. Treatment modifications (e.g. dose delay, reduction, retreatment, or discontinuation) will be based on specific laboratory and adverse event criteria, as described in Sections 7.4.1 and Section 8.

The mention of adolescents is not applicable for sites in Belgium or the Netherlands as adolescent participants will not be included in these countries.

7.2 Method of Treatment Assignment

All participants will be *assigned to treatment* using an Interactive Response Technology (IRT). Before the study is initiated, each user will receive log in information and directions on how to access the IRT.

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

7.3 Blinding

This is an open-label study, blinding procedures are not applicable.

7.4 Dosage Modification

Dose escalations or reductions of nivolumab or ipilimumab are not allowed. Participants may be dosed no less than 12 days from the previous dose during Q2W cycles. For Q4W dosing cycles, participants may be dosed within a ±3 day window, and there should be a minimum of 22 days between doses. Premedications are not recommended for the first dose of nivolumab or nivolumab combined with ipilimumab.

Participants should be carefully monitored for infusion reactions during nivolumab and ipilimumab administration. If an acute infusion reaction is noted, participants should be managed according to Section 7.

Doses of nivolumab and ipilimumab may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment. Dosing visits are not skipped, only delayed.

7.4.1 Dose Delay Criteria

Delay administration of both nivolumab and ipilimumab if any of the delay criteria in Section 7.4.1 are met. Delay nivolumab and ipilimumab dosing for any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Delay dosing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, either confirmed or suspected.

For participants who require delay of nivolumab and ipilimumab, re-evaluate weekly or more frequently if clinically indicated and resume dosing when criteria to resume treatment are met (see Section 7.4.2).

Continue tumor assessments per protocol even if dosing is delayed.

Table 7.4.1-1: Adverse Event Criteria for Delay, Resumption, and Discontinuation of Nivolumab and Ipilimumab

Drug-related Adverse Event (AE) per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resumption Criteria
Gastrointestinal			
Colitis or diarrhea	Grade 2	Delay dose	Dosing may resume when AE resolves to baseline.
	Grade 3	Nivolumab monotherapy: Delay dose	Dosing may resume when AE resolves to baseline.
		When administered with ipilimumab: Permanently discontinue ipilimumab	Nivolumab monotherapy may be resumed when AE resolves to baseline. If Grade 3 diarrhea or colitis recurs while on nivolumab monotherapy, permanently discontinue.
	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	Delay dose or 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

Table 7.4.1-1: Adverse Event Criteria for Delay, Resumption, and Discontinuation of Nivolumab and Ipilimumab

Drug-related Adverse Event (AE) per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resumption Criteria
			treatment, a discussion between the investigator and the Medical Monitor/designee must occur and approval from the Medical Monitor must be obtained prior to resuming therapy.
	Concurrent AST or ALT > 3 x ULN and T.bili > 2 x ULN, regardless of baseline value	Permanently discontinue	
Endocrinopathy			
Adrenal insufficiency	Grade 2 adrenal insufficiency	Delay dose	Dosing may resume after adequately controlled with hormone replacement.
	Grade 3 or 4 adrenal insufficiency or adrenal crisis	Delay dose or permanently discontinue	Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If adrenal insufficiency resolves or is adequately controlled with physiologic hormone replacement, participant may not require discontinuation of study 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 7.4.1-1: Adverse Event Criteria for Delay, Resumption, and Discontinuation of Nivolumab and Ipilimumab

Drug-related Adverse Event (AE) per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resumption 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.
	Any grade drug-related encephalitis	Permanently discontinue	
Myelitis	Any grade myelitis	Delay dose	After workup for differential diagnosis, (ie, infection, tumor-related), if myelitis is not drug related, then dosing may resume when AE resolves.

Table 7.4.1-1: Adverse Event Criteria for Delay, Resumption, and Discontinuation of Nivolumab and Ipilimumab

Drug-related Adverse Event (AE) per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resumption Criteria
	Any grade drug-related myelitis	Permanently discontinue	
Neurological (other than GBS, MG, encephalitis, or myelitis)	Grade 2	Delay dose	Dosing may resume when AE resolves to baseline.
	Grade 3 or 4	Permanently discontinue	
Myocarditis			
Myocarditis	Symptoms induced from mild to moderate activity or exertion	Delay dose	Dosing may resume after myocarditis has resolved.
	Severe or life threatening, with symptoms at rest or with minimal activity or exertion, and/or where intervention indicated	Permanently discontinue	
Other Clinical AEs			
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	

Table 7.4.1-1: Adverse Event Criteria for Delay, Resumption, and Discontinuation of Nivolumab and Ipilimumab

Drug-related Adverse Event (AE) per CTCAE V5	Severity	Action Taken	Clarifications, Exceptions, and Resumption Criteria
	Recurrence of Grade 3 AE of any duration	Permanently discontinue	
	Grade 4 or life-threatening adverse reaction	Permanently discontinue	
Other Laboratory Abnormalities			
Other drug-related laboratory abnormality **(not listed above)**	Grade 3	Delay dose	Exceptions: No delay required for: Grade 3 lymphopenia Permanent discontinuation for: Grade 3 thrombocytopenia > 7 days or associated with bleeding
	Grade 4	Permanently discontinue	Exceptions: The following events do not require discontinuation of study drug: • Grade 4 neutropenia ≤ 7 days • Grade 4 lymphopenia or leukopenia • Grade 4 isolated electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are responding to supplementation/appropriate management within 72 hours of their onset
Infusion Reactions (manifested by fever, chills, rigors, headache, rash, pruritus, arthralgia, hypotension, hypertension, bronchospasm, or other allergic-like reactions)			
Hypersensitivity reaction or infusion reaction	Grade 3 or 4	Permanently discontinue	Refer to Section 7.4.4.

7.4.2 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 7.4.1-1.

Participants with SARS-CoV-2 infection (either confirmed or suspected) 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 (e.g. reverse transcription polymerase chain reaction [RT-PCR] or viral antigen),
2) Resolution of acute symptoms (including at least 24 hours have passed since last fever without fever reducing medications),
3) Evaluation by the Investigator with confirmation that there are no sequelae that would place the participant at a higher risk of receiving investigational treatment, **and**
4) Consultation by the medical monitor.

For suspected cases, treatment may also resume if SARS-CoV-2 infection is ruled-out and other criteria to resume treatment are met.Prior to re-initiating treatment in a participant with a dosing delay lasting > 6 weeks for nivolumab or > 12 weeks for ipilimumab, the Medical Monitor (or designee) must be consulted. Continue tumor assessments per protocol even if dosing is delayed. Continue periodic study visits to assess safety and laboratory studies every 6 weeks or more frequently if clinically indicated during such dosing delays.

When criteria to resume treatment are met, resume both nivolumab and ipilimumab on the same day unless the investigator determines that one of the agents must be discontinued due to toxicity attributed to that agent alone.

7.4.3 Nivolumab and Ipilimumab or Nivolumab Treatment beyond Disease Progression

Accumulating evidence indicates a minority of participants treated with immunotherapy may derive clinical benefit despite initial evidence of progressive disease (PD).[52] Participants treated with nivolumab in combination with ipilimumab or nivolumab will be permitted to continue treatment beyond initial study criteria defined PD, 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 (e.g. CNS metastases)

- Participants provides written informed consent prior to receiving additional nivolumab in combination with ipilimumab or nivolumab treatment. All other elements of the main consent including description of reasonably foreseeable risks or discomforts, or other alternative treatment options will still apply.
- The maximum period allowed of study treatment is 24 months from date of first dose, including treatment beyond progression
- 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 in Section 2.

A radiographic assessment/scan should be performed within 6 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 treatment with nivolumab in combination with ipilimumab or nivolumab.

For the participants who continue nivolumab in combination with ipilimumab or nivolumab study therapy beyond initial progression, further progression is defined as following:

1) For solid tumors, 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.
2) For CNS tumors, an additional approximately 12.5% increase in tumor burden with a minimum 5 mm absolute increase of either diameter from time of initial PD; this includes an increase in the sum of the products of perpendicular diameters (SPD) and the sum of one diameter with larger increase of all target lesions and/or new measurable lesions compared to the time of initial PD.

New lesions are considered measureable 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-measureable at the time of initial progression may become measureable 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.

Nivolumab in combination with ipilimumab or nivolumab treatment should be discontinued permanently upon documentation of further progression.

7.4.3.1 Treatment with nivolumab and ipilimumab after disease progression during treatment with nivolumab monotherapy (Arm B rollover)

Participants who have progressed after treatment with nivolumab monotherapy may be allowed to receive treatment with nivolumab in combination with ipilimumab. Besides complying with all criteria described above, the following criteria must be met:

- Investigator-assessed clinical benefit by receiving nivolumab in combination with ipilimumab;
- Eligibility must be confirmed within 28 days prior to first dose with nivolumab and ipilimumab.

Participants do not need to be retested for TMB-H prior to moving to treatment with nivolumab and ipilimumab. Participants are not required to have TMB ≥ 10 at the time of rollover.

The investigator must discuss each case with the BMS Medical Monitor before initiating treatment with nivolumab and ipilimumab. Participants who meet study discontinuation criteria and move to follow-up are not eligible to re-start treatment.

The first infusion of nivolumab and ipilimumab for these participants should be at least 22 days after the last infusion of nivolumab 480mg (or 6mg/kg). Refer to Sections 7.1.1 and 7.1.2 for details related to administration of nivolumab and ipilimumab infusions. The PK and immunogenicity sampling schedule should resume following the schedule for nivolumab and ipilimumab combination as described in Section 9.5 and Table 9.5-1.

The maximum period allowed of study treatment is 24 months from date of first dose of nivolumab monotherapy.

7.4.4 Treatment of Nivolumab- and Ipilimumab-Related Infusion Reactions

Since nivolumab and ipilimumab 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, hypo- or hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported within 24 hours as SAEs if criteria are met. Infusion reactions should be graded according to NCI CTCAE (Version 5.0) guidelines.

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

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

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

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

- Stop the nivolumab or ipilimumab 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 nivolumab or ipilimumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the participant until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF).
- 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 nivolumab or ipilimumab infusions. If necessary, corticosteroids (up to 25 mg of hydrocortisone or equivalent) may be used.

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

- Immediately discontinue infusion of nivolumab or ipilimumab. 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. Nivolumab or ipilimumab 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).

7.4.5 Management Algorithms for Immuno-oncology Agents

Immuno-oncology (IO) agents are associated with AEs that can differ in severity and duration from AEs caused by other therapeutic classes. Nivolumab and ipilimumab are considered IO

agents, and the management algorithms in Appendix 5 provide guidance on assessing and managing the following groups of AEs:

- Gastrointestinal
- Renal
- Pulmonary
- Hepatic
- Endocrinopathy
- Skin
- Neurological
- Myocarditis

Treatment management algorithms are found in the nivolumab IB[47] and in Appendix 5.

7.5 Preparation/Handling/Storage/Accountability

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

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

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

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

Further guidance and information for final disposition of unused study treatment are provided in Appendix 2 and CA209848 Pharmacy Manual.

7.5.1 Retained Samples for Bioavailability / Bioequivalence

Not applicable.

7.6 Treatment Compliance

Study treatment compliance will be periodically monitored by drug accountability. Drug accountability should be reviewed by the site study staff at each visit to confirm treatment compliance. Sites should discuss discrepancies with the participant at each on-treatment study visit.

7.7 Concomitant Therapy

7.7.1 Prohibited and/or Restricted Treatments

The following medications are prohibited during the study (unless utilized to treat a drug-related adverse event). Medications taken within 2 weeks prior to initial study drug administration and medications taken during study must be recorded on the CRF.

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 7.7.2)
- Any concurrent antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents for treatment of cancer)
- Any complementary medications (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.
- Any live / attenuated vaccine (eg varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella (MMR)) during treatment and until 100 days post last dose.
- Use of any additional noninvasive medical device treatment of glioblastoma multiforme (eg, NovoTTF™, Optune®).
- Administration of a live (replication competent) coronavirus disease 2019 (COVID-19) vaccine within 30 days prior to randomization (or screening). Live COVID-19 vaccines should not be used during the study, including the treatment period and within 100 days following last dose of IP.

7.7.2 Permitted Therapy

Participants are permitted the use of topical, ocular, intra-articular, intranasal, and inhalation corticosteroids (with minimal system absorption). Adrenal replacement steroid doses > 10 mg daily prednisone are permitted. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (eg, for contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted. Prior palliative radiotherapy must have been completed at least 2 weeks prior to first dose of IP.

COVID-19 vaccines that are NOT live (not replication competent) are permitted during the study and after the last dose of IP. No data are available on the response to COVID-19 vaccines. The efficacy and safety of vaccination in participants who are receiving nivolumab in combination with ipilimumab or nivolumab monotherapy are unknown. Please contact the Clinical Trial Physician/Medical Monitor (or designee) with any questions related to COVID-19 vaccines.

7.7.3 Palliative Local Therapy

Palliative local therapy, including palliative radiation therapy- and palliative surgical resection, to symptomatic non-target bone lesions, skin lesions, or CNS lesions (only for peripheral solid tumors, not applicable for CNS primary tumor) is permitted prior to discontinuation of study

treatment for participants who do not have evidence of overall clinical or radiographic progression per study criteria. Palliative local therapy to lesions causing hemoptysis may also be permitted prior to discontinuation of study treatment in participants who do not have evidence of overall clinical or radiographic progression per study defined response criteria, provided that the lesions undergoing palliative local therapy are not the only sites of measurable disease and the case is discussed with and approved by the BMS Medical Monitor.

Participants requiring palliative local therapy should be evaluated for objective evidence of disease progression prior to the initiation of such therapy, particularly if the most recent tumor assessment was more than 4 weeks prior to the start of local therapy. If progression per study defined response criteria is identified on any tumor assessments prior to the initiation of palliative local therapy, then participants must either discontinue study drug treatment or they must meet criteria to continue treatment beyond progression in order to resume immunotherapy after palliative local therapy.

