Official Title of Study:

A Phase 1/2 Study of Nivolumab (BMS-936558) in Combination with Ipilimumab (BMS-734016) in Chinese Participants with Previously Treated Metastatic or Recurrent Solid Tumors

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CLINICAL PROTOCOL CA209672

A Phase 1/2 Study of Nivolumab (BMS-936558) in Combination with Ipilimumab (BMS-734016) in Chinese Participants with Previously Treated Metastatic or Recurrent Solid Tumors

Protocol Amendment Number: 07
Incorporates Administrative Letter 07

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DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Protocol Amendment 07	22-Aug-2022	Due to significant landscape change and shrinkage of eligible patient pool, Bristol-Myers Squibb made a decision to close the CA209672 Part 2 Study to enrollment in Dec-2021. Based on current timelines, projections show that the study will not be able to meet its scientific objectives in this rapidly evolving therapeutic landscape. Enrollment closure of the study is unrelated to safety. The protocol has been revised to modify or reduce the assessments and data collection to minimize the burden on study participants and site staff. Key changes in Protocol Amendment 07 include the removal of pharmacokinetic and immunogenicity sampling, as well as the tumor assessments and safety follow-up beyond 100 days post study drug discontinuation.
Administrative Letter 07	25-Feb-2022	The purpose of this letter is to change the contact information for the Medical Monitor.
Protocol Amendment 06	02-Jul-2021	• Updated study language for post-study access to therapy (criteria of study termination and disposition for those subjects still in study when the study terminates) and program level language for nivolumab and ipilimumab including language associated with SARS-CoV-2 infection • Added a section about outcome research analyses • Replaced older versions of appendices (management algorithms and WOCBP) with newer versions • Reported personnel changes • Incorporated Administrative Letter 06
Administrative Letter 06	02-Jul-2020	• Corrected inconsistencies in SAE collection period in Table 5.1-1, Table 5.1-2, and appendix 4.
Revised Protocol 05	09-Jan-2020	• Removal of sample collection as a control for MSI/MRR status confirmation
Administrative Letter 05	20-May-2019	• Change in Study Director/Medical Monitor
Revised Protocol 04	08-Apr-2019	• Incorporates Administrative Letter 01, 02, 03 and 04 • Added Part 2, Arm D, expansion cohort for recurrent or metastatic MSI-H/dMMR colorectal cancer subjects • Corrected inconsistencies, typographical and formatting errors, and updated all abbreviations throughout
Administrative Letter 04	11-Dec-2018	• Corrected inconsistencies in SAE collection period throughout the protocol
Administrative Letter 03	14-Mar-2018	• Provided rationale for modifying MSI testing requirement in the administrative letter 02.
Administrative Letter 02	25-Jan-2018	• Clarified MSI testing requirement in CRC subjects in revised protocol version 03.
Administrative Letter 01	22-Nov-2017	Corrected inconsistencies in Appendix 3 of the Chinese translation of revised protocol version 03

Document	Date of Issue	Summary of Change
Revised Protocol 03	26-Oct-2017	• Incorporates Amendment 03
Amendment 03	26-Oct-2017	• Removed RCC and NPC tumor types from and to add CRC MSI-H/dMMR to Arm B • Added of neutralizing antibody analysis as part of immunogenicity analysis • Appendix 3 updated Corrected inconsistencies, typographical and formatting errors, and make small language clarifications
Revised Protocol 02	20-Apr-2017	• Incorporates Amendment 02
Amendment 02	20-Apr-2017	• Defines 2 years or 24 months of treatment duration • Removal of tumor sample collection at screening and biomarker analysis of tumor sample • Incorporates nivolumab program updates To make any typographical edits, format updates and clarifications identified within and throughout the protocol
Revised Protocol 01	20-Dec-2016	• Incorporates Amendment 01
Amendment 01	20-Dec-2016	• Assessment of anti-tumor activity of nivolumab and ipilimumab changed to exploratory objective from secondary objective • Clarification to safety monitoring during the study. • Clarification to eligibility criteria for GC subjects. • Incorporates revised duration of contraception • Removal of less effective method of contraception and addition of progestogen only hormonal contraception • Updates to adverse event management algorithm in Appendix 3 To make any typographical edits, format updates and clarifications identified within and throughout the protocol
Original Protocol	25-Apr-2016	Not applicable

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 07:

Due to significant landscape change and shrinkage of eligible patient pool, Bristol-Myers Squibb (BMS) made a decision to close the CA209672 Part 2 Study to enrollment in Dec-2021. Based on current timelines, projections show that the study will not be able to meet its scientific objectives in this rapidly evolving therapeutic landscape. Enrollment closure of the study is unrelated to safety. The protocol has been revised to modify or reduce the assessments and data collection to minimize the burden on study participants and site staff.

Key changes in Protocol Amendment 07 include the removal of pharmacokinetic (PK) and immunogenicity sampling, as well as the tumor assessments and safety follow-up beyond 100 days post study drug discontinuation.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 07		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	Updated medical monitor information	Administrative update
Synopsis Section 1.3.2: Secondary Objectives Section 1.3.3: Exploratory Objectives Section 8.3.2.2: Part 2 Section 8.3.3.2: Part 2	Changed overall survival evaluation from secondary objective to exploratory objective	Due to early closure of the trial
Synopsis Section 1.3.3: Exploratory Objectives Section 5.1: Flow Chart/Time and Events Schedule Section 5.5: Pharmacokinetic and Immunogenicity Assessments Section 5.5.2: Pharmacokinetic Sample Analyses Section 5.9.1: Immunogenicity Assessment Section 8.3.3.2: Part 2	• Added language about the changes made to PK and immunogenicity sampling and assessments • Removed selected serum sample analysis	To reduce collection of samples due to early closure of the trial
Synopsis Section 1.3.3: Exploratory Objectives Section 5.1: Flow Chart/Time and Events Schedule	Removed the investigator-assessed second disease progression or death during next line of treatment (PFS2) for Part 2	PFS2 evaluation was removed due to limited number of participants enrolled in Part 2 up to study closure

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 07		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 8.3.3.2: Part 2 Section 8.4.2.2: Part 2		
Synopsis Section 1.3.3: Exploratory Objectives Section 8.3.3.2: Part 2 Section 8.4.5: Biomarker Analyses	Removed exploratory objectives for concordance rate of microsatellite instability/mismatch repair deficient (MSI/MMR) for Part 2	Removed due to limited number of patients enrolled in Part 2 up to study closure
Synopsis Section 3.1.1: Overall Design and Schematic Section 3.1.5: Follow-Up Section 5.1: Flow Chart/Time and Events Schedule Table 5.1-1: Screening Procedural Outline (CA209672) Section 5.1.1: Retest During Screening or Lean-in Period	Removed survival follow-up	Survival follow-up was removed due to early closure of the trial
Synopsis Section 3.1.1: Overall Design and Schematic Section 3.3: Study Population Section 8.1.2: Part 2	Added language about study enrollment status and Part 2 enrollment closure	To clarify early study closure and align with rest of changes
Synopsis Section 8.4.2.2: Part 2	Revised analysis methods for efficacy endpoints	To simplify efficacy analysis due to limited number of participants enrolled up to study closure
Section 1.1.1: Rationale to Support Dose/Schedule of Nivolumab Combined with Ipilimumab	Updated clinical data for nivolumab and ipilimumab based on the CHECKMATE-142 trial	To reflect clinical data updates from the study CHECKMATE-142
Section 1.5: Overall Risk/Benefit Assessment	Added text about the global coronavirus disease 2019 (COVID-19) pandemic being identified as a potential risk to clinical trial participants, mitigation, and reporting of adverse events and serious adverse events	To update the COVID-19-related benefit/risk and mitigation for protection of study participants in the context of the COVID-19 pandemic
Section 3.1.3.2: Screening Section 8.4.7.1: European Organization for Research and Treatment of Cancer	Corrected the descriptions about randomization	To clarify that this is not a randomized study

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 07		
Section Number & Title	**Description of Change**	**Brief Rationale**
Quality of Life Questionnaire (QLQ-C30)		
Section 3.1.5: Follow-Up Section 3.6: Post Study Drug Follow up Section 5.1: Flow Chart/Time and Events Schedule	Changed language about safety monitoring and tumor assessments	To describe the modifications made to assessments as a result of early enrollment termination
Section 3.1.6: Treatment beyond Progression	Deleted Section 3.1.6	To remove duplicate information already contained in Section 4.5.7
Section 3.4.1: Prohibited and/or Restricted Treatments	Added COVID-19 vaccine guidance	To state that the efficacy and safety of COVID-19 vaccination in participants who are receiving nivolumab and/or ipilimumab are unknown
Section 4.5.7: Treatment Beyond Disease Progression	Added language about maximum treatment duration of 2 years	Added for clarity
Section 8.2: Populations for Analyses	Removed outcomes research subjects (Part 2 only) from populations for analyses	To describe the modifications made to statistical analyses as a result of early enrollment termination
Section 8.4.3: Safety Analyses	Added vital signs, physical examination abnormality findings, and ECG readings to safety analyses for Part 2	To add additional details for Part 2 safety analyses
Section 8.4.4: Pharmacokinetic Analyses	Removed summary statistics for PK analyses for part 2	To describe the modifications made to statistical analyses as a result of early enrollment termination
Section 8.4.5: Biomarker Analyses	Added text stating that baseline MSI/MMR will be listed	To describe the modifications made to statistical analyses as a result of early enrollment termination
Section 9.5: Data Protection, Data Privacy, and Data Security	Added description of BMS policies regarding data protection, data privacy, and data security	To ensure the privacy, protection, and confidentiality of collected personal data
Throughout Document	• Changed “RECIST v1.1” to “RECIST 1.1” where applicable • Changed “subject” to “participant” where applicable • Changed “MMR/MSI” to “MSI/MMR” where applicable • Corrected minor and typographical and formatting errors	• To ensure alignment and consistency regarding terminology throughout the document • To correct formatting and typographical errors

SYNOPSIS

Clinical Protocol CA209672

Protocol Title: A Phase 1/2 Study of Nivolumab (BMS-936558) in Combination with Ipilimumab (BMS-734016) in Chinese Participants with Previously Treated Metastatic or Recurrent Solid Tumors

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s): Participants will receive

Part 1:

Arm A--nivolumab 3 mg/kg IV Q2W plus ipilimumab 1 mg/kg IV Q6W.

Arm B--nivolumab 3 mg/kg IV plus ipilimumab 1 mg/kg IV Q3W × 4, followed by nivolumab 240 mg IV Q2W

Arm C--nivolumab 1 mg/kg IV plus ipilimumab 3 mg/kg IV Q3W × 4, followed by nivolumab 240 mg IV Q2W

Part 2:

Arm D--nivolumab 3 mg/kg IV plus ipilimumab 1 mg/kg IV Q3W × 4, followed by nivolumab 240 mg IV Q2W

Study Phase: 1/2

Research Hypothesis:

Part 1: There is no formal primary research hypothesis for Arms A, B, and C to be statistically tested.

Part 2: Treatment with nivolumab combined with ipilimumab will have clinical activity in participants with recurrent or metastatic microsatellite instability-high (MSI-H)/DNA mismatch repair deficient (dMMR) colorectal cancer (CRC).

Objectives:

Primary Objectives:

Part 1: To establish the safety, tolerability and dose-limiting toxicities (DLTs) of nivolumab plus ipilimumab in Chinese participants with advanced or recurrent solid tumor.

Part 2: To evaluate the blinded independent central review (BICR)-assessed objective response rate (ORR) of nivolumab in combination with ipilimumab in Chinese participants with recurrent or metastatic MSI-H/dMMR CRC

Secondary Objectives:

Part 1:

- To characterize the pharmacokinetics of nivolumab and ipilimumab in Chinese participants when administered in combination.
- To assess the immunogenicity of nivolumab and ipilimumab in Chinese participants when administered in combination.

Part 2:

- To evaluate the investigator-assessed ORR of nivolumab in combination with ipilimumab in Chinese participants with recurrent or metastatic MSI-H/dMMR CRC.
- To evaluate the investigator- and BICR-assessed disease control rate (DCR) of nivolumab in combination with ipilimumab in Chinese participants with recurrent or metastatic MSI-H/dMMR CRC.
- To evaluate Investigator-assessed and BICR-assessed progression-free survival (PFS) in Chinese participants with recurrent or metastatic MSI-H/dMMR CRC who received nivolumab in combination with ipilimumab.
- To evaluate Investigator-assessed and BICR-assessed duration of response (DOR) in Chinese participants with recurrent or metastatic MSI-H/dMMR CRC who received nivolumab in combination with ipilimumab.

Exploratory Objectives:

Part 1:

- To assess preliminary anti-tumor activity of nivolumab and ipilimumab in Chinese participants when administered in combination.

Part 2:

Per Protocol Amendment 07, collection of pharmacokinetic (PK) and immunogenicity data is not applicable. PK sample analyses and immunogenicity assessments will be based on samples collected before the implementation of Protocol Amendment 07. No analyses of concordance rate between results from central and local testing, and investigator-assessed second disease progression or death during next line of treatment are planned due to the limited number of participants enrolled.

- To determine the safety and tolerability (defined as toxicity rates [worst Common Terminology Criteria (CTC) Grade per participant]) of AEs and specific laboratory tests of nivolumab in combination with ipilimumab in Chinese participants with recurrent or metastatic MSI-H/dMMR CRC.
- To characterize the PK of nivolumab and ipilimumab when administered in combination, and to explore exposure-response relationships.
- To characterize the immunogenicity of nivolumab and ipilimumab when administered in combination.
- To evaluate health-related quality of life using a validated instrument in the European Organisation for Research and Treatment of Care (EORTC) Quality of Life Questionnaire Core-30 (QLQ-C30).
- To evaluate patient-reported general health status as assessed by the EuroQol 5 Dimensions questionnaire (EQ-5D-3L).
- To evaluate overall survival (OS) in Chinese participants with recurrent or metastatic MSI-H/dMMR CRC who received nivolumab in combination with ipilimumab.

Study Design: This is an open-label, multi-dose, 2-part Phase 1/2 study of nivolumab in combination with ipilimumab in Chinese participants with previously treated metastatic or recurrent solid tumors.