The potential for overlapping toxicities with radiotherapy and nivolumab currently is not known; however, anecdotal data suggests that it is tolerable. As concurrent radiotherapy and nivolumab have not been formally evaluated, in cases where palliative radiotherapy is required for a tumor lesion, then nivolumab 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 should resolve to Grade ≤ 1 prior to resuming nivolumab.

7.7.4 Other Restrictions and Precautions

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

7.7.5 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.

7.7.6 Surgical Resection Following Initial Response

In some clinical scenarios, investigators may choose to resect solitary lesions in participants with metastatic disease and render the patient free of macroscopic disease. Participants enrolled in this

study may have lesions surgically resected only if confirmation of response is documented at least 4 weeks after previous scan and following consultation with the BMS Medical Monitor. If tumor shrinkage of the solitary lesion is noted on the re-staging assessment, it is highly encouraged that surgical resection be delayed until subsequent scans fail to demonstrate further shrinkage.

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 protocol Section 7.1. 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 nivolumab or ipilimumab 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

Nivolumab and/or ipilimumab treatment must be permanently discontinued per criteria in Section 7.4.1. Discontinue nivolumab and/or ipilimumab for any adverse event, laboratory abnormality, or intercurrent illness that, in the judgment of the Investigator, presents a substantial clinical risk to the participant with continued nivolumab and/or ipilimumab dosing.

Participants MUST discontinue IP (and non-IP 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 adverse event (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
- Confirmed disease progression after treatment beyond initial study criteria defined progression (see 7.4.3) for Arm A (combination of nivolumab and ipilimumab)
- Confirmed disease progression after treatment beyond initial study criteria defined progression (see 7.4.3) for Arm B unless the participants choose and are eligible for rollover to receive nivolumab in combination with ipilimumab)
- Termination of the study by Bristol-Myers Squibb (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.)

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

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

All participants who discontinue study treatment should comply with protocol specified follow-up procedures as outlined in Section 2. The only exception to this requirement is when a participant withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (i.e., 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 case report form (CRF) page.

The assessment for discontinuation of nivolumab should be made separately from the assessment made for discontinuation of ipilimumab. Although there is overlap among the discontinuation criteria, if discontinuation criteria are met for ipilimumab but not for nivolumab, treatment with nivolumab may continue if ipilimumab is discontinued.

If a participant in the nivolumab/ipilimumab combination arm meets criteria for discontinuation and investigator is unable to determine whether the event is related to both or one study drug, the participant should discontinue both nivolumab and ipilimumab and be taken off the treatment phase of the study.

8.1.1 Dose Discontinuation in Nivolumab and Ipilimumab Combination

Any event that leads to delay in dosing lasting > 6 weeks for nivolumab or > 12 weeks for ipilimumab from the previous dose requires discontinuation, with the following exceptions:

- Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events are allowed.
- Dosing delays from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS Medical Monitor (or designee).

Prior to re-initiating treatment in a participant with a dosing delay lasting > 6 weeks for nivolumab or >12 weeks for ipilimumab, the BMS Medical Monitor (or designee) must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.

Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the participant with continued nivolumab dosing.

The assessment for discontinuation of nivolumab should be made separately from the assessment made for discontinuation of ipilimumab. Although there is overlap among the discontinuation criteria, if discontinuation criteria are met for ipilimumab but not for nivolumab, treatment with nivolumab may continue if ipilimumab is discontinued.

If a participant in the nivolumab/ipilimumab combination arm meets criteria for discontinuation and the investigator is unable to determine whether the event is related to both or one study drug, the participant should discontinue both nivolumab and ipilimumab and be taken off the treatment phase of the study.

8.1.2 Dose Discontinuation in Nivolumab Monotherapy Arm

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

- Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events are allowed.
- Dosing delays that occur for non-drug-related reasons may be allowed if approved by the BMS Medical Monitor (or designee).

Prior to re-initiating treatment in a participant with a dosing delay lasting > 10 weeks, the BMS Medical Monitor (or designee) must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.

8.1.3 Post Study Treatment Study Follow-up

In this study, overall survival is a key endpoint of the study. Post treatment follow-up is of critical importance and is essential to preserving participant safety and the integrity of the study. Participants who discontinue study treatment must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with Section 5 until death or the conclusion of the study.

BMS may request that survival data be collected on all treated/randomized participants outside of the protocol defined window (See Table 2-5 in Schedule of Activities). At the time of this request, each participant will be contacted to determine their survival status unless the participant has withdrawn consent for all contacts or is lost to follow-up.

8.2 Discontinuation from the Study

Participants who request to discontinue study 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 (e.g. suspected drug induced liver enzyme evaluations) will be monitored during the follow-up phase via on-site/local labs until all study drug-related toxicities resolve, return to baseline, or are deemed irreversible.

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

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

9.1 Efficacy Assessments

Efficacy will be based on imaging assessments. For solid tumors, response will be assessed using RECIST 1.1 for solid tumors (see appendix 7). For CNS tumors, response will be assessed using RANO 2010 criteria [53] supplemented by clinical neurologic examination and performance status, as well as additional considerations as applicable e.g. adverse events or steroid requirement. (See Appendix 8).

9.1.1 Imaging Assessment for the Study

Images will be submitted to an imaging core lab and may undergo blinded independent central review (BICR) at any time during the study. Prior to scanning the first participant sites should be qualified as well as understand the image acquisition guidelines and submission process as outlined in the CA209848 Imaging Manual provided by the imaging core lab. For CNS participants, sites need to follow qualification procedures within the imaging manual to demonstrate the ability to perform required MRI sequences for this study.

Screening and on study tumor assessment will take place in accordance with the Section 2 Schedule of Activities, according to appropriate response criteria (Appendix 7 and Appendix 8).

Any additional imaging that may demonstrate tumor response or progression (including scans performed at unscheduled timepoints and/or at an outside institution) should be collected for RECIST 1.1 tumor assessment and submitted to the BICR.

Scans should be performed until BICR confirmation of progression or treatment discontinuation (including treatment beyond progression), whichever occurs later.

9.1.2 Methods of Measurement

9.1.2.1 Solid tumors

Contrast-enhanced CT of the chest, abdomen, pelvis, and all other known and/or suspected sites of disease should be performed for tumor assessments. Images should be acquired with slice thickness of 5 mm or less with no intervening gap (contiguous). Every attempt should be made to image each participant using an identical acquisition protocol on the same scanner for all imaging timepoints. Tumor measurements should be made by the same investigator or radiologist for each assessment whenever possible. Change in tumor measurements and tumor response to guide ongoing study treatment decisions will be assessed by the Investigator using the RECIST 1.1 criteria.

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

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

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

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

Bone scan or PET scan is not adequate for assessment of RECIST 1.1 response in target lesions. In selected circumstances where such modalities are the sole modality used to assess certain non-target organs, those non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

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

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

9.1.2.2 Primary CNS Neoplasms

Brain MRI without and with gadolinium contrast should be performed as outlined in Section 2 (Schedule of Activities). Participants who are unable (due to existent medical condition, ie, pacemaker or ICD device) or unwilling to have a contrast enhanced MRI of the brain at baseline are excluded from the study. Participants who become unable to undergo MRI imaging after the start of participation in the study may continue in the study for assessment of overall survival as long as there is no safety issue which would require monitoring by MRI.

9.1.3 Imaging and Clinical Assessment

Tumor assessments should continue even if dosing is delayed or discontinued. Changes in tumor measurements and tumor responses will be assessed by the same investigator. Investigators will report the number and size of new lesions that appear while on study. Assessments of PR and CR must be confirmed at least 4 weeks (28 days) after initial response. A Best Overall Response of SD requires a minimum of 77 days on study from date of first dose to the date of the first imaging assessment.

For participants with CNS malignancy, RANO 2010 criteria will be used.

Table 9.1.3-1: RANO Criteria for Time-point Response Assessment Incorporating MRI and Clinical Factors

Response	Criteria
CR	Requires all of the following: complete disappearance of all enhancing measurable and nonmeasurable disease; no new lesions; stable or improved nonenhancing (T2/FLAIR) lesions; participants must be off corticosteroids (or on physiologic replacement doses only); and stable or improved clinically. Note: Participants with nonmeasurable disease only cannot have a complete response; the best response possible is stable disease.
PR	Requires all of the following: ≥ 50% decrease compared with baseline in the sum of products of perpendicular diameters (SPD) of all measurable enhancing lesions; no progression of nonmeasurable disease; no new lesions; stable or improved nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan; the corticosteroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan; and stable or improved clinically. Note: Participants with nonmeasurable disease only cannot have a partial response; the best response possible is stable disease.
SD	Requires all of the following: does not qualify for complete response, partial response, or progression; stable nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan. In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.

Table 9.1.3-1: RANO Criteria for Time-point Response Assessment Incorporating MRI and Clinical Factors

Response	Criteria
PD	Defined by any of the following: ≥ 25% increase in sum of the products of perpendicular diameters of enhancing lesions compared with the smallest tumor measurement obtained either at baseline (if no decrease) or best response, on stable or increasing doses of corticosteroids (Stable doses of corticosteroids include participants not on corticosteroids); significant increase in T2/FLAIR nonenhancing lesions on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy not caused by comorbid events (eg, radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects); any new lesion; clear clinical deterioration not attributable to other causes apart from the tumor (eg, seizures, medication adverse effects, complications of therapy, cerebrovascular events, infection, and so on) or changes in corticosteroid dose; failure to return for evaluation as a result of death or deteriorating condition; or clear progression of nonmeasurable disease.

Table 9.1.3-2: Assessment of Best Overall Response

Best Overall Response	Criteria[54]
CR	CR observed in assessments ≥ 4 weeks apart per RANO
PR	PR observed in assessments ≥ 4 weeks apart per RANO
SD Note: To qualify for SD there must be a minimum on-treatment period of 6 weeks.)	SD observed and does not qualify for CR or PR or Suspected PD followed with histologic results not confirming PD, and no CR, PR or SD observed
Not Evaluable (NE)	Insufficient data to determine disease progression or response
PD	No CR, PR, or SD prior to PD

9.1.3.1 BICR Confirmation of Radiographic Progression

Sites should submit all scans to the imaging core lab on a rolling basis, throughout the duration of the study. BICR of scans will occur on a rolling basis, blinded to treatment arm, clinical data, and investigator assessment of submitted scans. When radiographic progression per RECIST 1.1 or RANO criteria is assessed by the investigator, the site will inform the imaging core lab, in order for BICR assessment of progression to be performed. The BICR review will be completed and the results provided to the site as specified in the imaging vendor documents, provided there are no pending imaging queries to the site. All details on the timelines and associated process requirements will be outlined in the Imaging Manual. Participants whose RECIST 1.1 or RANO radiographic progression is not confirmed by the BICR will be required to continue tumor assessments (if clinically feasible) according to the protocol-specified schedule, or sooner if clinically indicated. Also, if participants discontinue treatment without radiographic progression, tumor assessments will continue according to the protocol specified schedule, as noted in Section 2 (Schedule of Activities) until progression has been confirmed by BICR. All study treatment

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

BICR confirmation of disease progression is mandatory for participants in Arm B (nivolumab monotherapy) prior to enrolling in Arm B rollover to receive treatment with nivolumab in combination with ipilimumab. The participant will be re-baselined based on the investigator's assessment of the scans with which BICR progression was confirmed. Tumor assessments in participants in rollover cohort will be done by BICR and should comply with the requirements outlined in this protocol.

9.2 Adverse Events

The definitions of an AE or serious adverse event (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.

Contacts for SAE reporting specified in Appendix 3.

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

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

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 and for a minimum of 100 days following discontinuation of study treatment and at the timepoints specified in the Schedule of Activities (Section 2).

Sections 5.6.1 and 5.6.2 in the Investigator Brochure (IB) represent the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting.

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

All SAEs and all AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection must be collected from the time of signing the consent, including those thought to be associated with protocol-specified procedures and until 100 days following discontinuation of dosing.

Note: for participants who signed a pre-screening consent with submission of an archived tumor sample for eligibility assessment, SAE collection will start at the time of signature of the full informed consent. For participants who signed a pre-screening consent to agree to collection of a fresh biopsy, SAE collection will start at the time of signature of the pre-screening informed consent.

For participants randomized and never treated with study drug, SAEs should be collected for 30 days from the date of randomization.

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

- 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 module.
- All SAEs will be recorded and reported to Sponsor or designee within 24 hours, as indicated in Appendix 3.
- The investigator will submit any updated SAE data to the sponsor or designee within 24 hours of updated information being available.

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

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

9.2.2 Method of Detecting AEs and SAEs

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.

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

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

9.2.3 Follow-up of AEs and SAEs

- Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Appendix 3).
- Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study treatment and for those present at the end of study treatment as appropriate.

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, 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 participant is lost to follow-up (as defined in Section 8.3), or 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 Investigator Brochure 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 SUSAR (Suspected, Unexpected Serious Adverse Reaction) is a subset of SAEs and will be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

All SAEs must be collected that occur during the screening period and within 100 days of the last dose of study treatment. For participants randomized/assigned to treatment and never treated with study drug, SAEs should be collected for 30 days from the date of treatment assignment.

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.

9.2.6 Laboratory Test Result Abnormalities

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

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

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

9.2.7 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:

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

AND

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

AND

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

9.2.8 Immune-mediated Adverse Events

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

which were exacerbated by the induction of autoimmunity. Information supporting the assessment will be collected on the participant's case report form.

9.2.9 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 nonserious 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. Overdoses that meet the regulatory definition of SAE will be reported as an SAE (see Appendix 3).

In the event of an overdose the investigator should:

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

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the BMS Medical Monitor 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.

9.4.1 Physical Examinations

Refer to Schedule of Activities.

9.4.2 Vital signs

Refer to Schedule of Activities.

9.4.3 Clinical Safety Laboratory Assessments

Investigators must document their review of each laboratory safety report.

Hematology	
Hemoglobin	
Hematocrit	
Total leukocyte count, including differential	
Platelet count	
Serum Chemistry	
Aspartate aminotransferase (AST) Alanine aminotransferase (ALT)	Albumin - screening only Sodium

Total bilirubin Alkaline phosphatase (ALP) Lactate dehydrogenase (LDH) Creatinine Blood Urea Nitrogen (BUN) or serum urea Glucose	Potassium Chloride Calcium Phosphorous TSH, free T3 and free T4 - screening TSH, with reflexive fT3 and fT4 if TSH is abnormal - on treatment
Serology	
Hepatitis B/C, (HBV sAG, HCV antibody or HCV RNA) - screening only	
Serum for HIV testing where locally mandated	
Other Analyses	
Pregnancy test (WOCBP only: minimum sensitivity 25 IU/L or equivalent units of HCG).	
Follicle stimulating hormone (FSH) at screening - only required to confirm menopause in women < age 55)	

9.4.4 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 as per standard medical/clinical judgment.

9.5 Pharmacokinetics

Samples for pharmacokinetic and immunogenicity assessment will be collected for participants at the timepoints indicated in Table 9.5-1 and Table 9.5-2. All on treatment PK timepoints are intended to align with days on which study drug is administered. If it is known that a dose is going to be delayed, then the predose sample should be collected just prior to the delayed dose. However, if a predose sample is collected but the dose is subsequently delayed, an additional predose sample should not be collected.

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

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

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

Table 9.5-1: Pharmacokinetic and Immunogenicity Sampling Schedule – Arm A or Arm B Rollover – Nivolumab in Combination with Ipilimumab

Study Day 2 weeks/cycle	**Event**	**Time (Relative to Start of Infusion) Hour: Min**	**Nivolumab PK Blood Sample**	**Nivolumab Immunogenicity Sample**	**Ipilimumab PK Blood Sample[c]**	**Ipilimumab Immunogenicity Sample[c]**
C1 D1 Ipilimumab Dose 1	predose[a]	00:00	X	X	X	X
	EOI[b]		X		X	
C2D1	predose[a]	00:00	X	X	X	X
C5D1	predose[a]	00:00	X	X	X	X
C7 D1 Ipilimumab Dose 3	predose[a]	00:00	X	X	X	X
	EOI[b]		X		X	
C11 D1	predose[a]	00:00	X	X	X	X
C17 D1	predose[a]	00:00	X	X	X	X
C25 D1	predose[a]	00:00	X	X	X	X
After C25 D1, every 8th cycle (16th week) until discontinuation or up to 2 years	predose[a]	00:00	X	X	X	X
First 2 Follow-up Visits (Approximately 30 days and up to ~ 100 Days from the Discontinuation of Study treatment)	NA		X	X	X	X

[a] Predose samples should be collected just before the start of nivolumab infusion (preferably within 30 minutes). If it is known that a dose is going to be delayed, then the predose sample should be collected just prior to the delayed dose. However, if a predose sample is collected but the dose is subsequently delayed, an additional predose sample should not be collected.

[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 from which drug was administered.

[c] If ipilimumab is discontinued, resume ipilimumab PK and ADA (immunogenicity) sample collection for the next scheduled sample collection, then discontinue ipilimumab sample collection.

Table 9.5-2: Pharmacokinetic and Immunogenicity Sampling Schedule Arm B - Nivolumab Monotherapy

Study Day 4 weeks/cycle	**Event**	**Time (Relative to Start of Infusion) Hour: Min**	**Nivolumab PK Blood Sample**	**Nivolumab Immunogenicity Sample**
C1 D1	predose[a]	00:00	X	X
	EOI[b]	00:30	X	
C2 D1	predose[a]	00:00	X	X
C5 D1	predose[a]	00:00	X	X
	EOI[b]	00:30	X	
C9 D1	predose[a]	00:00	X	X
C13 D1	predose[a]	00:00	X	X
After C13 D1, every 4th cycle (16th week) until discontinuation or up to 2 years	predose[a]	00:00	X	X
First 2 Follow-up Visits (Approximately 30 days and up to ~ 100 Days from the Discontinuation of Study treatment)	NA		X	X

[a] Predose samples should be collected just before the start of nivolumab infusion (preferably within 30 minutes). If it is known that a dose is going to be delayed, then the predose sample should be collected just prior to the delayed dose. However, if a predose sample is collected but the dose is subsequently delayed, an additional predose sample should not be collected.

[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 from which drug was administered.

9.6 Pharmacodynamics

See Section 9.8.1 and 9.8.2

9.7 Pharmacogenomics

See Section 9.8.5.

9.8 Biomarkers

The key biomarker goal for this study is to identify factors that could potentially predict clinical responses to nivolumab in combination with ipilimumab. Peripheral blood and tumor specimens will be taken from all participants' prior to and on-treatment and as outlined in Table 9.8-1 and Table 9.8-2: Biomarker Tissue and Blood Samples: Arm B Nivolumab Monotherapy. Data will be evaluated for associations with clinical response and survival (OS) data. All samples collected may also be used for future exploratory analyses (unless restricted by local requirements) to assess biomarkers associated with immunotherapy treatment. Complete instructions on the collection, processing, handling and shipment of all samples described in this section will be provided in a separate procedure manual.

Table 9.8-1: Biomarker Tissue and Blood Samples: Arm A and Arm B Rollover - Nivolumab in Combination with Ipilimumab

Study Day 1 Cycle = 2 weeks	Archival Tumor or Fresh Biopsy Tissue	Whole Blood DNA	Myeloid-Derived Suppressor Cells (MDSCs)	Blood TMB	Plasma[a]
Pre-screening[b]	X[c]			X[d]	X[d]
C1D1		X[b]	X		X
C7D1					X
Every 6 Cycles (starting at C13D1) until end of treatment					X
Disease progression	X (optional)[e]				X

[a] Plasma samples could be used for evaluation of bTMB or other biomarkers

[b] For Arm B rollover, pre-screening samples and whole blood DNA are not applicable.

[c] Fresh biopsies are preferred; however, archival samples are acceptable if obtained within 9 months of signing the initial consent form (pre-screening) and no additional intervening therapy (excluding palliative therapy) in between.

[d] Blood TMB and plasma samples collected during pre-screening should be collected on the same day.

[e] If a biopsy has been performed and tissue is available, participants are requested to submit fresh tumor tissue at disease progression for biomarker research. Tissue submission is optional and biopsy is not required by protocol.

Table 9.8-2: Biomarker Tissue and Blood Samples: Arm B Nivolumab Monotherapy

Study Day 1 Cycle = 4 weeks	Archival Tumor or Fresh Biopsy Tissue	Whole Blood DNA	Myeloid-Derived Suppressor Cells (MDSCs)	Blood TMB	Plasma[a]
Pre-screening	X[b]			X[c]	X[c]
C1D1		X	X		X
C4D1					X
Every 3 Cycles (starting at C7D1) until end of treatment					X
Disease progression	X (optional)[d]				X

[a] Plasma samples could be used for evaluation of bTMB or other biomarkers.

[b] Fresh biopsies are preferred; however, archival samples are acceptable if obtained within 9 months of signing the initial consent form (pre-screening and no additional intervening therapy (excluding palliative therapy) in between.

[c] Blood TMB and plasma samples collected during pre-screening should be collected on the same day.

[d] If a biopsy has been performed and tissue is available, participants are requested to submit fresh tumor tissue at disease progression for biomarker research. Tissue submission is optional and biopsy is not required by protocol.

For biomarker research testing, tumor tissue (formalin-fixed, paraffin embedded archival or recent acquisition) must be received during the pre-screening period. Fresh biopsies are preferred; however, archival samples (within 9 months of signing the initial study consent form [pre-screening or screening]) are acceptable. If the required number of slides are not available, the BMS Medical Monitor must be consulted, prior to enrollment, to discuss acceptability of the tissue available. Please note that fine needle aspiration (FNA) and bone metastases samples are not acceptable for submission. Please see the CA209848 Laboratory Manual for more details regarding tumor sample collection.

If a fresh biopsy is warranted, the participant must have a lesion that can be biopsied at an acceptable clinical risk as judged by the investigator in order to be eligible for the study.

9.8.1 Additional Research Collection

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

For All US sites:

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

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

For non-US Sites

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

This collection for additional research is intended to expand the translational R&D capability at Bristol-Myers Squibb, 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.

- Residual tumor biopsy, residual whole blood and plasma from biomarker collection and PK collections (see Table 9.8.1-1) will also be retained for additional research purposes

Samples kept for future research will be stored at the BMS Biorepository in New Jersey, USA or an independent, BMS-approved storage vendor.

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

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

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

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

Table 9.8.1-1: Residual Sample Retention for Additional Research Schedule

Sample Type	Timepoints for which residual samples will be retained
Tumor biopsy	Screening and at disease progression (if available)
Residual whole blood, plasma and serum	All biomarker collections and all PK collection

9.8.2 Immunogenicity Assessments

Blood samples for immunogenicity analysis will be collected according to the schedule given in Section 9.5. Samples collected will be evaluated for development of Anti-Drug Antibody (ADA) by a validated electrochemiluminescent (ECL) immunoassay.

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

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

9.8.3 Blood-based Biomarkers

Blood samples will be collected from all participants. Circulating free tumor DNA (also known as cfDNA or ctDNA) will be extracted from blood to assess tumor mutational burden. Genomic DNA from whole blood will also be collected and may be used as a comparator for participants with tumors examined by whole exome sequencing for tumor mutational burden analyses. Whole blood will also be collected to assess myeloid derived suppressor cells (MDSCs) which may be associated with response to checkpoint inhibitors. Other biomarkers such as but not limited to cytokines, metabolites, etc. may be assessed in plasma. Blood sample collection will follow the same time points as mentioned in Table 9.8-1 and Table 9.8-2: Biomarker Tissue and Blood Samples: Arm B Nivolumab Monotherapy. Please see CA209848 Laboratory Manual for additional information.

9.8.4 Tissue-based Biomarkers

Tumor samples may be assessed for gene expression, protein expression, and/or for tumor mutational burden analyses (TMB) using a variety of methodologies inclusive of, but not limited to RNAseq, immunohistochemistry, whole exome sequencing [WES], Next-Generation Sequencing [NGS], etc. Immunohistochemistry (IHC) may be used to assess the number and composition of immune infiltrates in order to define the immune cell subsets present within formalin-fixed, paraffin embedded (FFPE) tumor tissue before and after exposure to therapy. These IHC analyses will include, but not necessarily be limited to, PD-L1, PD-L2, immune cell profiling to examine T cells, T regs, macrophages, MDSCs, and immune marker expression such as PD1, LAG3, IDO, etc. Please see CA209848 Laboratory Manual for additional information.

9.8.5 Other Assessments

With available archival tumor tissue and newly obtained biopsy tissue, plasma, and blood, genomic and genetic sequencing will be performed (using different sequencing methods, such as whole exome sequencing [WES], Next-Generation Sequencing [NGS], etc). Panels of specific genes will be performed to determine mutational burden and specific mutations that might affect response to nivolumab. Whole blood and plasma collection will follow the same timepoints as biomarker collection in Table 9.8-1 and Table 9.8-2: Biomarker Tissue and Blood Samples: Arm B Nivolumab Monotherapy. Please see CA209848 Laboratory Manual for additional information.

9.9 Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters will not be evaluated in this study.

9.10 Patient-Reported Outcomes

Participants, ≥18 years of age at baseline, will be asked to complete the 30-item European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and 3-level version of the EuroQol Group's EQ-5D (EQ-5D-3L) after randomization but prior to first dose, at on-study clinic visits planned to occur every 4 weeks (nivolumab arm) or 6 weeks (nivolumab plus ipilimumab arm) while on treatment, and at follow-up visits 1 and 2. In addition, the EQ-5D-3L will be completed at designated time points during the survival follow-up phase. In cases where a dose of treatment drug is delayed, the PRO assessment should also be delayed.

The EORTC QLQ-C30 will be used to assess the effects of disease symptoms on functioning and well-being. The QLQ-C30[55] is the most commonly used quality of life instrument in oncology trials. The instrument's 30 items are divided among five functional scales (physical, role, cognitive, emotional, and social), nine symptom scales (fatigue, pain, nausea/vomiting, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties), and a global health/quality of life scale. With the exception of two items included in the global health/quality of life scale, for which responses range from 1 (Very poor) to 7 (Excellent), item responses range from 1 (Not at all) to 4 (Very much). Raw scores for the QLQ-C30 are transformed to a 0-100 metric such that higher values indicate better functioning or quality of life or a higher level of symptoms. The questionnaire uses a 1-week recall period.

The EQ-5D-3L[56] will be used to assess treatment effects on perceived health status and to generate utility data for health economic evaluations. The EQ-5D-3L is a generic multi-attribute health-state classification system by which health is described in 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is evaluated using 3 levels: no problems, some problems, and severe problems. Responses to these 5 dimensions are converted into 1 of 243 unique EQ-5D health state descriptions, which range between no problems on all 5 dimensions (11111) to severe/extreme problems on all 5 dimensions (33333). Using appropriate country-specific value weighting algorithms, a respondent's self-described health state can be converted into a utility representing the societal desirability of his/her own health. In addition, the EQ-5D includes a visual analogue scale (VAS) allowing a respondent to rate his/her health on a

scale ranging from 0–100 with 0 being the worst health state imaginable and 100 being the best health state imaginable. The questionnaire uses a recall period of "today."

The questionnaires will be provided in the participant's preferred language, if available, and the EQ-5D-3L may be administered by telephone during survival follow-up. There exists a standardized guide that can be used to facilitate telephone administration of the EQ-5D-3L. If exceptional circumstances preclude the continued administration of measures using planned modalities, then alternate administration methods may be required after consultation with the Sponsor or the Sponsor's representative. Table 2-2 through Table 2-5 provide information regarding the timing of patient-reported outcomes assessments.