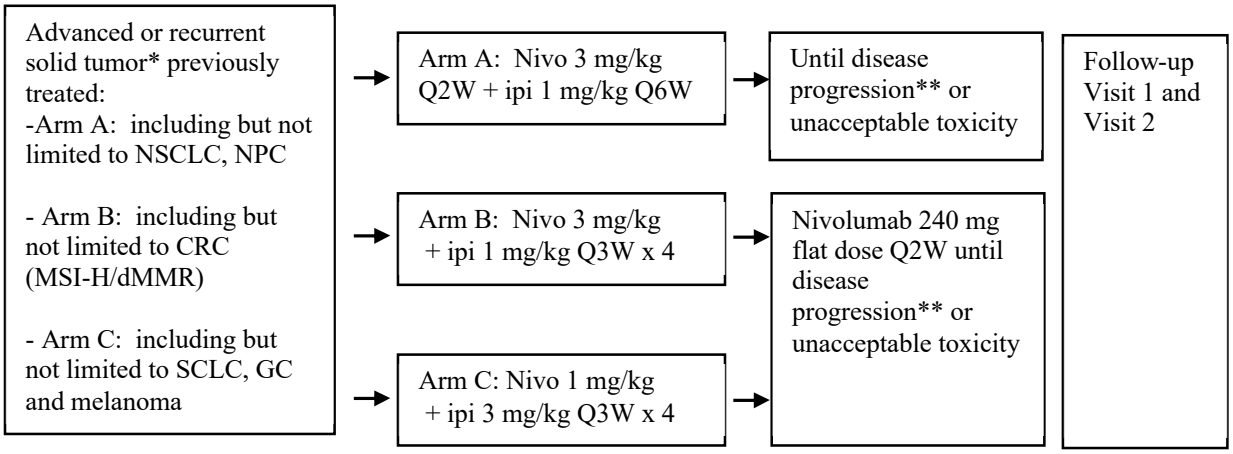
As of 20-Dec-2021, the study was closed to new enrollment for Part 2, and a total of 36 participants (9 participants each in Arms A, B, C, and D) were enrolled. The study will consist of 3 periods: screening period, treatment period (until disease progression, intolerable toxicities, withdrawal of consent, completion of maximum treatment duration specified in protocol Section 3.1.1, the study ends, or other reasons specified in the protocol, whichever occurs first); and a follow-up period (up to 100 days for Arms A, B, C, and D). The response assessment must be completed from date of first dosing every 6 weeks for the first 24 weeks, and then every 12 week thereafter until disease progression or unacceptable toxicities for Part 1, or until initiation of subsequent anti-cancer treatment for Part 2. Every effort should be made to schedule visits within the timeframe stated in the protocol. For Part 2 only, images will be submitted to a central imaging vendor for BICR during the study.

For Part 1, a safety evaluation is planned after a total of 9 participants completed the first 6 weeks of treatment and associated evaluation in a given arm. However, tolerability beyond 6 weeks may also be taken into consideration. Participants who do not complete the DLT observation period for reasons other than DLTs will be replaced. The following tables shows the guidance for safety monitoring based on observed toxicity outcome.

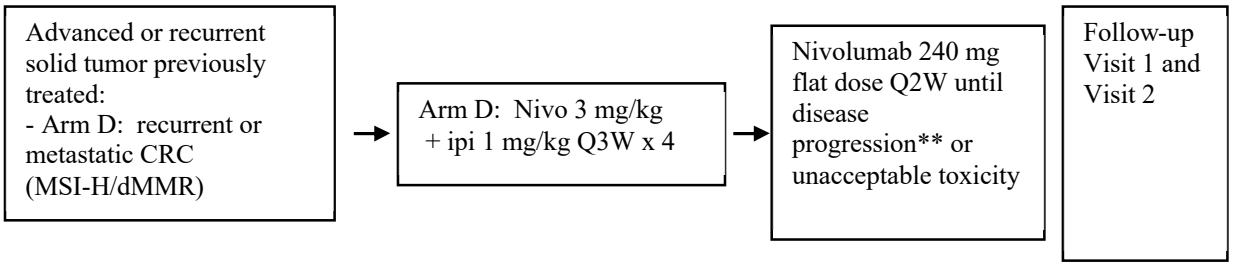
Number of participants treated and followed up for at least 6 weeks after start of study treatment	Number of participants with DLTs	Next Step
9	≤ 2	Tolerable
9	≥ 3	To be discussed between sponsor and Investigators to review benefit/risk ratio

Study Design Schematic

Part 1



Part 2



* If a participant with following tumor types is enrolled, he/she can only be treated using one specific dosing schedule, e.g. NSCLC, SCCHN or mesothelioma patient is to be treated in Arm A only. SCLC patients is to be treated in Arm C only.

** Participants may be treated beyond progression under protocol-defined circumstances. Treatment continues until progression, unacceptable toxicity, withdrawal of consent, completion of maximum treatment duration of 24 months EXCEPT in participants with late response (during second year of treatment) who may receive treatment for up to an additional 12 months after onset of response, the study ends, or other reasons specified in the protocol, whichever occurs first.

Study Population:

Key inclusion criteria:

- Mainland Chinese participants (at least 18 years of age).
- ECOG 0-1
- Have progression or refractory disease
  - Arm A: solid tumor including but not limited to NSCLC, NPC;

  - Arm B: solid tumor including but not limited to CRC MSI-H/dMMR;
  - Arm C: solid tumor including but not limited to SCLC, GC and melanoma.
  - Arm D: histologically confirmed recurrent or metastatic MSI-H/dMMR CRC;
  - If a participant with following tumor types is enrolled, he/she can only be treated using one specific dosing schedule, e.g. NSCLC, SCCHN or mesothelioma patient is to be treated in Arm A only. SCLC patient is to be treated in Arm C only.
- For Part 1, failing at least 1 line of systemic therapy for advanced disease; OR, well documented refusal of participants to receive chemo or biological therapy.
- For Part 2, additional criteria must be met for inclusion:
  - Participants must have shown progression during, after, or have been intolerant to ≥ 1 line treatment(s) for metastatic disease, which must include at least a fluoropyrimidine, and oxaliplatin or irinotecan (participants who receive oxaliplatin in an adjuvant setting should have progressed during or within 6 months of completion of adjuvant therapy in order for oxaliplatin to count as a prior therapy needed for entry)
  - Participants willing to comply to provide tumor tissue (archival or fresh biopsy specimen), including possible pre-treatment biopsy
- Women of childbearing potential (WOCBP) must not be nursing or pregnant and must be using an acceptable method of contraception. WOCBP must have a negative pregnancy test within 24 hours prior to dosing with study drug.

Study Drug: includes both investigational [medicinal] products (IP/IMP) and non-investigational [medicinal] products (Non-IP/Non-IMP) as listed:

Study Drug for CA209672

Medication	Potency	IP/Non-IP
Nivolumab (BMS-936558-01) Solution for Injection	100 mg (10 mg/mL)	IP
Ipilimumab Solution for Injection	50 mg (5 mg/mL), 200 mg (5-mg/mL)	IP

Maximum treatment duration: treatment with nivolumab or nivolumab with ipilimumab will be given for up to 24 months in the absence of disease progression or inacceptable toxicity EXCEPT in participant with late response (during second year of treatment) who may receive treatment for up to an additional 12 months after onset of response.

Study Assessments:

- Safety Outcome Measures: Safety assessments will be based on medical review of adverse event reports and the results of vital sign measurements, ECOG status, ECGs, physical examinations, and clinical laboratory tests. The incidence of observed adverse events will be tabulated and reviewed for potential significance and clinical importance. Toxicity will be evaluated by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0.
- Dose-Limiting Toxicity: DLTs are defined in protocol Section 4.5.1 and will be determined based on the incidence, intensity, and duration of adverse event (AE) that are related to study drug, and that occur within 42 days (6 weeks, through completion of cycle 1) of initiation of study drug;
- Not applicable per Protocol Amendment 07: Pharmacokinetic Evaluation: Serial blood samples for pharmacokinetic assessments will be collected from all participants at specified time points.
- Not applicable per Protocol Amendment 07: Immunogenicity Evaluations: Blood samples to evaluate development of positive anti-drug antibody (ADA) response will be collected at specified time points for all participants.

- Efficacy Assessment: Computed tomography/magnetic resonance imaging (CT/MRI) for chest, abdomen, pelvis, and brain will be performed at screening and at specified time points in Table 5.1-2, Table 5.1-3, and 5.1-4. Measurement of tumor burden must be reviewed and documented before initiating further treatment with nivolumab. Tumor response status will be assessed with RECIST 1.1.

Statistical Considerations:

Sample Size:

Part 1: With 9 participants in each arm, if 0, 1, 2, or 3 participants experienced DLTs, the upper limit of the one-sided exact 90% confidence interval (CI) for the true DLT rate will be less than 23%, 37%, 49%, and 60% respectively. The calculations are based on the Clopper-Pearson method for the exact confidence intervals.

Part 2: With an estimated discrepancy rate of 25% between local and repeating testing in central lab for MSI/MMR status, it is expected that approximately 33 patients with MSI-H/dMMR mCRC determined by local testing will be treated on study. A sample size of 33 will allow the lower bound of one-sided 95% CI excluding 35% when the observed ORR is 50% in the nivolumab/ipilimumab combination arm. The 35% ORR is expected for local diagnosed MSI-H/dMMR mCRC patients treated with PD-1 inhibitor monotherapy. This sample size will also provide at least 90% power to demonstrate statistical difference with historical ORR of 5% for TKI monotherapy in a similar setting at a two-sided alpha of 0.05.

Due to challenges with enrollment, the enrollment for Part 2 was closed after 9 participants were treated, out of the 33 participants planned.

Endpoints:

Primary endpoints:

Part 1:

- Frequency of adverse events occurring up to 100 days after the last dose of study drug
- Frequency of serious adverse events occurring up to 100 days after the last dose of study drug
- Frequency of adverse events leading to discontinuation occurring up to 100 days after the last dose of study drug
- Frequency of adverse events leading to death occurring up to 100 days after the last dose of study drug
- Frequency of participants with clinical laboratory abnormalities by worst toxicity grade by NCI CTCAE version 4.0 (as assessed at the planned times listed in Table 5.1-1, Table 5.1-2, Table 5.1-3, Table 5.1-4, Table 5.1-5, Table 5.1-6 and Table 5.1-7).

Part 2:

- BICR-assessed ORR: Defined as the number of participants with a best overall response (BOR) of confirmed complete response (CR) or partial response (PR), according to RECIST 1.1 criteria

Secondary endpoints:

Part 1:

- Pharmacokinetics: PK parameters including Cmax, Cmin, Ceoinf, Tmax, AUC(0-T), and AUC(TAU) of nivolumab and ipilimumab derived from serum concentration versus time data.
- Immunogenicity: The frequency of baseline ADA positive participants and ADA positive participants.

Part 2:

- Investigator-assessed ORR: defined as the BOR of confirmed CR or PR, according to RECIST 1.1 criteria.
- Investigator- and BICR-assessed DCR defined as number of participants with a BOR of confirmed CR, PR, or SD lasting at least 12 weeks divided by the number of treated participants.

- Investigator-assessed and BICR-assessed progression-free survival (PFS), defined as the time from the first dosing date to the date of first objectively documented disease progression per RECIST 1.1 (ie, radiologic) or death due to any cause, whichever occurs first.

Exploratory endpoints:

Part 1:

- ORR is defined as the proportion of all treated participants whose BOR is either a CR or PR by investigator using Response Evaluation Criteria in Solid Tumor (RECIST 1.1);
- The PFS Rate (PFSR) is defined as the proportion of treated participants remaining progression free and surviving at time T (eg, 24 weeks) since the first dosing date. The proportion will be calculated by the K-M estimate which takes into account censored data.
- Overall Survival (OS) for Arm B participants, defined as the time from the date of the first dose to the date of death due to any cause. A participant who has not died will be censored at last known date alive.

Part 2:

- To determine the safety and tolerability [defined as toxicity rates (worst CTC grade per participant) of adverse events and specific laboratory tests] of nivolumab in combination with ipilimumab in participants with recurrent or metastatic MSI-H/dMMR CRC.
- To characterize the PK of nivolumab and ipilimumab when combined, and to explore exposure-response relationships.
- To characterize the immunogenicity of nivolumab and ipilimumab when combined.
- To evaluate health-related quality of life using a validated instrument in the European Organisation for Research and Treatment of Care General Cancer Module (QLQ-C30).
- To evaluate patient reported general health status as assessed by the five item EQ-5D-3L.
- To evaluate OS, defined as the time from first dosing date to the date of death due to any cause. A participant who has not died will be censored at last known date alive.

Analyses:

Safety analysis

Part 1:

- All recorded AEs will be coded according to the most current version of MedDRA and listed by arm and overall. AEs will be summarized for each arm and overall by system organ class and preferred term using the worst grade within each category within a participant. Toxicity changes from baseline in clinical laboratory test results will be summarized by dose level and tumor type and overall using the worst on treatment CTC grade values. Vital signs, ECGs and clinical laboratory test results will be listed and summarized by arm and overall.

Part 2:

- Safety analyses will be performed in all treated participants. Descriptive statistics of safety will be presented using NCI CTCAE version 4.0. On-study AEs will be tabulated using worst grade per NCI CTCAE v4.0 criteria by system organ class and MedDRA preferred term. On-study lab parameters including hematology, chemistry, liver function, thyroid function, and renal function will be summarized using worst grade per NCI CTCAE v4.0 criteria.

Efficacy analysis

Part 1:

- Listing of tumor measurements will be provided by participant and study day in each arm. Individual participant's best overall response (BOR) will be listed based on RECIST 1.1. To describe the anti-tumor activity of nivolumab plus ipilimumab, ORR will be calculated. ORR and corresponding 2-sided exact 95% exact confidence interval by Clopper and Pearson will be provided by treatment arm and dose level. In addition, PFS rate, the probability of a participant remaining progression free or surviving to 24 weeks, will be estimated by Kaplan-Meier methodology, by treatment arm. The corresponding 90% confidence interval will be derived based on Greenwood formula.