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

Sample size calculation is based on BICR-assessed ORR and DOR.

The two primary objectives are to estimate ORR in tissue TMB (tTMB) high participants in the salvage setting and blood TMB (bTMB) high participants in the salvage setting enrolled in the nivolumab + ipilimumab arm. A key secondary objective is DOR in the nivolumab + ipilimumab arm.

In CA209227 study, an ORR rate of 45.3% was observed for nivolumab in combination with ipilimumab arm in tissue TMB ≥ 10 mut/Mb population. In CA209032, an ORR of 46% was observed for nivolumab + ipilimumab in high TMB SCLC participants and an ORR of 21% was observed for nivolumab.[57,58] The target ORR chosen in the study is 40% for TMB-high participants treated with nivolumab + ipilimumab.

A total of 76 TMB-evaluable subjects in the salvage setting treated with nivolumab + ipilimumab are required for each of the tTMB and bTMB populations. The sample size determination was not based on power consideration, but to provide precision on the estimation of ORR and DOR for TMB-high participants treated with nivolumab + ipilimumab. The following table summarizes the exact 95% CIs for a sample size of 76 in the nivolumab + ipilimumab arm when observed ORRs range from 25% to50%.

Sample size	Number of responses	Response rate	95% Confidence interval
76	19	0.25	(0.16, 0.36)
76	22	0.29	(0.19, 0.40)
76	24	0.32	(0.21, 0.43)
76	26	0.34	(0.24, 0.46)
76	28	0.37	(0.26, 0.49)
76	30	0.39	(0.28, 0.51)
76	32	0.42	(0.31, 0.54)
76	34	0.45	(0.33, 0.57)

Sample size	Number of responses	Response rate	95% Confidence interval
76	36	0.47	(0.36, 0.59)
76	38	0.50	(0.38, 0.62)

In addition, with ORR of 40% for a sample size of 76 treated participants, the mean percentage of responders with DOR ≥ 6 months is 70%, and the corresponding 95% lower bound for the responders with DOR ≥ 6 months is 50%, based on 10000 simulations. The calculations assume the median DOR for nivolumab + ipilimumab is 11.5 months based on CA209032[58] and CA209012[59] studies. Note for an ORR rate of 10%, typical for standard of care in this refractory population, and a median DOR of 5.5 months, the proportion of responders with DOR ≥ 6 months is 47%.

Seventy-six (76) participants in the salvage setting are required for each of tTMB and bTMB for nivolumab in combination with ipilimumab arm. Based on the currently observed approximate 40% concordance between tTMB-H and bTMB-H in this study, the total sample size for nivolumab in combination with ipilimumab arm will be approximately 122. Nivolumab monotherapy arm is a non-comparative arm to evaluate the contribution of components. Approximately 183 to 342 participants will be randomized into nivolumab in combination with ipilimumab (n=122) and nivolumab monotherapy (n=61) in a 2:1 randomization ratio. Moreover, if concordance rate between tTMB-H and bTMB-H is x%, sample size for nivolumab in combination with ipilimumab arm will be approximately 76+76-76*x% and total sample size will be approximately 1.5*(76+76-76*x%). For example, if x=30% the total sample size will be 194 and if x is close to 0% the total sample size will be 228. Note the sample sizes(s) for the primary endpoint of ORR in each of tTMB-H and bTMB-H in nivolumab + ipilimumab arm remains 76 regardless of the concordance but the final sample size required for the study may change depending on the observed concordance rate and depending on whether or not the bTMB cut-off is increased after the first interim analysis (see Section 10.3.6).

Should the tTMB-H population reach approximately 76 before the bTMB-H population, then enrollment will continue only with participants required to meet the eligibility criteria for bTMB until approximately 76 participants is reached in the bTMB-H population. Should the bTMB-H population reach approximately 76 before the tTMB-H population then enrollment will continue only with participants required to meet the eligibility requirement for tTMB-H until approximately 76 participants is reached in the tTMB-H population.

All tumor types will be pooled in the analysis. In order to ensure that 1 tumor type does not unduly impact the overall pooled final efficacy analysis, a cap of approximately 15% of participants per tumor type will be enforced.

The final analysis of the primary endpoint ORR based on BICR assessments for tTMB high population will be performed at least 12 months after all tTMB ≥ 10 mut/Mb participants in the salvage setting have been randomized and study randomization is completed. Final analysis of the primary endpoint ORR based on BICR assessments for bTMB high population will be performed

at least 12 months after approximately 76 participants with bTMB ≥ 10 mut/Mb (or higher bTMB cutoff determined by interim analysis; see Section 10.3.6) in the salvage setting are randomized in the nivolumab + ipilimumab arm and study randomization is completed.

Enrollment into the bTMB high population was closed in Dec-2019; enrollment into the tTMB high population remained ongoing. Given the approximate 40% concordance between tTMB high and bTMB high, a fraction of the tTMB high participants subsequently randomized into the study are also bTMB high. These participants will not be included in the primary bTMB efficacy analysis population (see Table 10.2-1).

There are two planned interim analyses. The first interim analysis will be used to determine the cut-off value for bTMB. The second interim analysis will be used to assess efficacy in the tTMB high population. These interim analyses are described in Section 10.3.6. The positive efficacy decision is determined when one or both primary endpoints exceed(s) a clinically relevant response rate. A search of ORR with salvage therapy yielded a relative wide range of responses ranging from no response to more than 30% in various tumor types.[60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78] Caution should be taken in referencing these observed ORRs given the limitations on small sample size and/or local definition of salvage therapy in some studies. Despite lack of a clearly defined clinical response rate across different tumor types, recent approvals by FDA have been granted for the treatment of several tumor types in a refractory/rare tumor setting with ORRs ranging from 12-14%, including small cell lung cancer, cervical cancer and neuroendocrine tumors.[12,79,80]

There is no formal comparison of ORR between treatment arms (and within tTMB and bTMB populations). However, a 95% confidence interval for the difference in ORR between the treatment arms will be computed for descriptive purposes for tTMB and bTMB populations separately.

10.2 Populations for Analyses

The following defined populations will apply to pooled tumor types unless otherwise specified:

Population	Description
Enrolled participants	All participants who signed an informed consent form and were registered into the IVRS.
Randomized participants	All participants who were randomized.
Treated participants	All participants who received at least 1 dose of nivolumab or ipilimumab.
Pharmacokinetics participants	All treated participants with available serum time-concentration data.
Immunogenicity participants	All treated participants with baseline and at least 1 post-baseline immunogenicity assessment.

The primary endpoint of the trial is BICR-assessed ORR in the tTMB high population and the bTMB high population in a salvage setting (Table 10.2-1).

Table 10.2-1: Timing of Analysis and Primary Populations for Primary Endpoint

Analysis	Timing	Primary Population to be Used for Primary Endpoint
bTMB interim analysis	Approximately the first 30 randomized participants in the nivolumab + ipilimumab arm with bTMB ≥ 10 mut/Mb at baseline have been randomized and followed for at least 6 months	All bTMB high randomized participants (followed for at least 6 months)
bTMB final analysis	At least 12 months after approximately 76 bTMB high participants are treated in the nivolumab + ipilimumab arm and study randomization is completed	All bTMB high participants randomized prior to the closure of the bTMB high population in Dec-2019
tTMB interim analysis	Approximately the first 50 randomized participants in the nivolumab + ipilimumab arm with tTMB ≥ 10 mut/Mb at baseline have been randomized and followed for at least 12 months and study randomization is completed	All tTMB high participants randomized at least 12 months prior to the LPLV for the analysis
tTMB final analysis	At least 12 months after all tTMB ≥ 10 mut/Mb participants have been randomized	All tTMB high randomized participants

10.3 Statistical Analyses

Unless otherwise specified, all analyses will be performed for all randomized participants in the salvage setting by treatment group as randomized and for tTMB and bTMB populations separately within each treatment group.

Demographic and baseline laboratory results will be summarized using descriptive statistics for all randomized participants. Baseline characteristics, including demographics (age, gender, geographic location, race/ethnicity) and clinical characteristics (date of diagnosis, disease stage, liver function status, performance status, co-morbidity/prognostic indicators, location of metastases) will be collected at the time of treatment initiation for each arm. General descriptive statistics, including mean and standard deviation (SD) for continuous variables, count and percentage for categorical variables will be used extensively to examine these variables.

The statistical analysis plan will be developed and finalized before database lock and will describe the selection of participants to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. A summary of planned statistical analyses of the primary and secondary endpoints is in Sections 10.3.2 and 10.3.3.

10.3.1 Efficacy Analyses

Endpoint Definition	Statistical Analysis Methods
Primary	
ORR (based on BICR assessments) is defined as the number of participants with a best overall response of confirmed CR or PR divided by the number of all randomized participants. Best overall response is defined as the best response designation, as determined by BICR, recorded between the date of randomization and the date of objectively documented progression (per RECIST v1.1 or RANO criteria) or the date of subsequent therapy, whichever occurs first. For participants without documented progression or subsequent therapy, all available response designations will contribute to the BOR determination. For participants who continue treatment beyond progression, the BOR will be determined based on response assessments up to the time of initial RECIST 1.1 progression.	BICR-assessed objective response rate (ORR) using disease specific response criteria: Response Evaluation Criteria in Solid Tumors (RECIST 1.1), and Response Assessment for Neuro-Oncology (RANO) criteria for primary CNS neoplasms. BICR-assessed ORR will be summarized by binomial response rates and their corresponding two-sided 95% exact CIs using Clopper-Pearson method.
Secondary	
DOR (based on BICR assessments) is defined as the time from first confirmed response (CR or PR) to the date of the first documented tumor progression as determined using RECIST 1.1 or RANO criteria or death due to any cause, whichever occurs first. Participants who start subsequent therapy without a prior reported progression will be censored at the last evaluable tumor assessments prior to initiation of the subsequent anticancer therapy. Participants who die without a reported prior progression will be considered to have progressed on the date of their death. Participants who neither progress nor die will be censored on the date of their last evaluable tumor assessment.	BICR-assessed duration of response (DOR) will be estimated for all randomized participants who achieve confirmed PR or CR using the Kaplan-Meier (KM) product-limit method. Median values of DOR, along with two-sided 95% CI using Brookmeyer and Crowley method, will also be calculated. Probability of achieving DOR≥ 6 months will be calculated using KM method with 95% CI.
The investigator-assessed ORR	Investigator-assessed ORR will be summarized by binomial response rates and their corresponding two-sided 95% exact CIs using Clopper-Pearson method.
The investigator-assessed DOR	Investigator- assessed duration of response (DOR) will be estimated for all randomized participants who achieve confirmed PR or CR using the Kaplan-Meier (KM) product-limit method. Median values of DOR, along with two-sided 95% CI using Brookmeyer and Crowley method, will also be calculated. Probability of achieving DOR≥ 6 months will be calculated using KM method with 95% CI.
TTR is defined as the time from randomization date to the date of the first confirmed response, as assessed by the BICR.	Time to response (TTR) will be summarized using descriptive summary statistics for the responders.

Endpoint Definition	Statistical Analysis Methods
CBR is defined as the number of participants with a best overall response (BOR) of confirmed complete response (CR) or partial response (PR) or stable disease (SD) divided by the number of randomized participants.	BICR and Investigator assessed CBR will be summarized by binomial response rates and their corresponding two-sided 95% exact CIs using Clopper-Pearson method.
OS is defined as the time from the randomization date to the date of death.	Time to event distribution will be estimated using Kaplan Meier techniques. Median OS along with 95% CI will be constructed based on a log-log transformed CI for the survivor function. Rates at some fixed timepoints (6, 12, 18 and 24 months) will be derived from the Kaplan Meier estimate and corresponding confidence interval will be derived based on Greenwood formula for variance derivation and on log-log transformation applied on the survivor function. Participants without documentation of death will be censored on the last date the participant was known to be alive.
PFS is defined as the time from randomization date to the date of the first documented tumor progression, determined by BICR assessments (per RECIST 1.1 or RANO), or death due to any cause, whichever occurs first.	BICR and investigator assessments will use Response Evaluation Criteria in Solid Tumors (RECIST 1.1), and Response Assessment for Neuro-Oncology (RANO) criteria for primary CNS neoplasms. Participants without a reported progression will be considered to have progressed on the date of their death if no subsequent anti-cancer therapy initiated. Participants who did not progress or die will be censored on the date of the last tumor assessment. Participants who did not have any on study tumor assessments and did not die will be censored on the first dosing date. Participants who started any subsequent anti-cancer therapy and without a prior reported progression will be censored at the last tumor assessment prior to initiation of the subsequent therapy. Time to event distribution will be estimated using Kaplan Meier techniques. Median PFS along with 95% CI will be constructed based on a log-log transformed CI for the survivor function. Rates at some fixed time points (6, 12, 18 and 24 months) will be derived from the Kaplan Meier estimate and corresponding confidence interval will be derived based on Greenwood formula for variance derivation and on log-log transformation applied on the survivor function.

10.3.2 Safety Analyses

Endpoint Definition	Statistical Analysis Methods
Primary	Not applicable

Endpoint Definition	Statistical Analysis Methods
Secondary	
Safety and tolerability	Descriptive statistics of safety will be presented using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 by tumor types. All on-study AEs and SAEs and drug-related AEs and SAEs will be tabulated using worst grade per NCI CTCAE version 5.0 criteria by system organ class and MedDRA preferred term. On-study lab parameters including hematology, coagulation, chemistry, liver function and renal function will be summarized using worse grade per NCI CTCAE version 5.0 criteria.
Exploratory	Will be described in the statistical analysis plan finalized before database lock

10.3.3 Pharmacokinetics Analysis

The nivolumab and ipilimumab concentration data obtained in this study may be combined with data from other studies in the clinical development program to develop population PK models. These models may be used to evaluate the effects of intrinsic and extrinsic covariates on the PK of nivolumab and to determine measures of individual exposure (such as steady state peak, trough and time averaged concentration). Model determined exposures may be used for exposure response analyses of selected efficacy and safety endpoints. If the analyses are conducted, the results of population PK and exposure response analyses will be reported separately.

10.3.4 Outcomes Research Analyses

The analysis of EQ-5D-3L and EORTC QLQ-C30 data will be performed in all treated participants who have an assessment at baseline and at least 1 subsequent assessment while on treatment. Questionnaire completion rate, defined as the proportion of questionnaires received out of the expected number, will be calculated and summarized at each assessment point. Analyses of PROs will be replicated for subjects that are treated with nivolumab combined with ipilimumab after disease progression under nivolumab monotherapy.

EQ-5D data will be described by treatment group in the following ways:

- EQ-5D 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).
- EQ-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 dimensions at each assessment time point. Participants with missing data will be excluded from the analysis.
- A by- participant listing of the level of problems in each dimension, corresponding EQ-5D health state (ie, 5-digit vector), EQ-5D index score, and EQ-VAS score will be provided.

EORTC QLQ-C30 data will be described by treatment group in the following ways:

- Scale and item 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).
- Changes from baseline in scale and item scores will be summarized at each post-baseline assessment time point using descriptive statistics (ie, N, mean with SD and 95% CI, median, first and third quartiles, minimum, maximum).

10.3.5 Other Analyses

Immunogenicity: Serum samples collected will be analyzed by a validated immunogenicity assay. Selected serum samples may be analyzed by an exploratory orthogonal method that measures anti-nivolumab. Potential results generated from any orthogonal method are intended as informational for technology exploration purposes and will not be reported.

In addition, ad hoc serum samples designated for pharmacokinetic or biomarker assessments may also be used for immunogenicity analysis if required (e.g., insufficient volume for complete immunogenicity assessment or to follow up on suspected immunogenicity related AE).

Other exploratory analyses will be described in the statistical analysis plan.

10.3.6 Interim Analyses

Adjust bTMB cut-off value

An interim analysis will be conducted to evaluate the cut-off value for bTMB using an adaptive enrichment procedure.[81,82] In order to ensure that 1 tumor type does not unduly impact the overall pooled efficacy analysis, a cap of approximately 15% participants per tumor type of the sample size for this interim analysis will be enforced. The analysis will be performed after approximately the first 30 randomized participants in nivolumab + ipilimumab arm with bTMB ≥ 10 mut/Mb at baseline have been randomized and followed for at least 6 months.

BICR-assessed ORR will be estimated in the following groups

- low group (10 ≤ bTMB < cut-off)
- enriched group (bTMB ≥ cut-off)

Decision rule:

If the following 2 criteria are satisfied at the interim analysis,

1) estimated ORR in enriched group minus estimated ORR in low group ≥ 16.5%
   and
2) estimated ORR in low group < 30%

then eligibility criteria will be restricted to participants with either tTMB ≥ 10 mut/Mb or bTMB ≥ new cut-off for the remainder of the trial until a total of approximately 114 participants (76 in nivolumab + ipilimumab arm and 38 in nivolumab arm) with bTMB ≥ new cut-off are enrolled

and a total of approximately 114 participants with tTMB ≥ 10 mut/Mb are enrolled. The maximum number of participants for the study may be up to 342 if cut-off value for bTMB is increased and all of the previously randomized bTMB participants need to be replaced with new participants who have bTMB ≥ new cut-off.

Should the tTMB-H (tTMB ≥ 10 mut/Mb) population reach the targeted sample size (approximately 76 participants in nivolumab + ipilimumab arm and approximately 38 in nivolumab arm), participants will continue to provide a tissue sample; however, eligibility will be based on a bTMB ≥ new cut-off only.

Simulations have been conducted to evaluate the operating characteristics, including the decision rule, and details are provided in Appendix 10. The Statistical Analysis Plan (SAP) will further describe the planned interim analyses.

Correlation between bTMB and tTMB will be assessed.

Efficacy for tTMB population

A formal interim analysis for BICR-assessed ORR will be conducted on tTMB high participants in the salvage setting after approximately the first 50 for nivolumab + ipilimumab arm and 25 for nivolumab monotherapy arm randomized participants in the salvage setting with tTMB ≥ 10 mut/Mb at baseline have been randomized and followed for at least 12 months (approximately 75 total tTMB high participants), and study-wide randomization has completed. In order to achieve the necessary number of study participants in the tTMB high population for the tTMB primary endpoint final analysis, enrollment into this population continued after the date on which criteria were met for the tTMB interim analysis. The primary analysis population for the interim analysis will be the interim tTMB high population (limited to all tTMB high participants randomized at least 12 months prior to the LPLV for the analysis).

BICR-assessed DOR will be analyzed for tTMB high participants who achieve confirmed PR or CR using the Kaplan-Meier (KM) product-limit method. Probability of achieving DOR≥ 6 months will also be calculated.

Similar interim analysis may be conducted on bTMB high population.

All of the interim analyses and other unblinded efficacy/safety data will be reviewed by the DMC while the Sponsor remains blinded (See DMC charter for more detail).

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

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12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
µ	micro
ADA	anti-drug antibody
AE	adverse event
ALT	alanine aminotransferase
AR	additional research
AST	aspartate aminotransferase
AT	aminotransaminases
BICR	blinded independent central review
BMS	Bristol-Myers Squibb Company
BOR	best overall response
BP	blood pressure
BSA	body surface area
bTMB	blood TMB
bTMB-H	blood TMB high
BUN	blood urea nitrogen
C	cycle
Ca	calcium
Cavg	average concentration
Cavgss	average steady-state exposure
CBC	complete blood count
CBR	clinical benefit rate
CFR	Code of Federal Regulations
cHL	classical Hodgkin's lymphoma
CI	confidence interval
Cl^-	chloride
CL	clearance
CLIA	Clinical Laboratory Improvement Amendments
CLcr	creatinine clearance
Cmax	maximum concentration

Term	Definition
Cmaxss	steady-state peak concentrations
CNS	central nervous system
COVID-19	coronavirus disease 2019
CR	Complete response
CRC	colorectal cancer
CRF	case report form, paper or electronic
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
CV	coefficient of variation
D	day
DC/D	discontinuation/death
dL	deciliter
DLT	Dose Limiting Toxicity
DMC	data monitoring committee
dMMR	deficient mismatch repair deficiency
DNA	deoxynucleic acid
DOR	duration of response
DRESS	drug reaction with eosinophilia and systemic symptoms
EC	endometrial cancer
ECG	electrocardiogram
ECL	electrochemiluminescent
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
eg	exempli gratia (for example)
eGFR	estimated glomerular filtration rate
EOI	end of infusion
EOI-PK	end of infusion pharmacokinetics
EORTC	European Organization for Research and Treatment of Cancer
EORTC-QLQ-C30	European Organization for Research and Treatment of Cancer quality of life questionnaire 30
EQ-5D	EuroQol questionnaire comprising 5 dimensions

Term	Definition
EQ-5D-3L	the 3-level version of the EuroQol questionnaire comprising 5 dimensions
ER	exposure response
EU	European Union
F1CDx	FoundationOne® Companion Diagnostic
FDG	fluorodeoxyglucose
FFPET	formalin-fixed, paraffin-embedded tumor tissue
FLAIR	fluid-attenuated inversion recovery
FMI	Foundation Medicine Incorporated
FNA	fine needle aspiration
FSH	follicle stimulating hormone
FU	follow-up
g	gram
GBS	Guillain-Barre syndrome
GC	gastric cancer
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
h	hour
H&N	head and neck
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCG	human chorionic gonadotropin
HCV	hepatitis C virus
HCO_3^-	bicarbonate
HIV	human immunodeficiency virus
HR	hazard ratio
IA	interim analysis
IB	Investigator Brochure
ICH	International Conference on Harmonisation

Term	Definition
IDO	indoleamine 2,3 dioxygenase
ie	id est (that is)
IEC	Independent Ethics Committee
IHC	immunohistochemistry
IMP	investigational medicinal products
IND	Investigational New Drug Exemption
IO	immuno-oncology
IP	investigational product
IRB	Institutional Review Board
IRC	Independent Review Committee
IRT	Interactive Response Technology
IU	International Unit
IV	intravenous
IVRS	interactive voice response systems
K^+	potassium
kg	kilogram
L	liter
LAG-3	Lymphocyte activation gene-3
LDH	lactate dehydrogenase
LPLV	last patient last visit
MDSC	myeloid-derived suppressor cell
mg	milligram
Mg^{++}	magnesium
MG	myasthenia gravis
MHC	major histocompatibility complex
MI	myocardial Infarction
min	minute
mL	milliliter
MMR	mismatch repair
mo	month

Term	Definition
mPFS	median progression-free survival
MRI	magnetic resonance imaging
MSI	microsatellite instability
MSI-H	microsatellite instability high
MTD	maximum tolerated dose
mut/Mb	mutations per megabase
N	number of subjects or observations
Na	sodium
N/A	not applicable
NCI	National Cancer Institute
NGS	Next-Generation Sequencing
NIMP	non-investigational medicinal products
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed death ligand 1
PET	positron emission tomography
PFS	progression free survival
PK	pharmacokinetics
PPK	population pharmacokinetics
PR	Partial response
PRO	Patient-reported outcome
Q2W	every 2 weeks
Q4W	every 4 weeks
Q6W	every 6 weeks
QOL	quality of life

Term	Definition
R&D	research and development
RANO	Response Assessment for Neuro-Oncology
RECIST	Response Evaluation Criteria in Solid Tumors
RBC	red blood cell
RCC	renal cell carcinoma
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCCHN	squamous cell carcinoma of the head and neck
SD	standard deviation
SD	stable disease
SJS	Stevens-Johnson syndrome
SOP	Standard Operating Procedures
SPD	Sum of the products of perpendicular diameters
t	temperature
T	time
t1/2	half-life
T2	transverse relaxation time
T3	triiodothyronine
T4	thyroxine
T.bili	total bilirubin
TEN	toxic epidermal necrolysis
TIA	transient ischemic attack
TMB	tumor mutational burden
TMB-H	high tumor mutational burden
Treg	regulatory T cell
tTMB	tissue TMB
TTR	time to response
TSH	thyroid stimulating hormone
UC	urothelial carcinoma

Term	Definition
ULN	upper limit of normal
USPI	United States Prescribing Information
WBC	white blood cell
VAS	visual analog scale
WHO	World Health Organization
WES	whole exome sequencing
WOCBP	women of childbearing potential
WNOCBP	women **not** of childbearing potential

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 Sponsor or designee immediately. A serious breach is a breach of the conditions and principles of Good Clinical Practice (GCP) (occurring in any country) in connection with that trial or the protocol to the trial which is likely to affect to a significant degree, the safety or physical or mental integrity of 1 or more subjects of the trial or the scientific value of the trial.

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 (e.g., 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 (e.g., advertisements), and any other written information to be provided to subjects. 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 and any updates.

The investigator, Sponsor or designee should provide the IRB/IEC with reports, updates and other information (e.g., 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.

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

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

Documentation of approval/favorable opinion signed by the chairperson or designee of the IRB(s)/IEC(s) and if applicable, also by 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 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 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 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, 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 (i.e., 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, 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' signed ICF and, in the US, the subjects' signed HIPAA Authorization.

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

The rights, safety, and well-being of the study subjects 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, 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 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

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

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

In addition, the study may be evaluated by 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 (e.g., relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g., 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 (e.g., 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) (examples include study treatments sourced from the sites stock or commercial supply, or a specialty pharmacy)	It is the investigator's or designee's responsibility to dispose of all containers according to the institutional guidelines and procedures.

It is the investigator's or designee's responsibility to arrange for disposal, 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, i.e., 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.

For this study, study treatments (those supplied by BMS or its vendors) such as full or partially used study treatment containers, vials, syringes cannot be destroyed on-site.

CLINICAL STUDY REPORT AND PUBLICATIONS

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

For this protocol, the Signatory Investigator will be selected as appropriate based on the following criteria:

- Participant recruitment (e.g., among the top quartile of enrollers)
- Involvement in trial design
- Regional representation (e.g., among top quartile of enrollers from a specified region or country)
- Other criteria (as determined by the study team)

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 (CTAg) 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 CTAg.

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 required method for SAE data reporting 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 form is 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.**

NOT APPLICABLE PER PROTOCOL AMENDMENT 04: CONTRACEPTION GUIDANCE FOR MALE PARTICIPANTS WITH PARTNER(S) OF CHILD BEARING POTENTIAL.

Male participants with female partners of childbearing potential are eligible to participate if they agree to the following during the treatment and until the end of relevant systemic exposure.

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Male participants are required to use a condom for study duration and until end of relevant systemic exposure defined as 7 months after the end of study treatment.
- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 7 months after the end of treatment in the male participant.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 7 months after the end of study treatment.
- Refrain from donating sperm for the duration of the study treatment and until 7 months after the end of study treatment.