Part 2:

- The BICR-assessed ORR will be summarized. A response rate estimate and corresponding two-sided 95% exact CI using the Clopper and Pearson method will be provided. BICR-assessed ORR will be further characterized by the rate of CR and PR.
- ORR based on investigators' assessment will be summarized and further characterized by rate of CR and PR similarly as above.
- BICR-assessed and Investigator-assessed DCR will be summarized and corresponding two-sided exact 95% CI using the Clopper-Pearson method will be provided.
- BICR-assessed and Investigator-assessed DOR will be listed for participants who achieve confirmed PR or CR.
- PFS and OS will be listed.

TABLE OF CONTENTS

1 INTRODUCTION AND STUDY RATIONALE

Cancer is now the leading cause of death in China, causing about one fourth of all death in China. Patients with metastatic or refractory solid tumors have very poor prognosis. Despite advances in multimodal therapy, improvement in overall survival has been limited. Thus, these patients represent a large population who have unmet medical needs and it is necessary to test compounds that have novel mechanisms of action in clinical studies.

Immune checkpoint blockade is a rapidly advancing therapeutic approach in the field of immuno-oncology (IO) and treatment with investigational agents targeting this mechanism has induced regressions in several types of cancer. Programmed death 1 (PD-1) receptor and cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) are two important cellular targets that play complementary roles in regulating adaptive immunity. Whereas PD-1 contributes to T-cell exhaustion in peripheral tissues, CTLA-4 inhibits at earlier points in T-cell activation. In preclinical models, combined blockade of PD-1 and CTLA-4 achieved more pronounced antitumor activity than blockade of either pathway alone, leading to the clinical development of immune checkpoint inhibitors both as monotherapy and as combination therapy in various tumor types.[1]

Nivolumab (also referred to as BMS-936558, MDX1106, or ONO-4538) is a human monoclonal antibody (mAb); immunoglobulin G4 [IgG4]-S228P) that targets the PD-1 cluster of differentiation (CD) 279 cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T- and B- lymphocytes. Binding of PD-1 to its ligands, programmed death-ligands 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens. Nivolumab is expressed in Chinese hamster ovary cells and is produced using standard mammalian cell cultivation and chromatographic purification technologies. The clinical study product is a sterile solution for parenteral administration.

Nivolumab (OPDIVO™) is approved for the treatment of several types of cancer in multiple regions including the United States (US, Dec-2014), the European Union (Jun-2015), and Japan (Jul-2014).[2,3,4,5,6,7]

Nivolumab has demonstrated durable responses exceeding 6 months as monotherapy in several tumor types, including non-small cell lung cancer (NSCLC), melanoma, renal cell carcinoma (RCC), classical Hodgkin lymphoma (cHL), small-cell lung cancer (SCLC), gastric cancer, squamous cell carcinoma of the head and neck (SCCHN), urothelial cancer, hepatocellular carcinoma (HCC), and colorectal carcinoma (CRC).[2,3,4,5,6,7] In confirmatory trials, nivolumab as monotherapy demonstrated a statistically significant improvement in overall survival (OS) as compared with the current standard of care in patients with advanced or metastatic NSCLC, unresectable or metastatic melanoma, advanced RCC, or recurrent or metastatic SCCHN. Details of the clinical activity in these various malignancies are provided in the United States Package Insert (USPI) and Summary of Product Characteristics (SmPC).

Ipilimumab (BMS-734016, MDX010, MDX-CTLA4) is a fully human monoclonal IgG1 kappa specific for human CTLA-4 (CD152), which is expressed on a subset of activated T-cells. CTLA-4 is a negative regulator of T-cell activity. Ipilimumab is a mAb that binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation, including the activation and proliferation of tumor-infiltrating T-effector cells. Inhibition of CTLA-4 signaling can also reduce T-regulatory cell function, which may contribute to a general increase in T-cell responsiveness, including the anti-tumor response.

Multiple clinical studies have evaluated nivolumab combined with ipilimumab at different doses and schedules. Based on Phase 3 data showing improved survival over standard of care therapies, nivolumab combined with ipilimumab has been approved in multiple countries for the treatment of patients with unresectable or metastatic melanoma, intermediate or poor risk, previously untreated advanced RCC, and microsatellite instability-high or mismatch repair deficient (MSI-H/dMMR) colorectal cancer. Details of the clinical activity in these various malignancies are provided in the USPI and SmPC.

CA209672 is an open-label, multi-dose, 2-part, Phase 1/2 study of nivolumab in combination with ipilimumab in Chinese participants with previously treated advanced or recurrent solid tumors.

1.1 Study Rationale

1.1.1 Rationale to Support Dose/Schedule of Nivolumab Combined with Ipilimumab

The combination of nivolumab and ipilimumab has been investigated in multiple studies and in several tumor types, and has demonstrated improved anti-tumor activity and overall survival benefits. In a Phase 1b multiple ascending dose study in subjects with advanced melanoma (CA209004), antitumor activity was observed in 5 different combination cohorts: nivolumab 0.3 mg/kg and ipilimumab 3 mg/kg (Cohort 1, n = 14), nivolumab 1 mg/kg and ipilimumab 3 mg/kg (Cohort 2, n = 17), nivolumab 3 mg/kg and ipilimumab 1 mg/kg (Cohort 2a, n = 16), nivolumab 3 mg/kg and ipilimumab 3 mg/kg (Cohort 3, n = 6), and nivolumab 1 mg/kg and ipilimumab 3 mg/kg (Cohort 8, n = 41). From this study, it has been found that the 3 mg/kg nivolumab and 3 mg/kg ipilimumab combination regimen exceeded the maximum tolerated dose (MTD). Even though the drug-related discontinuation rates in combination cohorts were approximately 26 - 27%, the objective response rate (ORR) in these cohorts were still higher compared to nivolumab monotherapy (42% - 44% versus 36%).

Additional studies have demonstrated the potential for IO combinations to improve antitumor responses across the nivolumab program.[8] An ORR of 62 - 65% has been observed in advanced melanoma (CA209067 and CA209069, N = 407) with a combination regimen of nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks (Q3W) × 4. In RCC patients (CA209016), both nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (n = 21) and nivolumab 1 mg/kg plus ipilimumab 3 mg/kg (n = 23) showed antitumor activity with an ORR of 38%-40%. Both nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (n = 54) and nivolumab 1 mg/kg plus ipilimumab 3 mg/kg (n = 61) showed antitumor activity with an ORR of 19%, and 23%, respectively, in patients with SCLC

whose disease progressed after ≥ 1 prior regimen (CA209032). In NSCLC patients (CA209012), both combination regimens resulted in high discontinuation rates (up to 39%); therefore, multiple alternative schedules were evaluated. Nivolumab 3 mg/kg combined with more extended ipilimumab dosing (1 mg/kg, every 6 weeks [Q6W] or every 12 weeks [Q12W]) was well tolerated, with similarly low discontinuation rates as monotherapy (10%, 5% respectively vs 10%) and promising response rates of 31-39% (48% in PD-L1+). Nivolumab in combination with ipilimumab has demonstrated remarkable benefit for several solid tumor types, including previously treated MSI-H/dMMR metastatic CRC (mCRC).[9] CA209142 is a Phase 2, open-label, multi-center trial of nivolumab monotherapy and nivolumab in combination with other agents in subjects whose colorectal tumors have defects in the deoxyribonucleic acid (DNA) mismatch repair system (MSI-H/dMMR) or in subjects whose colorectal tumors have proficient mismatch repair (pMMR/non-MSI-H).[10,11] Preliminary evidence from the nivolumab plus ipilimumab cohort (n = 119) in study CA209142 demonstrated additional clinical improvement of this combination in MSI-H mCRC patients over the cohort of subjects treated with nivolumab monotherapy (n = 74) beyond second-line (2L) of treatment. At data cutoff of September 2021, the median follow-up in the nivolumab plus ipilimumab combination therapy cohort was 64.0 months (range 60.0 to 75.8 months). The objective response rate (ORR) per investigator was achieved in 65% (95% confidence interval [CI]: 55, 73) of subjects, including 17% of subjects who demonstrated complete response (CR). This was numerically higher than the ORR observed in the cohort of 74 subjects who received nivolumab monotherapy (39%, 95% CI: 28, 51) in the same study with median follow-up of 70.0 months.[12] Thus, nivolumab plus ipilimumab combination therapy provided a numerically higher ORR, including CR, and disease control rate (DCR) relative to nivolumab monotherapy during a similar follow-up period. The improved ORR with nivolumab plus ipilimumab combination therapy was translated to the numerically improved progression-free survival (PFS) and OS rates over nivolumab monotherapy. In the combination cohort, Grade 3 to 4 treatment-related adverse events (AEs) occurred in 32% of patients and were manageable.[13]

Based on these data, the following three dose arms will be evaluated in CA209672:

- Arm A - nivolumab 3 mg/kg every 2 weeks (Q2W) + ipilimumab 1 mg/kg Q6W; for participants with solid tumor including but not limited to NSCLC, nasopharyngeal carcinoma (NPC);
- Arm B - nivolumab 3 mg/kg + ipilimumab 1 mg/kg, Q3W × 4, followed by nivolumab 240 mg Q2W; for participants with solid tumor including but not limited to metastatic CRC (mCRC) DNA mismatch repair deficient (dMMR)/MSI-H;
- Arm C - nivolumab 1 mg/kg + ipilimumab 3 mg/kg, Q3W × 4, followed by nivolumab 240 mg Q2W; for participants with solid tumor including but not limited to SCLC, gastric cancer (GC), and melanoma.
- Arm D - nivolumab 3 mg/kg + ipilimumab 1 mg/kg, Q3W × 4, followed by nivolumab 240 mg Q2W; for participants with recurrent or metastatic MSI-H/dMMR CRC.

1.1.2 Rationale for Nivolumab Flat Dose in Nivolumab Monotherapy Portion

The nivolumab dose of 240 mg Q2W was selected based on clinical data and modeling and simulation approaches using population pharmacokinetics (PPK) and exposure-response analyses of data from studies in multiple tumor types (melanoma, NSCLC, and RCC) where body weight normalized dosing (mg/kg) has been used.

Nivolumab pharmacokinetics (PK) has been extensively studied in multiple tumor types, including melanoma, NSCLC, RCC, cHL, SCCHN, CRC, and urothelial carcinoma and has been safely administered at doses up to 10 mg/kg Q2W. Nivolumab monotherapy was originally approved as a body-weight based dose of 3 mg/kg Q2W, and was updated to 240 mg Q2W or 480 mg every 4 weeks (Q4W) in multiple indications (Nivolumab USPI). Nivolumab 360 mg Q3W is also under evaluation in monotherapy and in combination therapy studies. Less frequent 360 mg Q3W and 480 mg Q4W dosing regimens can reduce the burden to patients of frequent, lengthy IV treatments and allow combination of nivolumab with other agents using alternative dosing regimens.

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

Extensive exposure-response (E-R) analyses of multiple PK measures (maximum serum concentration at Day 1, average serum concentration at Day 28 [Cavg28], and trough serum concentration at Day 28) and efficacy and safety endpoints indicated that the efficacy of the flat-dose 480 mg IV regimen are similar to that of 3 mg/kg Q2W IV regimen. In E-R efficacy analyses for OS and ORR conducted in melanoma, RCC, and NSCLC using Cavg28 as the exposure measure, probabilities of achieving a response and survival probabilities at 1 year and 2 years for IV 480 mg Q4W were similar to that of IV 3 mg/kg Q2W. In E-R safety analyses, it was demonstrated that the exposure margins for safety are maintained following nivolumab 480 mg Q4W, and the predicted risks of discontinuations due to AEs or death, AE Grade 3+, and immune-mediated AEs (IMAEs) Grade 2+ are similar following nivolumab 480 mg Q4W relative to nivolumab 3 mg/kg Q2W across tumor types. In addition, nivolumab exposures with 240 mg Q2W, 360 mg Q3W, and 480 mg Q4W flat-dose IV regimens across tumor types are maintained well below the corresponding exposures observed with the well-tolerated 10 mg/kg IV nivolumab Q2W dose regimen.

1.1.3 Rationale for Shorter Infusion Times for Nivolumab and Ipilimumab

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 in subjects will diminish the burden, provided that there is no change in 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 (60 minutes).

Nivolumab has been administered safely over 60 minutes at doses ranging up to 10 mg/kg safely over a long treatment duration. In subjects with advanced/metastatic clear cell RCC (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.

Similarly, ipilimumab at 10 mg/kg has been safely administered over 90 minutes. In subjects with advanced Stage III or Stage IV melanoma (CA184022), 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 (1.4%) subject in the 0.3-mg/kg and in 2 (2.8%) subjects 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 subjects. Administering 1 mg/kg of ipilimumab represents one-tenth 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. Furthermore, a 30-minute break after the first infusion for the combination cohort will ensure the appropriate safety monitoring before the start of the second infusion. Overall, a change in safety profile is not anticipated with 30-minute infusion of nivolumab, ipilimumab or combination.

1.1.4 Rationale for Restricting Specific Tumor Types to Specific Arm

If a participant with following tumor types is enrolled, he/she can only be treated using one specific dosing schedule.

A NSCLC participant is to be treated in Arm A only due to reasons described in Section 1.1.1 and Section 1.4.4.3.

A SCLC participant is to be treated in Arm C only. In Phase 1/2 Study CA209032, subjects with advanced SCLC progressing after ≥ 1 prior platinum-containing regimen received 3 mg/kg Q2W nivolumab (n=98), or nivolumab plus ipilimumab (1 mg/kg plus 1 mg/kg [n=3], 1 mg/kg plus 3 mg/kg [n=61], or 3mg/kg plus 1 mg/kg [n=54]) every 3 weeks for 4 cycles, followed by

nivolumab 3 mg/kg every 2 weeks. ORR were 10%, 23% and 19% for nivolumab-3, nivolumab-1/ipilimumab-3, and nivolumab-3/ipilimumab-1, respectively. 13%, 30%, and 19% experienced Grade 3 or 4 treatment-related AEs, and 4%, 11%, and 7% discontinued due to treatment-related AEs for nivolumab-3, nivolumab-1/ipilimumab-3, and nivolumab-3/ipilimumab-1, respectively. The study cohorts were not randomized and the study was not powered for formal comparisons across cohorts; however, cohorts were well balanced by baseline characteristics, and data suggest that the nivolumab-1/ipilimumab-3 regimen has higher efficacy than nivolumab-3/ipilimumab-1 or nivolumab-3. The combination regimen of nivolumab 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks is currently being evaluated in a Phase 3 study CheckMate 451 and a Phase 1/2 study CheckMate 032.