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 MANAGEMENT ALGORITHMS FOR STUDIES UNDER CTCAE VERSION 5.0

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

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

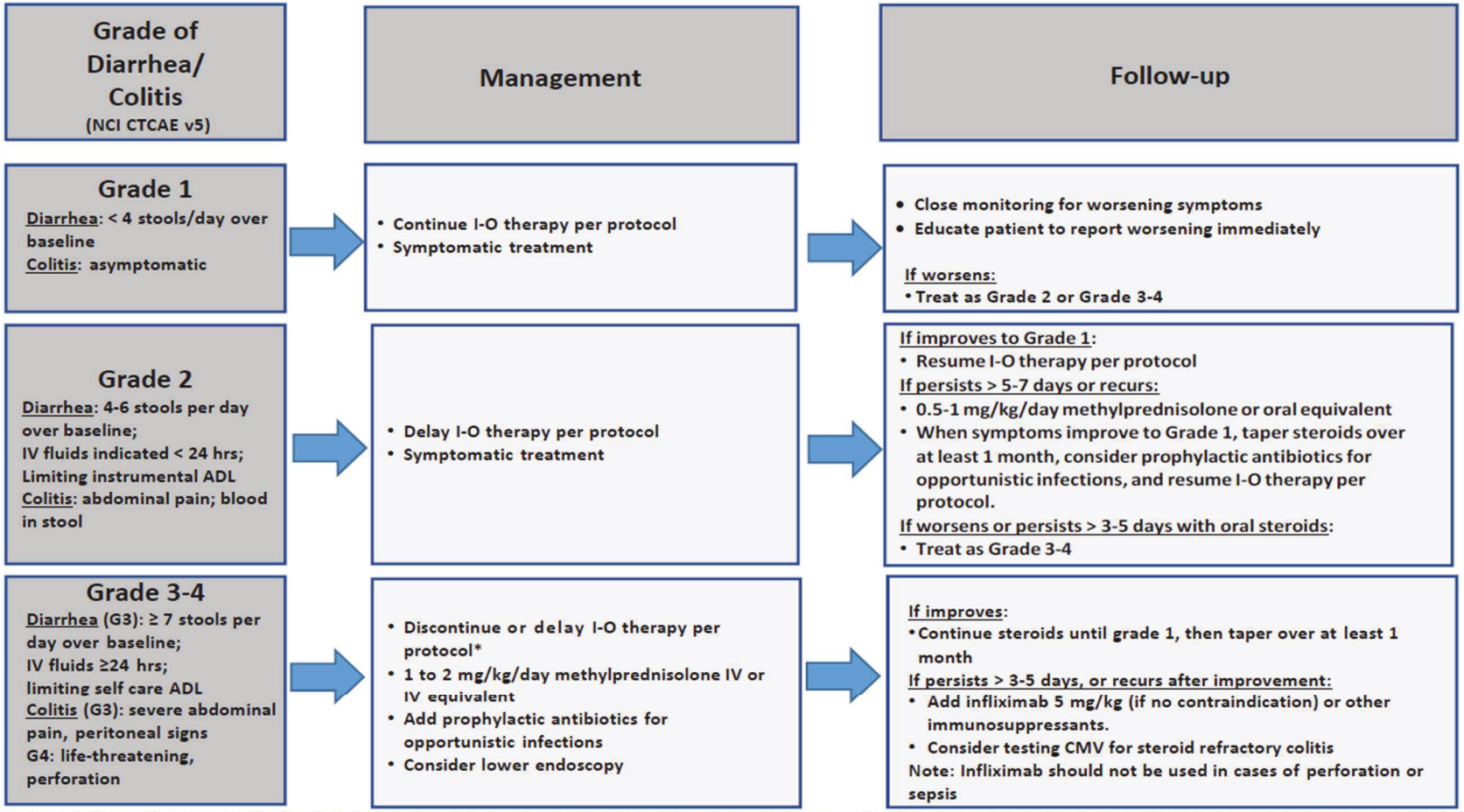
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the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

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

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

GI Adverse Event Management Algorithm

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



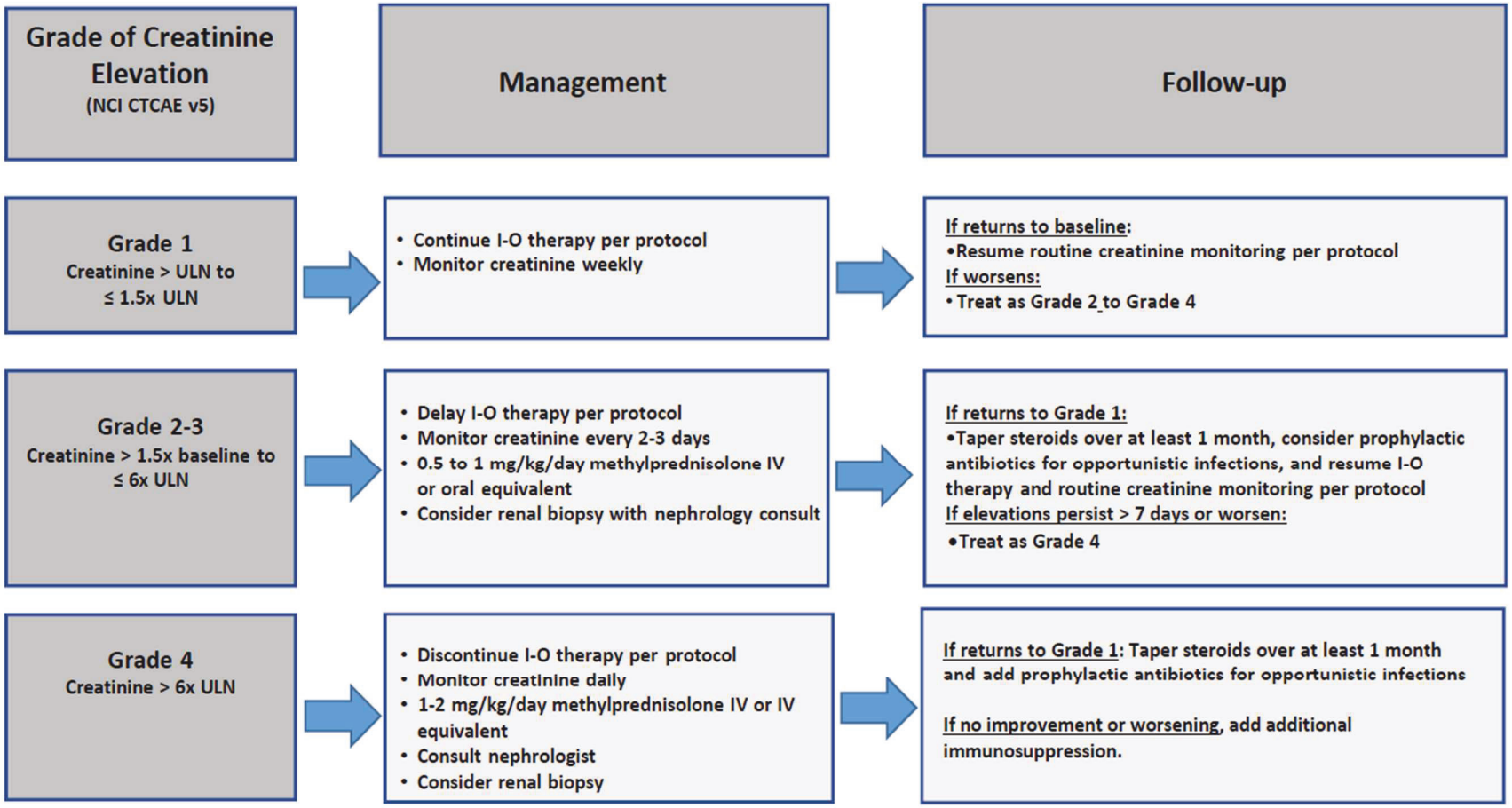
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