If a squamous cell cancer of the head and neck (SCCHN) or mesothelioma participant is to be enrolled, he/she can be treated in Arm A only. The two tumor types are believed to respond to nivolumab similarly to NSCLC.

1.1.5 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 tumor types in the nivolumab and ipilimumab development program indicated that most of the responses occur early, with a median time to response of 2-4 months,[14,15,16,17,18] and emerging data suggests that benefit can be maintained in the absence of continued treatment. A retrospective pooled analysis of 2 melanoma studies suggested the majority of patients who discontinue nivolumab and/or ipilimumab for toxicity maintain disease control in the absence of further treatment.[19] 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.[20]

Accumulating data suggested 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 patients with NSCLC), specified a maximum treatment duration of 2 years. Among 16 patients with non-small cell lung cancer (NSCLC) who discontinued nivolumab after completing 2 years of treatment, 12 patients were alive > 5 years and remained progression-free without any subsequent therapy. In the CA209003 NSCLC cohort, the overall survival (OS) curve began to plateau after 2 years, with an OS rate of 25% at 2 years and 18% at 3 years.[21] These survival outcomes were 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% to 18% for squamous and non-squamous NSCLC respectively).[22]

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 PFS compared to those who were randomized to stop treatment, with median PFS (post-randomization) not reached vs 10.3 months, respectively; hazard ration (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 (ie, 2 years after treatment initiation), suggesting that there may be minimal benefit in extending treatment beyond a total of 2 years.

Collectively, these data suggest that there is minimal, if any benefit, derived from continuing IO treatment beyond 2 years in advanced tumors. Even though immunotherapy is well tolerated, patients will be at risk for additional toxicity with longer-term treatment.

Recent analysis of the data from CA209-142 study in patients with MSI-H mCRC tumors suggests that minority of the patients experience relatively late objective response to nivolumab monotherapy (up to Month 23) or nivolumab plus ipilimumab combination (up to Month 14).[23] It's not known yet if treatment discontinuation after 2 years in participants with late partial response impacts on duration of response. Therefore, to minimize the potential risk of disease recurrence as a result of premature treatment discontinuation, all patients who achieved objective response within second year of treatment, will continue to receive study therapy for additional 12 months. Thus, the proposed approach for treatment duration will not only mitigate the potential risk of disease recurrence in patients with late partial response, but also ensures that patients with objective response to be followed for at least 12 months from the onset of response.

For these reasons, in study CA209672, treatment with nivolumab or nivolumab with ipilimumab will be given for up to 24 months in the absence of disease progression or inacceptable toxicity, EXCEPT in participants with late response (during second year of treatment). In participants with late response study treatment will continue for up to an additional 12 months after onset of response, in absence of disease progression, unacceptable toxicity, withdrawal of consent. Above defined maximum treatment duration of 2 years includes treatment beyond progression.

1.2 Research Hypothesis

Part 1: There is no formal primary research hypothesis for Arms A, B, and C to be statistically tested.

Part 2: Treatment with nivolumab combined with ipilimumab will have clinical activity in participants with recurrent or metastatic MSI-H/dMMR CRC.

1.3 Objectives(s)

1.3.1 Primary Objectives

The primary objective for Part 1 is to establish the safety, tolerability, and dose-limiting-toxicities (DLTs) of nivolumab plus ipilimumab in Chinese participants with advanced or recurrent solid tumor.

The primary objective for Part 2 is to evaluate the blinded independent central review (BICR)-assessed ORR of nivolumab in combination with ipilimumab in Chinese participants with recurrent or metastatic MSI-H/dMMR CRC.

1.3.2 Secondary Objectives

The secondary objectives of Part 1 are:

- To characterize the pharmacokinetics of nivolumab and ipilimumab in Chinese participants when administered in combination.
- To assess the immunogenicity of nivolumab and ipilimumab in Chinese participants when administered in combination.

The secondary objectives of Part 2 are:

- To evaluate the Investigator-assessed ORR of nivolumab in combination with ipilimumab in Chinese participants with recurrent or metastatic MSI-H/dMMR CRC.
- To evaluate the Investigator-assessed and BICR-assessed disease control rate (DCR) of nivolumab in combination with ipilimumab in Chinese participants with recurrent or metastatic MSI-H/dMMR CRC.
- To evaluate Investigator-assessed and BICR-assessed progression-free survival (PFS) in Chinese participants with recurrent or metastatic MSI-H/dMMR CRC.
- To evaluate Investigator-assessed and BICR-assessed duration of response (DoR) in Chinese participants with recurrent or metastatic MSI-H/dMMR CRC.

1.3.3 Exploratory Objectives

The exploratory objective for Part 1 is:

- To assess preliminary anti-tumor activity of nivolumab and ipilimumab in Chinese participants when administered in combination.

The exploratory objectives for Part 2 are:

Per Protocol Amendment 07, collection of PK and immunogenicity data is not applicable. PK sample analyses and immunogenicity assessments will be based on samples collected before the implementation of protocol amendment 07. No analyses of concordance rate between results from central and local testing and the investigator-assessed second disease progression or death during next line of treatment are planned due to the limited number of participants enrolled.

- To determine the safety and tolerability (defined as toxicity rates [worst Common Terminology Criteria (CTC) Grade per participant]) of AEs and specific laboratory tests of nivolumab in combination with ipilimumab in Chinese participants with recurrent or metastatic MSI-H/dMMR CRC.
- To characterize the PK of nivolumab and ipilimumab when administered in combination, and to explore exposure-response relationships.
- To characterize the immunogenicity of nivolumab and ipilimumab when administered in combination.
- To evaluate health-related quality of life using a validated instrument in the European Organisation for Research and Treatment of Care (EORTC) Quality of Life Questionnaire Core-30 (QLQ-C30).
- To evaluate subject-reported general health status as assessed by the EQ-5D-3L questionnaire.
- To evaluate overall survival (OS) in Chinese participants with recurrent or metastatic MSI-H/dMMR CRC who received nivolumab in combination with ipilimumab.

1.4 Product Development Background

1.4.1 Pharmacology

Detailed information can be found in the current version of the BMS-936558 Investigator's Brochure (IB) and BMS-734016 IB.[8,24]

1.4.2 Toxicity

Detailed information can be found in the current version of the BMS-936558 IB and BMS-734016 IB.[8, 24]

1.4.3 Preclinical Metabolism and Pharmacokinetics

Detailed information can be found in the current version of the BMS-936558 IB and BMS-734016 IB.[8, 24]

1.4.4 Clinical Pharmacology and Safety

1.4.4.1 Pharmacokinetics of Nivolumab

The PK of single-agent nivolumab was studied in patients over a dose range of 0.1 to 20 mg/kg administered as a single dose or as multiple doses of nivolumab as a 60-minute intravenous infusion every 2 or 3 weeks. Nivolumab clearance (CL) decreases over time, with a mean maximal reduction (% coefficient of variation [CV%]) from baseline values of 24.5% (47.6%) resulting in a geometric mean steady-state clearance (CLss) of 8.2 mL/h (CV% = 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) is 6.8 L (CV% = 27.3%), and geometric mean elimination half-life 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 (average concentration and maximum observed concentration [Cmax]) of nivolumab after a 30-minute infusion is comparable to that observed with a 60-minute infusion. Full details on the clinical pharmacology aspects of nivolumab can be found in the IB.[8]

1.4.4.2 Pharmacokinetics of Ipilimumab

The PPK of ipilimumab was studied with 785 subjects and demonstrated that the PK of ipilimumab is linear and exposures are dose proportional across the tested dose range of 0.3 to 10 mg/kg, and the model parameters are time invariant. Upon repeated dosing of ipilimumab administered every three weeks, minimal systemic accumulation was observed by an accumulation index of 1.5-fold or less and ipilimumab steady-state concentrations were achieved by the third dose. The ipilimumab clearance of 16.8 mL/h from PPK analysis is consistent with that determined by non-compartmental PK analysis. The terminal half-life (T-HALF) and Vss of ipilimumab calculated from the model were 15.4 days and 7.47 L, which are consistent with that determined by non-compartmental analysis. Volume of central (Vc) and peripheral compartment were found to be 4.35 L and 3.28 L, respectively, suggesting that ipilimumab first distributes into plasma volume and subsequently into extracellular fluid space. Clearance of ipilimumab and Vc were found to increase with increasing body weight. Nevertheless, there was no significant increase in exposure with increase in body weight when dosed on a mg/kg basis, supporting dosing of ipilimumab based on a weight normalized regimen.

Full details on the clinical pharmacology aspects of ipilimumab can be found in the IB.[24]

1.4.4.3 Pharmacokinetics of 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 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 lactate dehydrogenase (LDH), PD-L1 expression, solid tumor type, tumor size, renal impairment, and mild hepatic impairment.

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

Hepatic Impairment: The effect of hepatic impairment on the clearance of nivolumab was evaluated by population PK analyses in patients with HCC and in patients with other tumors with mild hepatic impairment (total bilirubin [TB] less than or equal to the upper limit of normal (ULN) and aspartate aminotransferase (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 > 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[8] and product label.

1.4.4.4 Safety Summary of Nivolumab in Combination with Ipilimumab

The combination of nivolumab and ipilimumab has been studied in a number of clinical studies across multiple tumor types. The combination of nivolumab and ipilimumab was initially evaluated in CA209004 (MDX1106-04), a Phase 1b multiple ascending dose study in subjects with treatment-naive and previously treated advanced melanoma. Results showed promising activity with higher, but tolerable toxicity than ipilimumab alone.

Extensive details on the safety profile of nivolumab are available in the Investigator Brochure (IB),[8] and will not be repeated here. Additional details on the safety profile of nivolumab, including results from other clinical studies, are also available in the nivolumab IB. The safety profile of nivolumab in combination with ipilimumab therapy is generally consistent with the safety profiles observed with either agent alone and, in some cases, both frequency and severity of AEs were greater than that observed with either agent alone. The safety profile of nivolumab + ipilimumab combination therapy is also consistent with the mechanisms of action of nivolumab and ipilimumab. A dose of 3 mg/kg nivolumab/3 mg/kg ipilimumab exceeded the MTD, and both 1 mg/kg nivolumab/3 mg/kg ipilimumab and 3 mg/kg nivolumab/1 mg/kg ipilimumab were identified as the MTD. For nivolumab monotherapy and combination therapy, most AEs were low grade (Grade 1 to 2) with relatively few related high-grade (Grade 3 to 4) AEs. Most high-grade events were manageable with use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in established management guidelines.

Safety of Nivolumab and Ipilimumab Combination in Melanoma

This section presents the safety data observed in the melanoma clinical studies (CA209069, CA209067, CA209066, CA209037) conducted with nivolumab monotherapy and nivolumab in combination with ipilimumab.

Safety data for nivolumab monotherapy was pooled and presented from the nivolumab treatment groups in CA209067 (N = 313), CA209066 (N = 200), and CA209037 (N = 268). Safety data for nivolumab + ipilimumab combination therapy was pooled and presented from the nivolumab + ipilimumab treatment groups in CA209067 (N = 313) and CA209069 (N = 94).

Key safety findings:[25]

- One (0.1%) death in the pooled monotherapy group and 2 (0.5%) deaths in the pooled combination therapy group within 100 days of the last dose were reported by the investigators due to study drug toxicity. After database lock, a third death occurred in the pooled combination therapy group.
- Overall, AEs were manageable, primarily Grade 1/2 and considered not related to study drug. The types of AEs (all grades, all causality) were similar between the treatment groups; however, the frequency and severity of AEs was generally higher in the pooled combination therapy group than in the pooled monotherapy group.
  - The most frequently reported drug-related AEs (≥ 15% of subjects) in the pooled monotherapy group were fatigue (29.2%), pruritus (18.4%), diarrhea (17.2%), and rash (16.9%).
  - The most frequently reported drug-related AEs (≥ 15% of subjects) in the pooled combination therapy group were diarrhea (43.0%), fatigue (35.4%), pruritus (33.4%), rash (31.0%), nausea (24.8%), pyrexia (18.7%), alanine aminotransferase (ALT) increased (18.2%), aspartate aminotransferase (AST) increased (16.7%), and decreased appetite (16.2%).
- The overall frequency of serious adverse events (SAEs) occurring up to 30 days after last dose (regardless of causality) was lower in the pooled monotherapy group (40.5%) than in the pooled combination therapy group (67.6%).
- Select AEs are AEs of special clinical interest that include preferred terms (PTs) describing specific events rather than events belonging to broader categories. These analyses included relevant events occurring within 30 days of the last dose and regardless of causality.
  - The most frequently reported (≥ 10% of subjects) drug-related select AEs (all grades) in the pooled monotherapy group were select AEs for skin (38.4%), gastrointestinal (GI) (17.7%), and endocrine (10.8%) categories.
  - The most frequently reported (≥ 10% of subjects) drug-related select AEs (all grades) in the pooled combination therapy group were select AEs for skin (61.9%), GI (46.4%), endocrine (29.7%), and hepatic (29.0%) categories.
  - No Grade 5 select AEs were reported in either group.
  - Immune-mediated AEs were manageable using the recommended treatment guidelines for early work-up and intervention.
  - Most Grade 3/4 select AEs resolved, except for events belonging to the endocrine select AE categories.
- For nivolumab-treated subjects in the primary studies CA209067, CA209069, and CA209004 Cohort 8, the safety profile in the subgroups (age, gender, race, and region) was consistent with the overall safety profile.
- Early safety signals were identified through the dose-escalation Cohorts 1-3 in CA209004.
- Hematology laboratory results, liver function, renal function, and thyroid function remained stable in the majority of subjects; however, there was a higher frequency of liver (alkaline phosphatase [ALP], ALT, AST, and total bilirubin) and thyroid test abnormalities reported in the pooled combination therapy group compared with the pooled monotherapy group.

One (0.1%) subject in the pooled monotherapy group and 18 (4.6%) subjects in the pooled combination therapy group were persistent positive (anti-drug antibody [ADA]-positive sample at 2 or more consecutive time points, where the first and last ADA-positive samples are at least 16 weeks apart) or positive for neutralizing antibodies. There was no evidence of an altered safety profile with ADA development.

Safety of Nivolumab and Ipilimumab Combination in Lung Cancer

Study CA209012 is a multi-arm, Phase 1 safety study of nivolumab in combination with gemcitabine/cisplatin, pemetrexed/cisplatin, carboplatin/paclitaxel, bevacizumab maintenance, erlotinib, ipilimumab or as monotherapy in subjects with stage IIIB/IV NSCLC.

In CA209012, the combination of nivolumab and ipilimumab has been studied as first-line therapy for subjects with previously untreated stage IV or recurrent NSCLC at several different doses and schedules. The original cohorts (Arms G, H, I, and J) resulted in significant toxicity, with 39% of patients discontinuing treatment due to a treatment-related AE.

- nivolumab 1 mg/kg + ipilimumab 3 mg/kg, Q3W × 4, followed by nivolumab 3 mg/kg Q2W (Arms G and H, n = 24);
- nivolumab 3 mg/kg + ipilimumab 1 mg/kg, Q3W × 4, followed by nivolumab 3 mg/kg Q2W (Arms I and J, n = 25).

In order to improve the safety of the nivolumab and ipilimumab combination in chemotherapy naive NSCLC, an additional 117 subjects have been treated in the newer 3 cohorts, and the safety profile appears much improved. Only 8% of subjects have discontinued treatment due to a treatment related AE, a rate similar to what has been observed with nivolumab monotherapy; 31% have experienced Grade 3/4 treatment-related AEs. The regimen of nivolumab 3 mg/kg every 2 weeks with ipilimumab 1 mg/kg every 6 weeks is currently being evaluated in a Phase 3 study, CheckMate 227. This regimen provides the highest dose density for nivolumab when combined with ipilimumab.

Table 1.4.4.4-1: First-Line Nivolumab + Ipilimumab Safety Summary

	Treatment-Related AEs, %	Treatment-Related AEs leading to discontinuation, %
Nivo 1 Q2W + Ipi 1 Q6W (n=40)		
Any Grade	73	8
Grade 3-4	35	8
Nivo 3 Q2W + Ipi 1 Q12W (n=38)		
Any Grade	74	5
Grade 3-4	29	3
Nivo 3 Q2W + Ipi 1 Q6W (n=39)		
Any Grade	69	10
Grade 3-4	28	10

Abbreviations: AEs = adverse events; Ipi = ipilimumab; Q2W = every 2 weeks; Q6W = every 6 weeks; Q12W = every 12 weeks.

Patients with advanced SCLC progressing after ≥ 1 prior platinum-containing regimen were treated with nivolumab monotherapy or nivolumab and ipilimumab combination in Phase 1/2 study CA209032. Most toxicities in the nivolumab-3 (n=98) and nivolumab-3/ipilimumab-1 (n=54) cohorts were mild to moderate, with only 4 (4%) and 4 (7%) subjects discontinuing due to toxicity, respectively. A higher rate of treatment-related Grade 3 or 4 AEs was seen in the nivolumab-1/ipilimumab-3 cohort (n = 61; 30% vs 13% for nivolumab-3), with 7 (11%) subjects discontinuing due to toxicity. This regimen was used effectively and safely in a Phase 3 trial in subjects with melanoma, suggesting that this schedule is feasible in subjects with SCLC. In all cohorts, fewer treatment-related toxicities were reported when compared with trials of topotecan or amrubicin.

Safety of Nivolumab and Ipilimumab Combination in MSI-H/dMMR Metastatic Colon Cancer

Study CA209142 is a multi-arm, Phase 2, clinical trial of nivolumab or nivolumab combinations, in recurrent and metastatic MSI-H and non-MSI-H colon cancer.

In the nivolumab + ipilimumab (N+I) cohort, 119 pre-treated MSI-H/dMMR CRC subjects were treated with nivolumab in combination with ipilimumab, as well as a subset of 82 subjects who had received prior 5-fluoropyrimidine, oxaliplatin, and irinotecan (5FU-Oxa-Iri): nivolumab administered intravenously (IV) over 60 minutes at 3 mg/kg combined with ipilimumab administered IV over 90 minutes at 1 mg/kg every 3 weeks for four doses followed by nivolumab administered IV over 60 minutes at 3 mg/kg every 2 weeks until progression.

The overall safety profile of nivolumab in combination with ipilimumab was acceptable in subjects with recurrent or metastatic MSI-H/dMMR CRC who had progression during or after, or have been intolerant to ≥ 1 line of treatment(s) for their metastatic disease. No new safety concerns with

combination treatment were identified. As of DBL of 19-Feb-2019 (hereafter, the Feb-2019 DBL) with a clinical data cutoff date of 07-Jan-2019, and a minimum follow-up of 27.5 months for subjects treated with nivolumab + ipilimumab in CA209142, 33 deaths were reported, all of which were due to disease progression and there were no deaths attributed to study drug toxicity. The frequencies of drug-related SAEs were 22.7% for any-grade and 20.2% for Grade 3-4, the frequencies of drug-related AEs leading to discontinuation were 13.4% for any-grade and 10.1% for Grade 3-4. Drug-related AEs of any grade occurred in 95 of 119 evaluable patients (79.8%). Grade 3/4 AEs were reported in 31.9% of subjects. The most common drug-related AEs occurring in ≥ 15% of subjects were diarrhea (25.2%), pruritus (20.2%), fatigue (18.5%), hypothyroidism (17.6%), AST increased (16%), pyrexia (15.1%), and rash (15.1%). A similar safety profile was observed between the all-combination treated subjects and the subset of subjects treated with prior 5FU-Oxa-Iri.

Most select AEs and immune-mediated AEs were Grade 1/2. The majority of select AEs and immune-mediated AEs resolved and were manageable using the recommended treatment guidelines for early work-up and intervention.

Abnormalities in hematology laboratory results, liver tests, kidney function tests, and electrolytes in nivolumab combined with ipilimumab treated subjects were primarily Grade 1 or 2.

With 27.5 months of minimum safety follow-up for MSI-H/dMMR mCRC subjects treated with nivolumab + ipilimumab combination followed by nivolumab monotherapy in CA209142, the overall safety profile of the nivolumab + ipilimumab combination regimen was acceptable based on the Feb-2019 DBL and continues to support a positive benefit-risk profile for the nivolumab + ipilimumab combination regimen.

1.5 Overall Risk/Benefit Assessment

The combination of nivolumab and ipilimumab has the potential for increased benefit compared to both ipilimumab monotherapy and nivolumab monotherapy. In Study CA209004, 53% of the subjects with advanced melanoma treated at the dose level of nivolumab 1 mg/kg combined with ipilimumab 3 mg/kg had an objective response, the majority of which had deep tumor reduction of 80% or more. This deep response compares favorably to results with 3 mg/kg ipilimumab monotherapy or nivolumab monotherapy and is the basis for an ongoing randomized Phase 3 study in advanced melanoma (CA209067), in which the ORR were 57.6% in the nivolumab + ipilimumab group, 43.7% in the nivolumab group, and 19.0% in the ipilimumab group; median PFS was 11.5 months with nivolumab plus ipilimumab, as compared with 2.9 months with ipilimumab, and 6.9 months with nivolumab. Studies investigating the efficacy and safety of nivolumab in combination with ipilimumab are ongoing in various tumor types.

The combination of nivolumab and ipilimumab has the potential for increased frequencies of AEs compared to ipilimumab monotherapy or nivolumab monotherapy. The most common (reported at > 10% incidence) treatment-related AEs are fatigue, rash, pruritus, diarrhea, lipase increased, pyrexia, ALT increase, AST increased, amylase increased, and vitiligo. This class of AEs are expected for the combination of nivolumab and ipilimumab based on the known AE profile of each drug alone. In addition, many of the Grade 3/4 AEs were laboratory in nature (ie, liver

function tests [LFTs], lipase, amylase), were without clinical sequalae and have been manageable and reversible following intervention dose delays or with systemic steroid treatment. However, these AEs have the potential to be fatal if not detected early and managed per the established algorithm and fatal AEs have been reported for both ipilimumab and nivolumab monotherapy. As of June 2013, one subject died because of a study treatment-related AE (toxic epidermal necrolysis [TEN]) in the nivolumab + ipilimumab development program. Fatal TEN has previously been reported for ipilimumab monotherapy.

Across multiple tumors, 3 mg/kg nivolumab as well as 3 mg/kg ipilimumab monotherapy have demonstrated a tolerable AE profile in hundreds, respectively thousands of subjects that appears to be independent of tumor type. The combination of 1 mg/kg nivolumab + 3 mg/kg ipilimumab has demonstrated an acceptable AE profile in melanoma in Phase 3 CA209067 study. Both 1 mg/kg nivolumab/3 mg/kg ipilimumab and 3 mg/kg nivolumab/1 mg/kg ipilimumab were identified as the MTD in Phase 1b CA209004 study. Less frequent dosing of ipilimumab at 1 mg/kg Q6W when given with nivolumab 3 mg/kg Q2W was found to have a similar discontinuation rate to that observed in nivolumab monotherapy (11% vs 10%) in preliminary data from CA209012. These 3 combination dosing regimens are currently being studied in various tumor types.

Nevertheless, these safety data were established in a population mainly of Caucasians. Therefore, it is possible that Chinese participants may experience unanticipated AEs. This protocol has been designed to minimize overall risk to participants. Adverse events will be reviewed expeditiously by the medical monitor and discussed with the study investigators. Also, there are detailed management guidelines for AEs listed in the protocol. To assure an ongoing safety assessment for participants enrolled in CA209672, clinical safety monitoring during the study will be performed on regular basis.

The global coronavirus disease 2019 (COVID-19) pandemic has been identified as a potential risk to clinical trial participants in general and may particularly affect individuals with CRC on IO therapy. It is not known whether taking nivolumab plus ipilimumab increases the risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or the duration or severity of COVID-19. Therefore, this study has been designed with study visits that allow for close monitoring of participants' safety throughout the clinical trial (Section 5.1), and participants are encouraged to contact the investigator if an intercurrent illness develops between study visits. Testing for COVID-19 to inform decisions about clinical care during the study should follow local standard practice. Meanwhile, in order to facilitate enhanced reporting of COVID-19 events that occur during the study, all AEs and SAEs reported after the time of consent that are related to SARS-CoV-2 infection or COVID-19 will be reported (Section 6).

In conclusion, the overall risk-benefit assessment for Study CA209672 does justify the conduct of the trial.

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the participant informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

All potential serious breaches must be reported to Bristol-Myers Squibb (BMS) immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the participants of the study or the scientific value of the study.

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

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

2.2 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, participant recruitment materials (eg, advertisements), and any other written information to be provided to participants. The investigator or BMS should also provide the IRB/IEC with a copy of the IB or product labeling information to be provided to participants and any updates.

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

2.3 Informed Consent

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

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

BMS will provide the investigator with an appropriate (ie, Global or Local) sample informed consent form(s) 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(s) 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(s) and any other information to be provided to the participants, prior to the beginning of the study, and after any revisions are completed for new information.
- If informed consent is initially given by a participant's legally acceptable representative or legal guardian, and the participant subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the participant.
- Revise the informed consent whenever important new information becomes available that is relevant to the participant's consent. The investigator, or a person designated by the investigator, should fully inform the participant or the participant's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the participant's willingness to continue participation in the study. This communication should be documented.

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

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

Participants unable to give their written consent (eg, stroke or participants with or severe dementia) may only be enrolled in the study with the consent of a legally acceptable representative. The participant must also be informed about the nature of the study to the extent compatible with his or her understanding, and should this participant become capable, he or she should personally sign and date the consent form as soon as possible. The explicit wish of a participant who is unable to give his or her written consent, but who is capable of forming an opinion and assessing information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

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

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

3.1.1 Overall Design and Schematic

This is an open-label, multi-dose, 2-part, Phase 1/2 study of nivolumab in combination with ipilimumab in Chinese participants with previously treated metastatic or recurrent solid tumors.

As of 20-Dec-2021, the study was closed to new enrollment for Part 2, and a total of 36 participants (9 participants each in Arms A, B, C, and D) were treated in the 3 nivolumab/ipilimumab combination dosing regimens as described below and in Table 3.1.1-1. For all arms, treatment was not randomized.

In Part 1, 9 participants were treated in each of the three arms:

- **Arm A:** Nivolumab administered IV over 30 minutes at 3 mg/kg every 2 weeks combined with ipilimumab administered IV over 30 minutes at 1 mg/kg every 6 weeks
- **Arm B:** Nivolumab administered IV over 30 minutes at 3 mg/kg combined with ipilimumab administered IV over 30 minutes at 1 mg/kg every 3 weeks for 4 doses followed by nivolumab administered IV over 30 minutes at 240 mg every 2 weeks
- **Arm C:** Nivolumab administered IV over 30 minutes at 1 mg/kg combined with ipilimumab administered IV over 30 minutes at 3 mg/kg every 3 weeks for 4 doses followed by nivolumab administered IV over 30 minutes at 240 mg every 2 weeks

In Part 2, a total of 9 participants with recurrent or metastatic MSI-H/dMMR CRC determined by local testing were treated in the following treatment arm:

- **Arm D:** Nivolumab administered IV over 30 minutes at 3 mg/kg combined with ipilimumab administered IV over 30 minutes at 1 mg/kg every 3 weeks for four doses followed by nivolumab administered IV over 30 minutes at 240 mg every 2 weeks.

Table 3.1.1-1: Nivolumab and Ipilimumab Dose Levels

Dosing Arm	Nivolumab (mg/kg, frequency)	Ipilimumab (mg/kg, frequency)
A	3 mg/kg, Q2W	1 mg/kg, Q6W
B	3 mg/kg, Q3W × 4 240 mg, Q2W thereafter	1 mg/kg, Q3W × 4
C	1 mg/kg, Q3W × 4 240 mg, Q2W thereafter	3 mg/kg, Q3W × 4
D	3 mg/kg, Q3W × 4 240 mg, Q2W thereafter	1 mg/kg, Q3W × 4

Abbreviations: AEs = adverse events; Ipi = ipilimumab; Q2W = every 2 weeks; Q3W = every 3 weeks; Q6W = every 6 weeks.