28-Sep-2020

Renal Adverse Event Management Algorithm

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

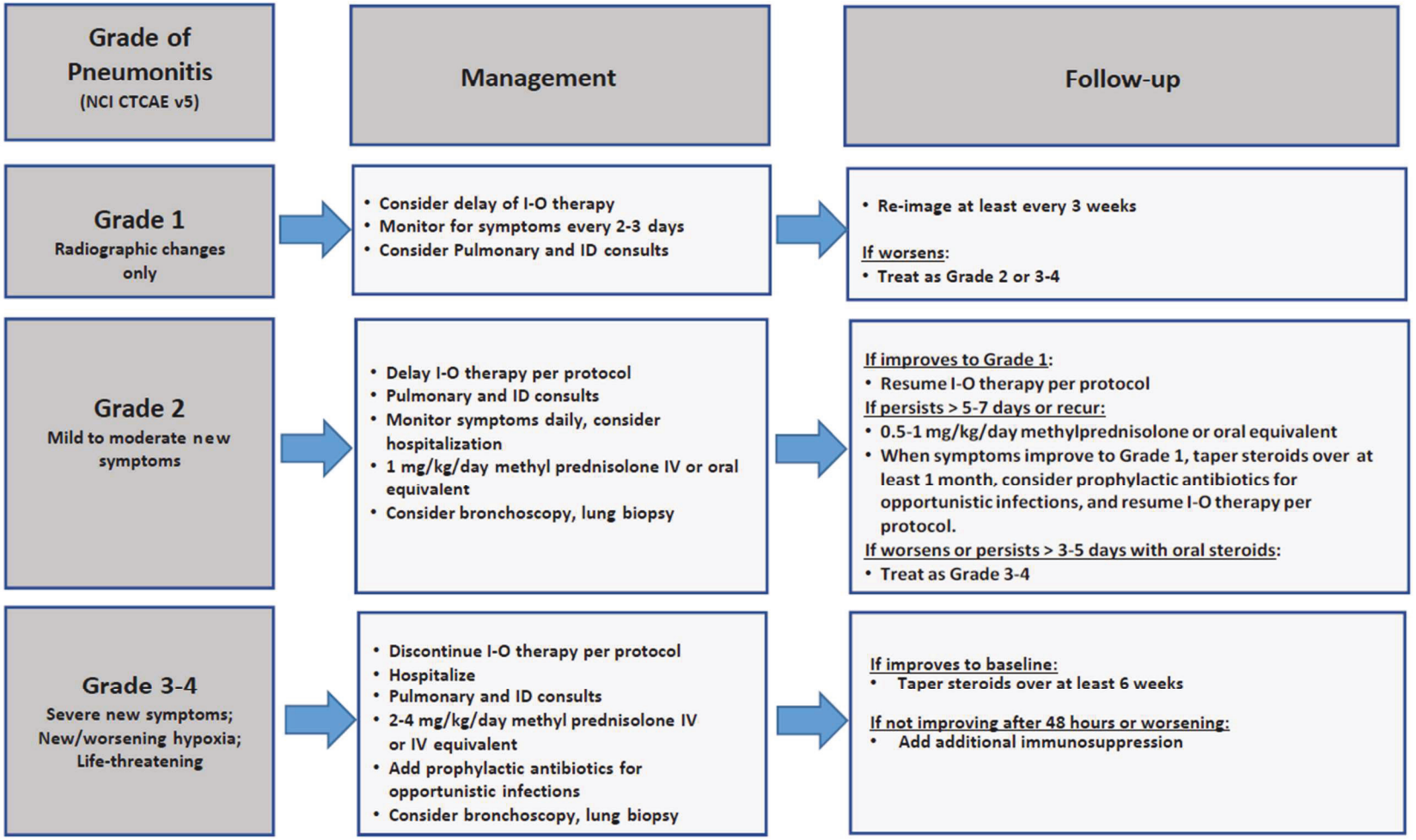


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

28-Sep-2020

Pulmonary Adverse Event Management Algorithm

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

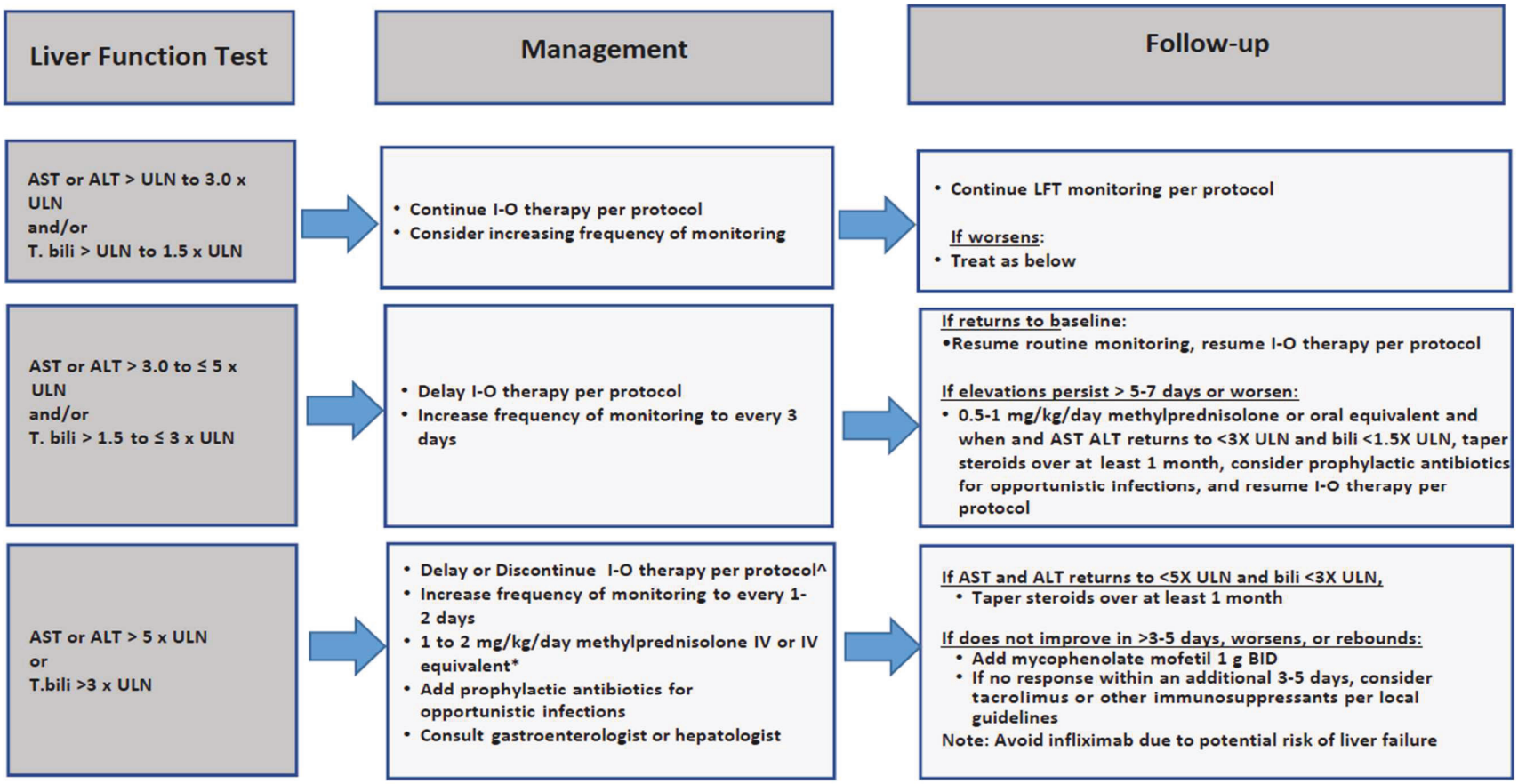


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

28-Sep-2020

Hepatic Adverse Event Management Algorithm

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

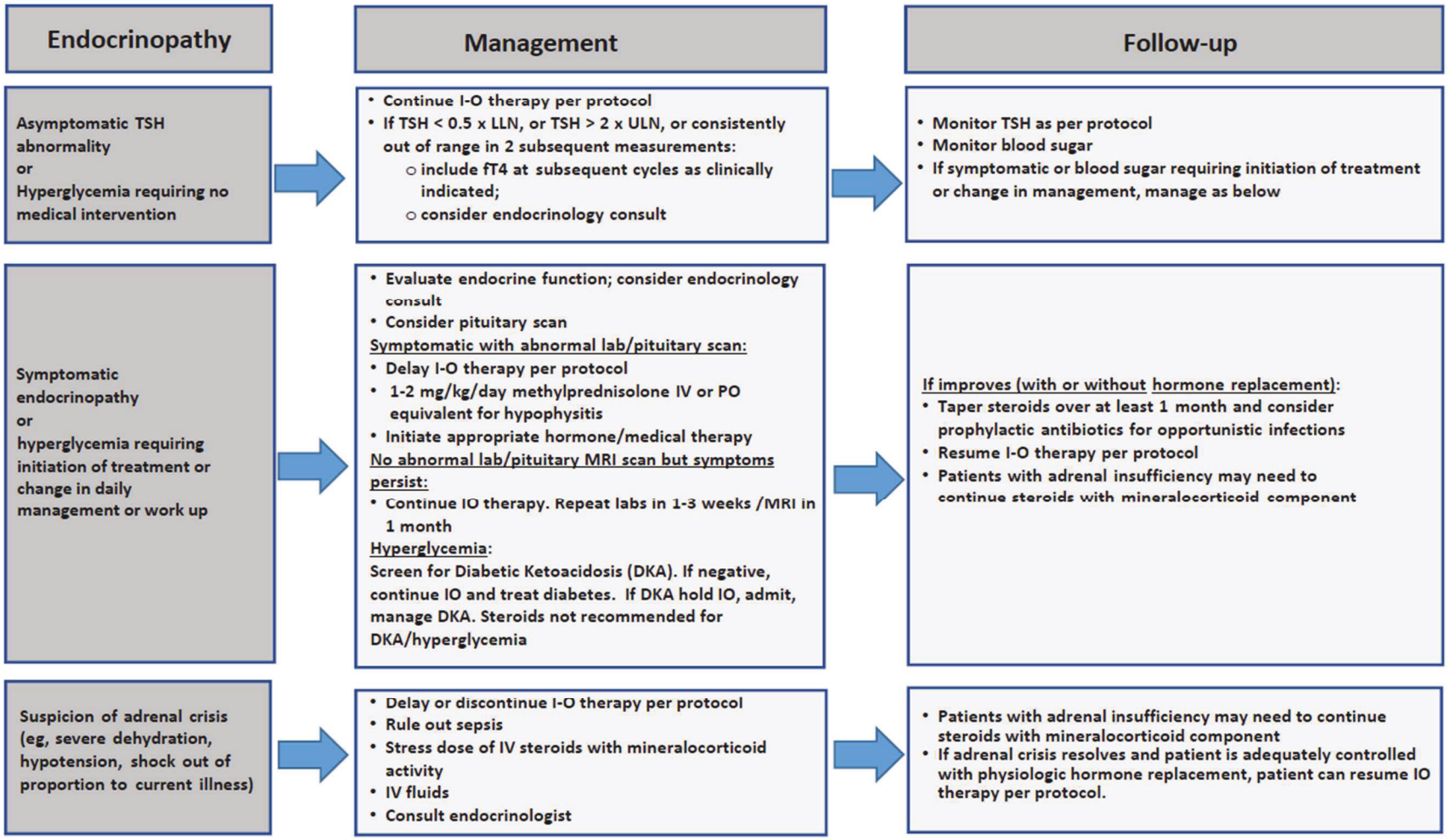


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

28-Sep-2020

Endocrinopathy Adverse Event Management Algorithm

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

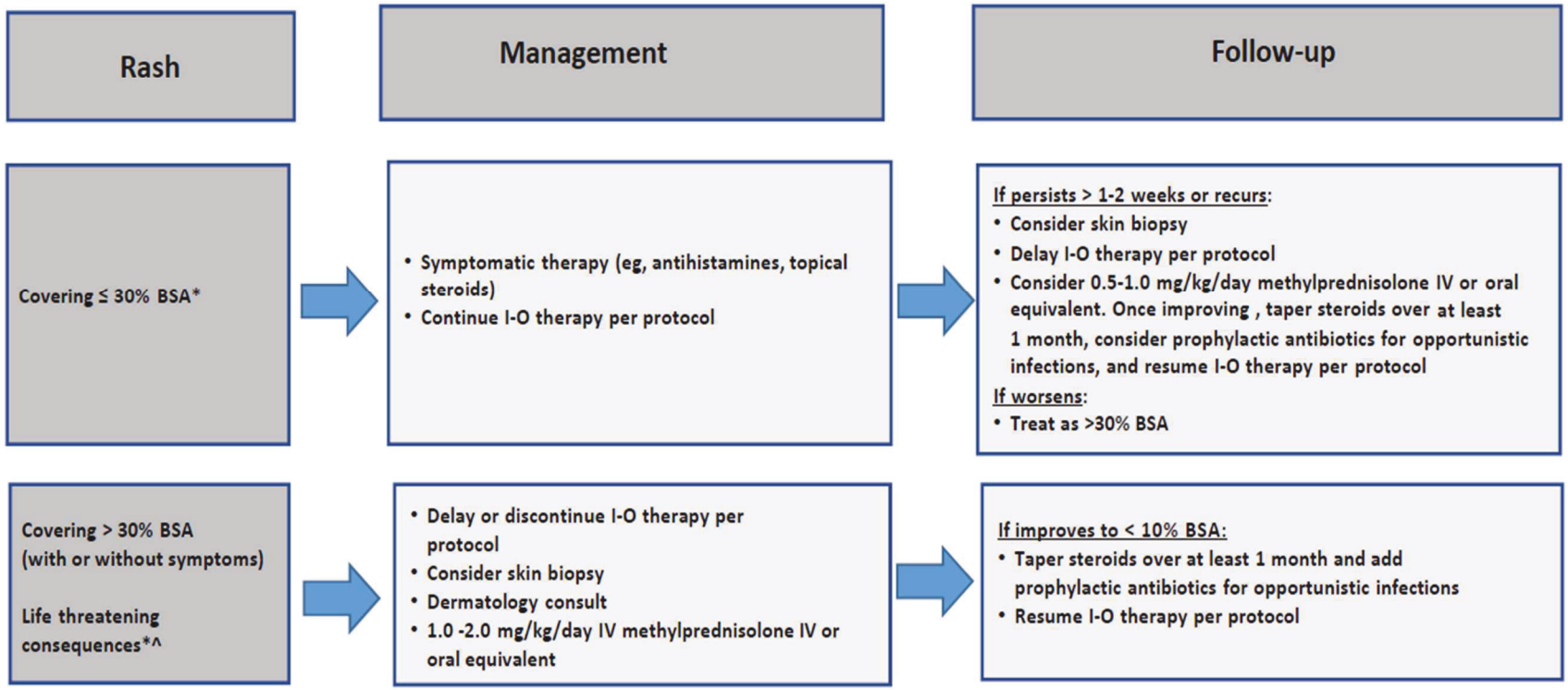


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

28-Sep-2020

Skin Adverse Event Management Algorithm

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



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

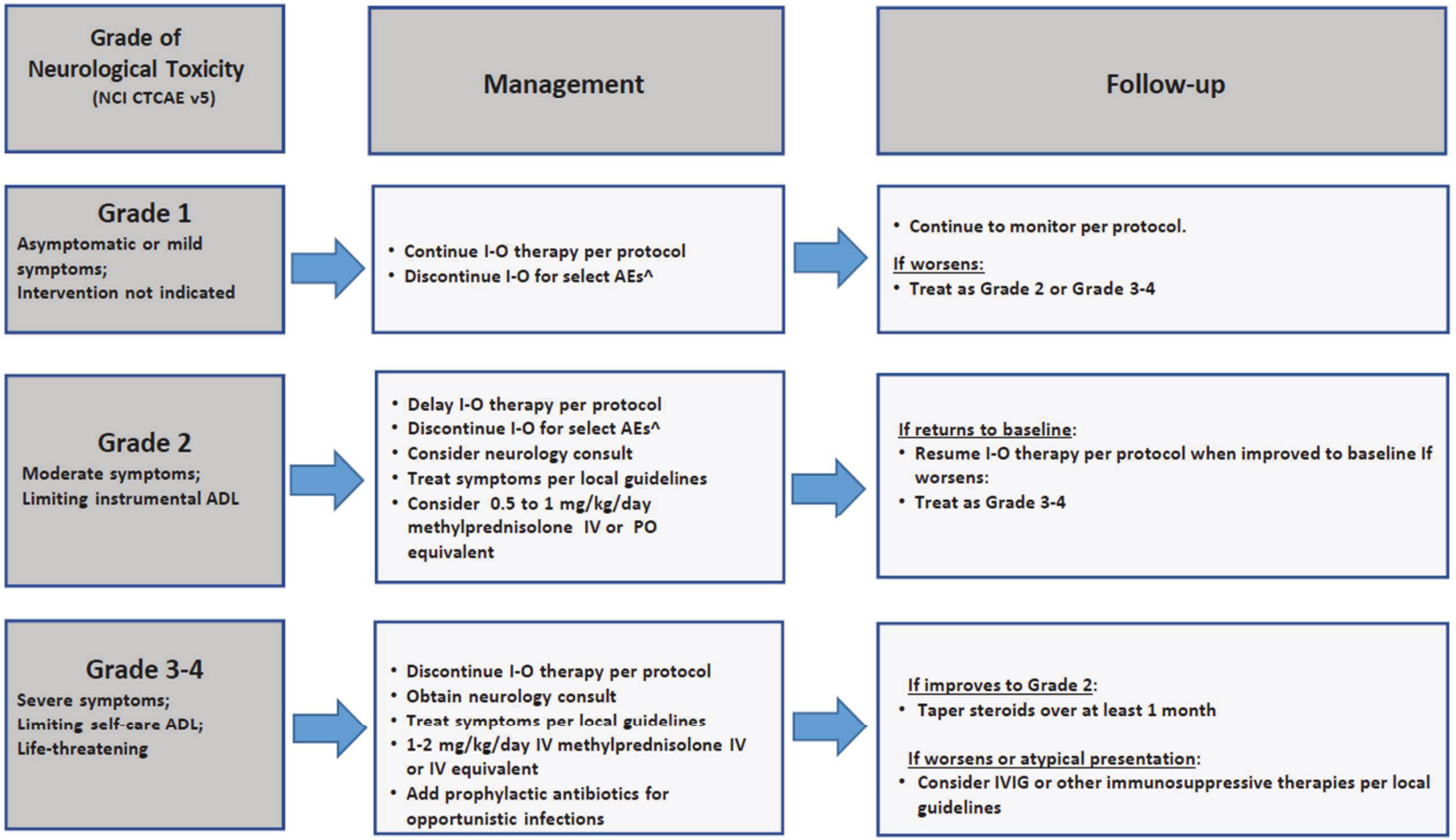
*Refer to NCI CTCAE v5 for term-specific grading criteria.