Treatment continues until progression, unacceptable toxicity, withdrawal of consent, completion of **maximum treatment duration**, the study ends, or other reasons specified in the protocol, whichever occurs first. Treatment beyond initial Investigator-assessed Response Evaluation Criteria in Solid Tumors (RECIST) 1.1-defined progression is permitted if the participant has investigator assessed clinical benefit and is tolerating nivolumab, as specified in Section 4.5.7.

Maximum treatment duration will be 24 months from the first dose of study treatment EXCEPT in participants with late response (during second year of treatment) who may receive for up to an additional 12 months after onset of response, in absence of disease progression, unacceptable toxicity and withdrawal of consent. Above defined maximum treatment duration includes treatment beyond progression.

The study will consist of 3 periods: screening period; treatment period (until disease progression, intolerable toxicities, withdrawal of consent, completion of maximum treatment duration, the study ends, or other reasons specified in the protocol, whichever occurs first); and a follow-up period (up to 100 days for Arms A, B, C, and D). For Part 1, tumor assessment must be completed every 6 weeks for the first 24 weeks from date of first dosing, and then every 12 weeks thereafter until disease progression (including treatment beyond progression) or unacceptable toxicities. For Part 2, tumor assessment must be completed every 6 weeks from date of first dosing for the first 24 weeks, and then every 12 weeks thereafter (including treatment beyond progression) until initiation of subsequent anticancer treatment. See Section 5.4 for details of imaging assessment requirement.

Every effort should be made to schedule visits within the timeframe stated in the protocol.

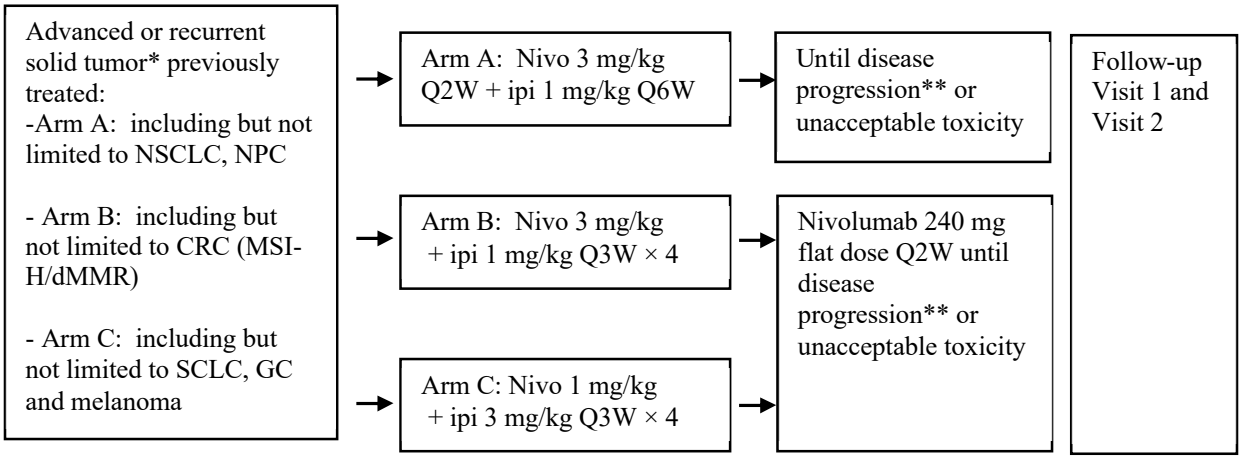
Participants will undergo screening evaluations to determine eligibility prior to administration of study drug. For Part 1 only, for the purpose of PK sample collection, participants will be admitted to the clinical facility prior to dosing (Day -1) only on Cycle 1/Day 1 and Cycle 3/Day 1 for Arm A, and Cycle 1/Day 1 and Cycle 2/Day 22 for Arms B and C, and will remain in the clinical facility until 24 hours after study drug administration.

For Part 2 only, images will be submitted to a central imaging vendor for BICR during the study. Prior to scanning first participant sites should be qualified and understand the image acquisition guidelines and submission process as outlined in the CA209-672 Imaging Manual provided by the central imaging vendor.

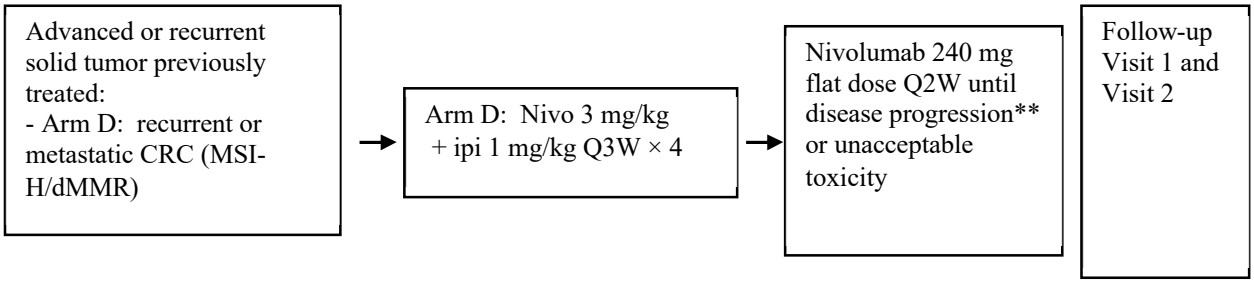
The study design schematic is presented in Figure 3.1.1-1.

Figure 3.1.1-1: Study Design Schematic

Part 1



Part 2



* If a participant with following tumor types is enrolled, he/she can only be treated using one specific dosing schedule, eg, NSCLC, SCCHN, or mesothelioma participant is to be treated in Arm A only. SCLC participant is to be treated in Arm C only.

** Participants may be treated beyond progression under protocol-defined circumstances. Treatment continues until progression, unacceptable toxicity, withdrawal of consent, completion of maximum treatment duration of 2 years EXCEPT in participants with late response (during second year of treatment) who may receive treatment for up to an additional 12 months after onset of response, the study ends, or other reasons specified in the protocol, whichever occurs first.

3.1.2 Part 1 - Safety Monitoring

Physical examinations, vital sign measurements, 12-lead electrocardiograms (ECG), and clinical laboratory evaluations will be performed at selected times throughout the dosing interval. Participants will be closely monitored for adverse events throughout the study. Blood samples will be collected before and after study drug administration for PK analysis.

Less than 350 mL of blood will be drawn from each participant during the study.

In part 1, safety evaluation is planned after a total of 9 participants completed the first 6 weeks of treatment and associated evaluation in a given arm. However, tolerability beyond 6 weeks may

also be taken into consideration. Participants who do not complete the DLT observation period for reasons other than DLTs will be replaced.

The participants' safety will be monitored on an ongoing basis. Adverse events will be reviewed expeditiously by medical monitor and discussed with the study investigators. The sponsor and the study investigators will make an assessment on the tolerability of each combination regimen. Existing clinical safety database from earlier studies may be referred to. The criteria for tolerability Table 3.1.2-1 are based on dose limiting toxicities (listed in Section 4.5.1) and include:

- If no more than two out of the nine participants in a given treatment arm permanently discontinue study medication prior to Week 6 due to treatment related adverse events, then this dose arm will be deemed as tolerable.
- If at least three out of the nine participants in a treatment arm permanently discontinue study medication prior to Week 6 due to treatment-related AEs, then the safety, tolerability, and efficacy of that treatment arm will be reviewed and discussed by the sponsor and investigators for benefit/risk ratio.

Table 3.1.2-1: Guidance for Safety Monitoring Based on Observed Toxicity Outcomes

Number of participants treated and followed up for at least 6 weeks after start of study treatment	Number of participants with DLTs	Next Step
9	≤ 2	Tolerable
9	≥ 3	To be discussed between sponsor and investigators to review benefit/risk ratio

The duration of the study is anticipated to be approximately 2 years. The end of the trial will occur on the day of the last visit of the last participant.

3.1.3 Part 2

3.1.3.1 Mismatch Repair/Microsatellite Instability Testing

MSI testing

Microsatellite instability - high is most frequently determined by polymerase chain reaction (PCR). MSI-H in tumors refers to changes in two or more of the five microsatellite markers in tumor tissue identified by National Cancer Institute (NCI)-recommended panels. The original Bethesda guidelines (1997) proposed a panel of five microsatellite markers for the uniform analysis of MSI in hereditary non-polyposis colorectal cancer (HNPCC). This panel, which is referred to as the Bethesda panel, included two mononucleotide (BAT-25 and BAT-26) and three dinucleotide (D5S346, D2S123, and D17S250) repeats.[26] Individual testing sites may utilize a slightly different panel of markers incorporating alternative mononucleotide and/or dinucleotide markers. Regardless of the panel of markers, samples with instability in ≥ 30% or more of these markers

are defined as MSI-H, whereas those with < 30% unstable markers are designated as MSI-Low (MSI-L). Samples with no detectable alterations are MSS.

MMR testing

DNA mismatch repair deficiency determined by immunohistochemistry (IHC) refers to the loss of expression of one or more of the mismatch repair proteins (MLH1, MSH2, MSH6, or PMS2). Loss of expression is restricted to tumor cells, with preserved expression in immune infiltrate, and normal adjacent tissue. Loss of MLH1 expression is usually accompanied by loss of PMS2, and loss of MSH2 is usually accompanied by the loss of MSH6 expression.

In Part 2, participants with MSI-H/dMMR status determined prior to screening by local testing as part of the standard of care assessment can be eligible to the study. Please refer to Appendix 4 regarding MSI/MMR testing panel descriptions and classification of MSI/MMR status to ensure historical MSI/MMR status determination is aligned with the protocol requirements prior to enrollment.

3.1.3.2 Screening

A complete schedule of activities for screening can be found in Table 5.1-1.

Before Protocol Amendment 07, enrollment had stopped.

- Begins by establishing the participant's initial eligibility and signing of the informed consent form (ICF).
- Inclusion/Exclusion criteria are assessed during the screening period and must be confirmed prior to first dose
- All medical history relevant to the disease under study should be collected.
- Tumor tissue obtained from primary or metastatic site of disease.
  - Sufficient tumor tissue obtained before start of study treatment in the primary or metastatic sites (block or minimum of 10 slides, obtained from core biopsy, punch biopsy, excisional biopsy, or surgical specimen) will be submitted to the central laboratory.
  - For participants where a fresh biopsy is not feasible, archival tumor material are required.
  - An additional source of tumor tissue must be available if the tissue obtained adhering to the above guidelines cannot be tested due to poor quality or insufficient quantity.
  - Central lab must confirm receipt of evaluable tumor tissue prior to vial assignment for MSI/MMR testing (see Section 5.6.2).
- Prior to screening, medical record documentation of MSI/MMR testing results must be available. Related pathology reports must be available. Reports must contain MSI/MMR status results, and specific results per markers tested for MSI/MMR are also required if available.
- Collect RAS and BRAF mutation status, if available. Tests for these alterations are expected to be already performed for Arm D participants.
- Eligibility and baseline assessments should be performed within required timeframe according to Table 5.1-1. The screening phase either ends with confirmation of full eligibility and treatment assignment for the participant or with the confirmation that the participant is a screen failure.

3.1.3.3 Review of Safety

The participants' safety will be monitored on an ongoing basis as described fully in Section 6. In addition, a BMS medical safety team (MST) routinely reviews safety signals across the entire nivolumab program including combination studies with ipilimumab.

3.1.4 Intra-Subject Dose Reductions

Intra-subject dose reduction is not permitted for any reason. Dose delays for the management of study treatment-related AEs are described in Section 4.5.3.

3.1.5 Follow-Up

Follow-up begins when the decision to discontinue a participant from study therapy is made (no further treatment with study therapy).

Participants will be followed for drug-related toxicities until these toxicities resolve, return to baseline, or are deemed irreversible up to follow-up visit 2 (FU2) or 100 days of study drug discontinuation, whichever occurs later. All AEs occurring within 100 days after last dose will be documented.

Tumor assessments for Arm D will continue until FU2 or 100 days after last dose, whichever is later.

Refer to Table 5.1-5, Table 5.1-6, and Table 5.1-7 for additional follow-up assessments.

3.2 Post Study Access to Therapy

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 of 2 years specified in protocol Section 3.1.1. 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 and/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.

3.3 Study Population

For entry into the study, the following criteria MUST be met prior to dosing on Day 1. No exceptions will be granted. As of 20-Dec-2021, enrollment into this study Part 2 was closed.

3.3.1 Inclusion Criteria

1) Signed Written Informed Consent

a) Participants must have signed and dated an IRB/IEC approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained

before the performance of any protocol related procedures that are not part of normal participant care.

b) Participants must be willing and able to comply with scheduled visits (including overnight stays), treatment schedule, laboratory tests and other requirements of the study.

2) Target Population

a) Chinese participants with advanced or recurrent solid tumors

i) histologically confirmed

(1) All CRC participants must be histologically confirmed metastatic or recurrent, with historically documented MSI-H or dMMR status by local testing (please refer to Appendix 4 for definition of MSI-H/dMMR and panel to be used by local testing).

ii) must have failed at least one prior systemic chemotherapy for advanced disease, OR, well documented refusal of participants to receive chemo or biological therapy

(1) SCLC participant must have failed at least one prior systemic therapy for advanced disease including one platinum based regimen.

iii) must have at least 1 measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST 1.1) (Appendix 1).

(1) GC participants must have at least one measurable lesion or evaluable disease by computed tomography (CT) or magnetic resonance imaging (MRI) per RECIST 1.1 criteria.

(2) Participants with lesions in a previously irradiated field as the sole site of measurable disease will be permitted to enroll provided the lesion(s) have demonstrated clear progression and can be measured accurately.

b) Eastern Cooperative Oncology Group Performance Status of 0 or 1 (Appendix 2).

c) Life expectancy ≥ 3 months.

d) Not applicable per Protocol Amendment 04.

e) Not applicable per Protocol Amendment 04.

f) Not applicable per Protocol Amendment 04.

g) Not applicable per Protocol Amendment 04.

h) Not applicable per Protocol Amendment 04.

i) Not applicable per Protocol Amendment 04.

ii) Not applicable per Protocol Amendment 04.

iii) Not applicable per Protocol Amendment 04.

iv) Not applicable per Protocol Amendment 04.

v) Not applicable per Protocol Amendment 04.

vi) Not applicable per Protocol Amendment 04.

vii) Not applicable per Protocol Amendment 04.

viii) Not applicable per Protocol Amendment 04.

i) Participant Re-enrollment: This study permits the re-enrollment of a participant that has discontinued the study as a pre-treatment failure (ie, participant has not been treated). If re-enrolled, the participant must be re-consented. Obtain agreement from the Medical Monitor prior to re-enrolling a participant.