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

28-Sep-2020

Neurological Adverse Event Management Algorithm

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



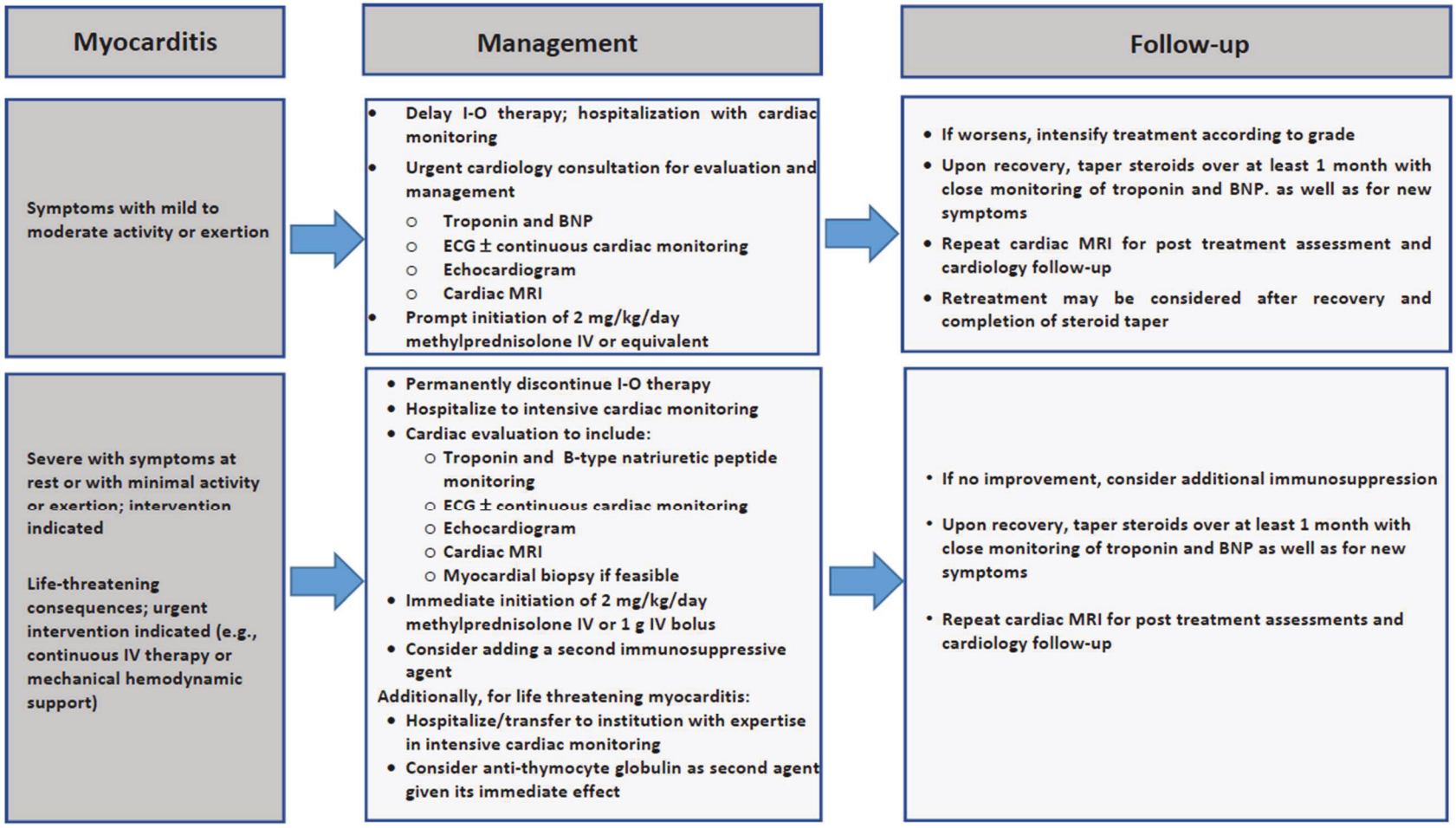
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

28-Sep-2020

Myocarditis Adverse Event Management Algorithm

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



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

28-Sep-2020

APPENDIX 6 ECOG PERFORMANCE STATUS

Table 1: ECOG Performance Status

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

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

APPENDIX 7 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:

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

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

2.3 Response Assessment

2.3.1 Evaluation of Best Overall Response

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

2.3.2 Time Point Response

At each protocol specified time point, a response assessment occurs. Table 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 8 RADIOGRAPHIC ASSESSMENT FOR NEURO-ONCOLOGY (RANO) CRITERIA FOR HIGH-GRADE GLIOMAS

Table 1: Summary of Proposed Radiographic Assessment for Neuro-Oncology

Criterion	Complete Response	Partial Response	Stable Disease	Progressive Disease
T1 gadolinium enhancing disease	None	≥ 50% ↓	< 50% ↓ but < 25% ↑	≥ 25% ↑*
T2/FLAIR	Stable or ↓	Stable or ↓	Stable or ↓	↑*
New lesion	None	None	None	Present*
Corticosteroids	None	Stable or ↓	Stable or ↓	NA†
Clinical status	Stable or ↑	Stable or ↑	Stable or ↑	↓*
Requirement for response	All	All	All	Any*

Abbreviations: RANO, Response Assessment in Neuro-Oncology; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; FLAIR, fluid-attenuated inversion recovery; NA, not applicable.

* Progression occurs when this criterion is present.

† Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

NOTE. All measurable and nonmeasurable lesions must be assessed using the same techniques as at baseline.

Reference: Wen PY, Macdonald DR, Reardon DA, et al. Updated Response Assessment Criteria for High-Grade Gliomas: Response Assessment in Neuro-Oncology Working Group J Clin Oncol 2010;28-1:3059-3067.

APPENDIX 9 KARNOFSKY AND LANSKY CRITERIA

STATUS		STATUS
KARNOFSKY	**LANSKY**	**KARNOFSKY or LANSKY**
Normal, no complaints	Fully active, normal	100
Able to carry on normal activities; minor signs or symptoms of disease	Minor restrictions in physically strenuous activity	90
Normal activity with effort; some signs or symptoms of disease	Active, but tires more quickly	80
Cares for self. Unable to carry on normal activity or to do active work	Substantial restriction of, and less time spent, in play activity	70
Requires occasional assistance, but able to care for most of his needs	Out of bed, but minimal active play; keeps busy with quiet activities	60
Requires considerable assistance and frequent medical care	Gets dressed, but inactive much of day; no active play, able to participate in quiet play	50
Disabled. Requires special care and assistance	Mostly in bed; participates in some quiet activities	40
Severely disabled. Hospitalization indicated though death non imminent	In bed; needs assistance even for quiet play	30
Very sick. Hospitalization necessary. Active supportive treatment necessary	Often sleeping; play limited to passive activities	20
Moribund	No play; does not get out of bed	10

APPENDIX 10 SIMULATION RESULTS

Simulations have been conducted under the following assumed scenarios:

- Proportions for enriched group and low group: 0.75 vs. 0.25, 0.7 vs. 0.3, 0.6 vs. 0.4, 0.5 vs. 0.5
- True ORRs for enriched group and low group: 40% vs. 25%, 35% vs. 10%, 20% vs. 10%, 10% vs. 10%

10,000 replications of trials were simulated with a total of 76 bTMB evaluable participants and 30 bTMB ≥ 10 mut/MB participants at the time of interim analysis. As shown in Table 1, the simulated power for the adaptive procedures (power adapt) and non-adaptive procedures (power non-adapt) are calculated for each assumed scenario.

Table 2: The power for adaptive vs. non-adaptive procedures

Group	Proportion of entire population	True ORR	Power non-adapt	Power adapt
Enriched group	0.75	40%	0.723	0.999
Low group	0.25	25%		
Enriched group	0.75	35%	0.726	0.987
Low group	0.25	10%		
Enriched group	0.75	20%	0.411	0.471
Low group	0.25	10%		
Enriched group	0.75	10%	0.019	0.020
Low group	0.25	10%		
Enriched group	0.7	40%	0.660	0.999
Low group	0.3	25%		
Enriched group	0.7	35%	0.636	0.979
Low group	0.3	10%		
Enriched group	0.7	20%	0.346	0.442
Low group	0.3	10%		
Enriched group	0.7	10%	0.016	0.017
Low group	0.3	10%		
Enriched group	0.6	40%	0.602	0.999
Low group	0.4	25%		
Enriched group	0.6	35%	0.467	0.948
Low group	0.4	10%		
Enriched group	0.6	20%	0.226	0.383
Low group	0.4	10%		

Table 2: The power for adaptive vs. non-adaptive procedures

Group	Proportion of entire population	True ORR	Power non-adapt	Power adapt
Enriched group	0.6	10%	0.012	0.015
Low group	0.4	10%		
Enriched group	0.5	40%	0.570	0.999
Low group	0.5	25%		
Enriched group	0.5	35%	0.342	0.896
Low group	0.5	10%		
Enriched group	0.5	20%	0.149	0.347
Low group	0.5	10%		
Enriched group	0.5	10%	0.013	0.017
Low group	0.5	10%		

Note: Enriched group include participants with bTMB>=cut-off and Low group include participants with 10<=bTMB<cut-off

The simulation result shows that adaptive enrichment procedure appears to increase the power in most scenarios. In addition, type I error is well controlled (<0.025).

APPENDIX 11 COUNTRY SPECIFIC AMENDMENTS

Argentina, France, Germany, Italy, Spain, 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 1.a	"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 12 REVISED PROTOCOL SUMMARY OF CHANGE HISTORY

Overall Rationale for Revised Protocol 03:

This protocol revision serves to update the protocol per program requirements, company and document standards, as well as make changes per the Administrative Letter 02 and 03. The following content has also been updated:

- Updated the range and number of participants and clarified statistical analyses and sample size.
- Provided clarification on requirements for pre-screening and eligibility.
- Added language regarding adolescent participants not being included for sites in Belgium and the Netherlands per the Country Specific Amendment 03.

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	Updated Study Director and Medical Monitor information	Updated study personnel
Section 2 Schedule of Activities Table 2-1	Added the following language- tTMB and bTMB results should be ≥ 10 mut/Mb (tTMB ≥ 10 mut or the new cutoff value of bTMB determined by the 1st interim analysis)	Provided clarification on pre-screening requirements and interim analyses
Section 2 Schedule of Activities Table 2-1 Table 2-2 Table 2-3 Table 2.4 Section 3.1.3 Rationale for Inclusion of Adolescent Participants Section 3.2.4 Nivolumab Combined with Ipilimumab and Nivolumab Monotherapy Clinical Activity in Adolescents Section 3.3.2 Adolescent Patients Section 5.5.3 Dose for Adolescents Section 7.1 Treatments Administered Table 7.1-1 Section 7.1.1 Arm A or Arm B Rollover - Nivolumab in Combination with Ipilimumab	Added content regarding Belgium and the Netherlands not enrolling adolescents into study sites	At the request of Belgium and the Netherlands sites

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 7.1.2 Arm B – Nivolumab Monotherapy		
Section 2 Schedule of Activities Table 2-2 Table 2-3 Table 2-4	Added the following language in the Outcomes research row- If the dose is delayed, then PRO completion should also be delayed.	Bring protocol in line with drug program standards
Section 3.2.5 Nivolumab Clinical Pharmacology	Added updated clinical pharmacology section to background	Bring protocol in line with document standards
Section 4 Objectives and Endpoints Table 4-1	Clarified endpoints for exploratory objectives	Provide further detail on study scope
Section 5.1 Overall Design Figure 5.1-1	Updated figure to include language regarding tTMB ≥ 10 mut or the new cutoff value of bTMB determined by the 1st interim analysis Added content regarding Belgium and the Netherlands not enrolling adolescents into study sites	Provided clarification on pre-screening requirements and interim analyses At the request of Belgium and the Netherlands sites
Section 5.2 Number of Participants	Updated the range of participants and rationale of participant range	Provide further detail on study scope
Section 5.5.5 Rationale for 30-Minute infusion	Removed text regarding 30 minute break after first infusion for combination cohort	Not applicable to study
Section 6.1 Inclusion Criteria	Updated language regarding palliative local therapy Added content regarding Belgium and the Netherlands not enrolling adolescents into study sites	Bring protocol in line with drug program standards At the request of Belgium and the Netherlands sites
Section 6.1 Inclusion Criteria Figure 6.1-1	Updated figure to include language regarding biomarker testing, prescreening and ≥ 10 mut or the new cutoff value of bTMB determined by the 1st interim analysis	Provided clarification on pre-screening requirements and interim analyses
Section 6.2 Exclusion Criteria	Added content regarding Belgium and the Netherlands not enrolling adolescents into study sites Corrected typo in regarding creatinine clearance	At the request of Belgium and the Netherlands sites Administrative change.
Section 7 Treatment	Added clarification on weight based dosing calculations	Bring protocol in line with drug program standards
Section 7.4.5 Management Algorithms for Immuno-Oncology Agents	Added Myocarditis to the list of management algorithms	Bring protocol in line with drug program standards
Section 9.1.2.1 Solid tumors	Added language regarding CT component of a PET-CT Scanner	Bring protocol in line with document standards

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 9.1.3.1 BICR Confirmation of Radiographic Progression	Added language regarding BICR confirmation of disease progression.	Bring protocol in line with drug program standards
Section 9.8 Biomarkers Table 9.8-1 and Table 9.8-2	Clarified prescreening procedure and footnotes were updated for bTMB and tumor	Provided clarification on pre-screening requirements
Section 9.10 Patients Reported Outcomes	Indicated PRO assessments should be delayed in the event dose of treatment drug is also delayed	Bring protocol in line with drug program standards
Section 10.1 Sample Size Determination	Updated content regarding sample size and enrollment based on tTMB and bTMB pre-screening	Provided clarification on pre-screening requirements and participant population
Section 10.3.6 Interim Analyses	Updated content regarding sample size and enrollment based on tTMB and bTMB pre-screening	Provided clarification on pre-screening requirements and participant population
All	Minor formatting and typographical corrections	Minor, therefore have not been summarized

Overall Rationale for Revised Protocol 02:

This amendment incorporates feedback received from FDA on pursuing a tumor-agnostic indication with TMB for the study design of CA209-848. The key changes include:

1) Revision of the statistical method to be based on precision of the estimation of ORR. The efficacy decision is revised to be based on the lower limit of a 95% confidence interval to exceed a clinically relevant response rate. Previously, the primary endpoint is to be compared with a historical control with a type I error rate set to 0.05.
2) Clarification on targeted population as in a salvage setting. The inclusion criteria is revised to stress participants being "refractory to standard local therapies, or for which no standard treatment is available". Previously, it was "received at least one prior line of therapy including standard of care, if available".

SUMMARY OF KEY CHANGES OF REVISED PROTOCOL 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Document History	Included Revised Protocol 02; incorporated Administrative Letter 01.	Updated summary of changes.
Section 2, Schedule of Activities, Table 2-1, Screening Procedural Outline (CA209848)	Revised Notes for Pre-screening for TMB-H.	Provided more clarity on the pre-screening and screening procedures.
Section 2, Schedule of Activities, Table 2-1, Screening Procedural Outline (CA209848)	Revised Notes for Tumor tissue collection.	Added section reference regarding details for tumor tissue collection.

Overall Rationale for Revised Protocol 01:

This protocol is listed a "Revised protocol 1" to remain Title 21 CFR Part 11 compliant (FDA regulations on electronic records and electronic signatures). The initial protocol CA209848 was never activated as initially written. The study was fully revised and, therefore, there are no summary of changes to compare to the initial protocol.