Additional Criteria for Participants Enrolled in Part 2

j) Participants must have shown progression during, after, or have been intolerant to ≥ 1 line treatment(s) for metastatic disease, which must include at least a fluoropyrimidine, and oxaliplatin or irinotecan (participants who receive oxaliplatin in an adjuvant setting should have progressed during or within 6 months of completion of adjuvant therapy in order for oxaliplatin to count as a prior therapy needed for entry).

k) Participant willing to comply to provide tumor tissue (archival or fresh biopsy specimen) (see Section 5.6.2 for additional details regarding the requirements for tumor tissue).

3) Age and Reproductive Status

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

a) Female Participants

i) Females ages 18 years, or age of majority, or older at time of consent

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

iii) Women participants must have documented proof that they are not of childbearing potential.

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

v) Additional requirements for pregnancy testing during and after study intervention are located in Section 5, Schedule of Assessments.

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

vii) WOCBP must agree to follow instructions for method(s) of contraception defined in Appendix 5 and as described below and included in the ICF.

viii) WOCBP are permitted to use hormonal contraception methods (as described in Appendix 5)

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

(1) Is not a WOCBP
OR
(2) Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of < 1% per year), with low user dependency, as described in Appendix 5 during the intervention period and for at least 5 months and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction for the same time period

b) Male Participants

i) Males, ages 18 years, or age of majority, or older at time of consent

3.3.2 Exclusion Criteria

1. Target Disease Exceptions

a) Participants with untreated symptomatic central nervous system (CNS) metastases are excluded. Participants are eligible if CNS metastases are adequately treated and participants are neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to enrollment. In addition, participants must be either off corticosteroids, or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent). Imaging performed within 28 days prior to treatment assignment must document radiographic stability of CNS lesions and be performed after completion of any CNS directed therapy.

b) Participants with leptomeningeal metastases.

2. Medical History and Concurrent Diseases

a) Participants with previous malignancies or concurrent malignancies (present during screening) requiring treatment (except non-melanoma skin cancers, and the following in situ cancers: bladder, gastric, colon, endometrial, cervical/dysplasia, melanoma, or breast) are excluded unless a complete remission was achieved at least 2 years prior to study start AND no additional therapy is required or anticipated to be required during the study period.

b) Participants with active, known or suspected autoimmune disease. Participants with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement are permitted to enroll.

c) Not applicable per Protocol Amendment 04.

d) Active Tuberculosis (TB) infection based on chest X-ray, sputum tests, and clinical examination. Participants with a history of active TB infection within the last 1 year are excluded, even if it was treated. Participants with a history of active TB infection greater than 1 year ago are excluded unless there is documentation of adequate prior anti-TB treatment.

e) Not applicable per Protocol Amendment 04.

f) Not applicable per Protocol Amendment 04.

g) Not applicable per Protocol Amendment 04.

h) Not applicable per Protocol Amendment 04.

i) Not applicable per Protocol Amendment 04.

j) Not applicable per Protocol Amendment 04.

k) Any other sound medical, psychiatric and/or social reason as determined by the investigator.

l) Participants with interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity.

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

n) Not applicable per Protocol Amendment 04.

o) All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue (which can be Grade 2) must have been resolved to ≤ Grade 1, or returned to baseline, or stabilized before administration of study drug. Participants with toxicities attributed to prior anti-cancer therapy which are not expected to resolve to Grade 1 and result in long lasting sequelae, such as neuropathy after platinum based therapy, are permitted to enroll.

p) Any serious or uncontrolled medical disorder that, in the opinion of the investigator, may increase the risk associated with study participation or study drug administration, impair the ability of the participant to receive protocol therapy, or interfere with the interpretation of study result.

q) Women who are of childbearing potential or breastfeeding

3. Physical and Laboratory Test Findings

a) Not applicable per Protocol Amendment 04.

b) Not applicable per Protocol Amendment 04.

c) Not applicable per Protocol Amendment 04.

d) WBC < 2000/μL

e) Neutrophils < 1500/μL

f) Platelets < 100×10^3/μL

g) Hemoglobin < 9.0 g/dL

h) Serum creatinine > 1.5× ULN, unless creatinine clearance ≥ 40 mL/min (measured or calculated using the Cockroft-Gault formula):

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

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

i) AST: > 3.0× ULN

j) ALT: > 3.0× ULN

k) Bilirubin > 1.5× ULN (except participants with Gilbert Syndrome who must have total bilirubin < 3.0× ULN)

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

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

m) Positive blood screen for human immunodeficiency virus (HIV)-1, or -2 antibody.

4. Allergies and Adverse Drug Reaction

a) 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 BMS approval is required).

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

c) Inability to comply with restrictions and prohibited activities/treatments as listed in Section 3.4

6. Prior /Concomitant Therapy

a) Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways, including prior therapy with anti-tumor vaccines or other immuno-stimulatory antitumor agents

b) Treatment with any chemotherapy, curative intent radiation therapy, biologics for cancer, or investigational therapy must have been completed at least 28 days before first administration of study treatment. Prior focal palliative radiotherapy must have been completed at least 2 weeks before study drug administration. Participants with prior cytotoxic or investigational products < 4 weeks prior to treatment might be eligible after discussion between investigator and sponsor, if toxicities from the prior treatment have been resolved to ≤Grade 1 (NCI Common Terminology Criteria for Adverse Events [CTCAE] version 4.0) or returned to baseline.

c) Participants who have received a live / attenuated vaccine within 30 days of first treatment

d) Prior major surgery requiring general anesthesia must be completed at least 2 weeks before study drug administration. Surgery requiring regional/epidural anesthesia must be completed at least 72 hours before study drug administration and participants must be recovered. Cutaneous biopsies with only local anesthesia should be completed at least 1 hour prior to study drug administration.

e) Any use of immunosuppressive systemic medications, such as steroids (dose > 10 mg/day prednisone or equivalent) within 2 weeks of study drug administration.

f) Any use of traditional medicinal herbal preparations within 2 weeks of study drug administration.

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.

3.3.3 Women of Childbearing Potential

See Appendix 5.

3.4 Concomitant Treatments

3.4.1 Prohibited and/or Restricted Treatments

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

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids. Participants are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Adrenal replacement steroid doses > 10 mg daily prednisone are permitted. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.
- Any concurrent systemic anti-neoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents for treatment of CRC)
- Any non-palliative radiation therapy. Radiation therapy administered with palliative intent (ie, for pain, bleeding, spinal cord compression, brain metastasis, new or impending pathologic fracture, superior vena-cava syndrome, or obstruction) is permitted.
- Any complementary medications (eg, herbal supplements or traditional Chinese medicines) intended to treat the disease under study. Such medications are permitted if they are used as supportive care.
- Any live / attenuated vaccine (eg, varicella; zoster; yellow fever; rotavirus; oral polio; and measles, mumps, rubella) during treatment and until 100 days post last dose.
  - COVID-19 vaccines that are NOT live are allowed and should be handled in the same manner as other vaccines. Administration may occur during the study, including during the administration of the BMS study treatment and after the last administration of the BMS study treatment. Non-live COVID-19 vaccination is considered a simple concomitant medication within the study. However, the efficacy and safety of non-live vaccines (including non-live COVID-19 vaccines) in participants receiving nivolumab and/or ipilimumab are unknown.

3.4.2 Other Restrictions and Precautions

Participants are permitted the use of topical, ocular, intra-articular, intranasal and inhalational corticosteroids (with minimal systemic absorption). Physiologic replacement doses of systemic corticosteroids (ie, prednisone ≤ 10 mg/day) are permitted. A brief course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-

type hypersensitivity reaction caused by a contact allergen) or for management of study drug-induced adverse events are permitted.

Surgical Resection following Initial Response

Investigators may choose to resect solitary lesions in participants with residual disease and render the participant free of macroscopic disease. Participants enrolled in this study may have lesions surgically resected only following consultation with the medical monitor and following the Week 24 tumor imaging assessments. If additional tumor shrinkage is noted compared to the tumor imaging assessments at Week 18, it is highly encouraged that surgical resection be delayed until subsequent scans fail to demonstrate further shrinkage. Participants with a confirmed partial response (PR) who go on to have surgical resection of remaining disease will be considered a PR. Participants with stable disease (SD) who go on to have surgical resection of remaining disease will be considered a SD. Participants may continue treatment after surgery. Tumor tissue of any resected solitary lesion should be submitted to BMS (see Section 5.6.2). Detailed instructions of the obtaining, processing, labeling, handling, storage, and shipment of these specimens will be provided in a separate procedure manual at the time of study initiation.

3.5 Discontinuation of Participants following any Treatment with Study Drug

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

- Participant's request to stop study treatment and/or participation in the study
- Any clinical AE, laboratory abnormality, or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant
- Pregnancy*
- Termination of the study by BMS
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Inability to comply with protocol
- Documented disease progression (or documentation of further progression for participants receiving treatment beyond progression; see Section 4.5.7). Participants without documented disease progression can discontinue study treatment if they have investigator assessed clinical deterioration that is unstable to perform further tumor assessment, and it should be well documented).
- Any AE meeting discontinuation criteria (see Section 4.5.6).

* In the case of pregnancy, the investigator must immediately notify the BMS Medical Monitor/designee of this event. In most cases, the study drug will be permanently discontinued in an appropriate manner. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug, a discussion between the investigator and the BMS Medical Monitor/designee must occur

All participants who discontinue investigational product should comply with protocol specified follow-up procedures as outlined in Section 5. The only exception to this requirement is when a participant withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study drug 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.

3.6 Post Study Drug Follow up

Participants who discontinue study treatment must continue to be followed for safety up to 100 days following drug discontinuation.

3.6.1 Withdrawal of Consent

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

3.6.2 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 as noted above. Lost to follow-up is defined by the inability to reach the participant after a minimum of three documented phone calls, faxes, texts, 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 the 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.

4 STUDY DRUG

Study drug includes both investigational [medicinal] product (IP/IMP) and non-investigational [medicinal] product (Non-IP/Non-IMP) and can consist of the following:

- All products, active or placebo, being tested or used as a comparator in a clinical trial.
- Study required premedication,
- Other drugs administered as part of the study that are critical to claims of efficacy (eg, background therapy, rescue medications)
- Diagnostic agents: (such as glucose for glucose challenge) given as part of the protocol requirements must also be included in the dosing data collection.

Product description and storage information is described in Table 4-1.

Table 4-1: Study Drugs for CA209672 - Treatment Period

Product Description Class and Dosage Form	Potency	Primary Packaging (Volume)/Label Type	Secondary Packaging (Qty)/Label Type	Packaging/Appearance	Storage Conditions (per label)
Nivolumab (BMS-936558-01) Solution for Injection	100 mg (10 mg/mL)	10 mL vial/ Open-label	5 vials per carton/ Open-label	Clear to opalescent colorless to pale yellow liquid. May contain particles	Store at 2 to 8°C. Protect from light and freezing
Ipilimumab Solution for Injection	200 mg (5 mg/mL) 50 mg (5 mg/mL)	40 mL vial 10 mL vial/ Open-label	4 vials per carton 1 vial per carton / Open-label	Clear to opalescent colorless to pale yellow liquid. May contain particles	Store at 2 to 8°C. Protect from light and freezing

4.1 Investigational Product

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

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

4.2 Non-investigational Product

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-investigational products.

4.3 Storage and Dispensing

The product storage manager should ensure that the study drug 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 drug arise, the study drug should not be dispensed and contact BMS immediately.

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

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

For nivolumab and ipilimumab, please refer to the current version of the IBs and/or pharmacy reference sheets for complete storage, handling, dispensing, and infusion information.

Nivolumab is to be administered as an approximately 30-minute IV infusion. At the end of the infusion, flush the line with a sufficient quantity of normal saline or dextrose solution. Ipilimumab is to be administered as an approximately 30-minute IV infusion. At the end of the infusion, flush the line with a sufficient quantity of normal saline or 5% dextrose solution. When both study drugs are to be administered on the same day, separate infusion bags and filters must be used for each infusion. Nivolumab is to be administered first. The nivolumab infusion must be promptly followed by a saline flush to clear the line of nivolumab before starting the infusion. The second infusion will always be ipilimumab and will start at least 30 minutes after completion of the nivolumab infusion, filters changed, and patient observed to ensure no infusion reaction has occurred. Begin study treatment within 3 calendar days of treatment assignment.

4.4 Method of Assigning Participant Identification

CA209672 is an open-label, non-randomized, parallel-arm study. During the screening visit, the investigative site will call into the enrollment option of the Interactive Voice Response System (IVRS) designated by BMS for assignment of a 5-digit participant number that will be unique. Enrolled participants, including those not dosed, will be assigned sequential participant numbers starting with [redacted]. The patient identification number (PID) will ultimately be comprised of the site number and participant number. Those enrolled participants meeting inclusion and exclusion criteria will be eligible to be dosed. Specific instructions and procedures for using IVRS will be provided to the investigational site in a separate document/ manual.

4.5 Selection and Timing of Dose for Each Participant

4.5.1 Dose Limiting Toxicities

Dose limiting toxicities are defined as any of the items listed below which occur during the first 6 weeks.

- Any Grade 2 drug-related uveitis or eye pain that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any Grade 2 drug-related pneumonitis or interstitial lung disease that does not resolve to dose delay and systemic steroids.
- Any Grade 3 non-skin drug-related adverse event regardless of duration with the exception of laboratory abnormalities
- Any Grade 4 drug-related adverse event including laboratory abnormalities except Grade 4 leukopenia or neutropenia lasting < 7 days
- Any of the following drug-related hepatic function laboratory abnormalities:
  - Grade ≥ 3 drug-related AST, ALT or Total bilirubin
  - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2x ULN
  - Grade 3 thrombocytopenia associated with bleeding

4.5.2 Dose Adjustment

Dosing calculations should be based on the body weight assessed at baseline. If the participant's weight on the day of dosing differs by > 10% from the weight used to calculate the prior dose, the dose must be recalculated. All doses should be rounded to the nearest milligram. There will be no other dose modifications allowed.

4.5.3 Dose Delay Criteria

Study treatment should be delayed for the following:

- Any Grade ≥ 2 non-skin, drug-related AE, except for fatigue
- Grade 2 drug-related creatinine, AST, ALT, and/or Total Bilirubin Abnormalities, with the following exceptions:

  - If a participant has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity
  - See Section 4.5.6 for discontinuation criteria for drug-related ALT, AST and/or Total Bilirubin Abnormalities
- Any Grade ≥ 3 skin drug-related AE
- Any Grade 3 drug-related laboratory abnormality with the following exceptions:
  - Grade 3 lymphopenia or asymptomatic amylase or lipase does not require a dose delay
- Any AE, laboratory abnormality or inter-current illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Dosing of nivolumab and ipilimumab should be delayed for any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication. Study therapy should also be delayed in cases of confirmed or suspected severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection regardless of the severity.

Participants receiving nivolumab in combination with ipilimumab who have drug-related toxicities that meet the criteria for dose delay should have both drugs (nivolumab and ipilimumab) delayed until treatment resumption criteria are met.

Participants who require delay of nivolumab and/or ipilimumab should be re-evaluated weekly or more frequently if clinically indicated and resume nivolumab and/or ipilimumab dosing when retreatment criteria are met.

Dose delay criteria apply for all drug-related adverse events regardless of whether the event is attributed to nivolumab or ipilimumab or both.

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

Rescheduling

Participants who require delay of treatment should be re-evaluated weekly or more frequently if clinically indicated and resume dosing when re-treatment criteria are met. Continue tumor assessments per protocol even if dosing is delayed.

Arm A:

- Nivolumab may be delayed until the next planned ipilimumab dose if the next ipilimumab dose is scheduled within the next 12 days. This will permit periodic ipilimumab dosing to be synchronized with nivolumab dosing.
- Ipilimumab should be dosed at the specified interval regardless of any delays in intervening nivolumab doses. However, in order to maintain periodic synchronized dosing of ipilimumab and nivolumab, the dosing days of nivolumab and ipilimumab may be adjusted within the permitted ± 2 day window, as long as consecutive nivolumab doses are given at least 12 days

apart. Ipilimumab may be delayed beyond the 2-day window if needed to synchronize with the next nivolumab dose.

- If an ipilimumab dose is delayed beyond 6 weeks from the prior ipilimumab dose, then subsequent ipilimumab doses should be rescheduled to maintain the 6-week interval between consecutive ipilimumab doses.
- A dose delay of ipilimumab which results in no ipilimumab dosing for > 12 weeks requires ipilimumab discontinuation, with exceptions as noted in Section 4.5.5.

Arm B, C and D: Participants may be dosed no less than 12 days and 19 days from the previous treatment during Q2W (nivolumab) and Q3W (nivolumab combined with ipilimumab) dosing, respectively.

4.5.4 Dose Reduction

There will be no dose reductions for nivolumab or ipilimumab.

4.5.5 Criteria to Resume Treatment

Participants may resume study treatment when the drug-related AE(s) resolve(s) to Grade ≤ 1 or baseline, with the following exceptions:

- Participants may resume treatment in the presence of Grade 2 fatigue.
- Participants who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- For participants with Grade 2 AST, ALT and/or Total Bilirubin Abnormalities, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete. Participants with baseline Grade 1 AST/ALT or total bilirubin elevations who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT OR total bilirubin.
- Participants with isolated AST/ALT elevations or combined with total bilirubin elevations meeting discontinuation parameters (Section 4.5.6) should have treatment permanently discontinued, except situations outlined in the Section 4.5.6.
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed. Participants with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by the BMS Medical Monitor.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the BMS Medical Monitor. If participant experienced Grade 3 adrenal insufficiency study treatment should not be resumed regardless of control with hormone replacement.

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

- At least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared or positive test result (eg, reverse transcription polymerase chain reaction or viral antigen)
- Resolution of acute symptoms (including at least 24 hours has passed since last fever without fever reducing medications)
- Evaluation by the investigator with confirmation that there are no sequelae that would place the participant at a higher risk of receiving investigational treatment.

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 > 8 weeks, 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 8 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 1 of the agents must be discontinued due to toxicity attributed to that agent alone.

4.5.6 Treatment Discontinuation Criteria

Treatment should be permanently discontinued for any of the following:

- Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related AE lasting > 7 days, with the following exceptions for drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, infusion reactions, endocrinopathies, diarrhea, colitis, neurologic toxicity and laboratory abnormalities:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, diarrhea, colitis, myocarditis, neurologic toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation. Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation. Grade 3 adrenal insufficiency requires discontinuation regardless of control with hormone replacement.
    - ♦ Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
      - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation.
      - Grade ≥ 3 drug-related AST, ALT or Total Bilirubin requires discontinuation*
      - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2x ULN*
  - *In most cases of Grade 3 AST or ALT elevation, study drug(s) will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug(s), a discussion between the investigator and the BMS Medical Monitor/designee must occur.

- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events, which do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia or leukopenia
  - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis. The BMS Medical Monitor should be consulted for Grade 4 amylase or lipase abnormalities
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
  - Grade 4 drug-related endocrinopathy adverse events such as hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS Medical Monitor
- Dosing delays lasting > 6 weeks for Q2W dosing (nivolumab monotherapy) or > 8 weeks for Q3W dosing (nivolumab combined with ipilimumab) from the previous dose requires discontinuation. The following exceptions apply:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events are allowed.
  - Dosing delays lasting > 6 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS medical monitor.
- 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.

Prior to re-initiating treatment in a participant with a dosing delay lasting > 6 weeks, the BMS medical monitor 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.

The assessment for discontinuation of ipilimumab should be made separately from the assessment made for discontinuation of nivolumab. Although there is an 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 meets the criteria for discontinuation of ipilimumab but not nivolumab, treatment with nivolumab may not resume until the AE/SAE has fully resolved and the participant has discontinued steroids, if they were required for treatment of the AE/SAE. The relationship to ipilimumab should be well documented in the source documents. Nivolumab should be resumed at the dose according to the treatment schedule (Table 5.1-2, Table 5.1-3 and Table 5.1-4).

Participants receiving nivolumab plus ipilimumab treatment arm, who meet criteria for treatment discontinuation and an 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.

4.5.7 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).[27]

Participants treated with nivolumab or nivolumab plus ipilimumab combination will be permitted to continue treatment beyond initial RECIST 1.1-defined PD, assessed by the investigator up to a maximum of 24 months from date of first dose as long as they meet the following criteria: The 24-month maximum treatment duration of the study includes time spent in treatment beyond progression.

- Investigator-assessed clinical benefit
- Tolerance of study treatment
- Stable performance status
- Participant provides written informed consent prior to receiving additional 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.

Radiographic assessment/scan(s) in accordance with the Section 5.1 Flow Chart/Time and Events Schedule for the duration of the treatment beyond progression and should be submitted to the central imaging vendor for Part 2 only. Balance the assessment of clinical benefit with clinical judgment as to whether the participant is clinically deteriorating and unlikely to receive any benefit from continued treatment with nivolumab.

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 Time and Events Schedule on Table 5.1-2 to Table 5.1-7.

For the participants who continue nivolumab study therapy beyond progression, further progression is defined as an additional 10% increase in tumor burden with a minimum 5 mm absolute increase from time of initial PD. This includes an increase in the sum of diameters of all target lesions and/or the diameters of new measurable lesions compared to the time of initial PD. Upon documentation of further progression, permanently discontinue nivolumab treatment unless the clinical judgement of the investigator is that continuing treatment is in the patient's best interest. New lesions are considered measurable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). Any new lesion considered non-measurable at the time of initial progression may become measurable and therefore included in the tumor burden if the longest diameter increases to at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). In situations where the relative increase in total tumor burden by 10% is solely due to

inclusion of new lesions which become measurable, these new lesions must demonstrate an absolute increase of at least 5 mm.

4.5.8 Management Algorithms for Immuno-Oncology Agents

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

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

The above algorithms are found in both the nivolumab and ipilimumab IBs,[8] as well as in Appendix 3.

4.5.9 Treatment of Nivolumab or Ipilimumab 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 symptoms. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the BMS Medical Monitor and reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE (Version 4.0) guidelines.

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

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

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

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

- Immediately discontinue infusion of 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).

4.6 Blinding/Unblinding

This is an open-label study. Treatment assignments will be released to the bioanalytical laboratory in order to minimize unnecessary analysis of samples.

4.7 Treatment Compliance

Study drug will be administered in the clinical facility. Treatment compliance will be monitored by drug accountability as well as the participant's medical record and eCRF.

4.8 Destruction of Study Drug

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

Any unused study drugs can only be destroyed after being inspected and reconciled by the responsible BMS study monitor unless study drug containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics).

On-site destruction is allowed provided the following minimal standards are met:

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

If conditions for destruction cannot be met the responsible BMS study monitor will make arrangements for return of study drug.

4.9 Return of Study Drug

If study drug will not be destroyed upon completion or termination of the study, all unused and/or partially used study drug that was supplied by BMS must be returned to BMS. The return of study drug will be arranged by the responsible study monitor.

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

4.10 Retained Samples for Bioavailability/Bioequivalence

Not applicable.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Study assessments and procedures are presented in Table 5.1-1, Table 5.1-2, Table 5.1-3, Table 5.1-4, Table 5.1-5, Table 5.1-6, and Table 5.1-7.

Table 5.1-1: Screening Procedural Outline (CA209672)

This study is not actively enrolling participants.

Procedure	Screening Visit	Notes
Eligibility Assessments		
Informed Consent	x	A participant is considered enrolled only when a protocol specific informed consent is signed. Study allows for re-enrollment of a participant that has discontinued the study as a pre-treatment failure. If re-enrolled, the participant must be re-consented and assigned a new participant number from IRT.
Inclusion/Exclusion Criteria	x	Must be confirmed prior to treatment assignment. See Section 3.3.
Medical History	x	Include any toxicities or allergy related to previous treatments.
Diagnosis confirmation and stage	x	
Tumor-specific therapy information	x	
MSI Status (CRC Participants Only)	x	For CRC participants in Arms B and D, sites should record historically documented MSI/MMR testing results on the CRF. Pathology reports containing MSI/MMR testing results must be available. Reports must contain MSI/MMR status results, and specific results per markers tested for MSI/MMR are also required if available.
Tumor Tissue Sample	x	For Part 2 only, sufficient evaluable tumor tissue obtained before start of study treatment in the metastatic setting or from an unresectable site (block or minimum of 10 slides, obtained from core biopsy, punch biopsy, excisional biopsy or surgical specimen). For participants where a fresh biopsy is not feasible, archival tumor material must be available. Central laboratory must confirm receipt of evaluable tumor tissue prior to vial assignment (Section 5.6.2).
RAS Mutation Status	x	For Part 2 only, if available, record result.
BRAF Mutation Status	x	For Part 2 only, if available, record result.
History of Lynch Syndrome		For Part 2 only, if available, record result.
Safety Assessments		
Physical Examination (PE)	x	To be collected within 14 days prior to date of first dosing.
Physical Measurements	x	Includes height, weight; should be recorded within 14 days prior to date of first dosing.

Table 5.1-1: Screening Procedural Outline (CA209672)

This study is not actively enrolling participants.

Procedure	Screening Visit	Notes
ECOG Performance Status	x	See Appendix 2; should be recorded within 14 days prior to date of first dosing.
Vital Signs and Oxygen Saturation	x	Includes body temperature, respiratory rate, and seated or supine blood pressure and heart rate, O2 saturation by pulse oximetry at rest. Blood pressure and heart rate should be measured after the participant has been resting quietly for at least 5 minutes. Vital signs should be obtained at screening and within 72 hours prior to date of first dosing.
Electrocardiogram (ECGs)	x	ECGs should be recorded after the participant has been supine for at least 5 minutes; should be recorded within 14 days prior to date of first dosing.
Monitor for Serious Adverse Events	x	All SAEs that occur during the screening period and within 100 days of discontinuation of dosing must be collected. All AEs (SAEs or non-serious AEs) associated with SARS-CoV-2 infection collected from time of consent.
Concomitant Medication Collection	x	All medications taken within 14 days prior to date of first dosing will be recorded.
Laboratory Tests	x	CBC w/differential; Full Chemistry Panel: LDH, AST, ALT, ALP, T.Bili, (Direct Bili if T.Bili > ULN), BUN (or serum urea level), creatinine, Ca+, Mg+, Na+, K+, Cl-, glucose, albumin, T.Protein. Lab tests should be completed within 14 days prior to date of first dosing.
Serology (HCV, HBV, HIV)	x	Includes hepatitis C antibody or HCV RNA, hepatitis B surface antigen, and HIV-1 and -2 antibody. If anti-HCV test is positive, then HCV RNA is mandatory. Viral testing to be performed within 28 days prior to date of first dosing. Serology test result must be available and reviewed prior to dosing on Day 1.
Pregnancy Test	x	All WOCBP must have a negative urine or serum β-HCG pregnancy test minimum sensitivity 25 IU/L or equivalent units of HCG within 24 hours before the first infusion; FSH > 40 mIU/mL is required to confirm menopause. See Appendix 5.
Baseline Tumor Assessment	x	Contrast enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all known sites of disease should be performed within 28 days prior to date of first dosing. See Section 5.4.
CT/MRI (brain)	x	MRI of the brain without and with contrast is required if participant is symptomatic or has a history of brain metastasis, and has not had brain imaging within 28 days prior to date of first dosing. CT of the Brain (without and with contrast) can be performed if MRI is contraindicated. See Section 5.4.

Table 5.1-1: Screening Procedural Outline (CA209672)

This study is not actively enrolling participants.

Procedure	Screening Visit	Notes
Other Imaging (eg, Bone Scan)	x	As clinically indicated per local standards. Performed within 28 days prior to date of first dosing. See Section 5.4

Table 5.1-2: On-Treatment Procedural Outline (CA209672) - Part 1, Arm A: nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W combination

Procedure	Cycle 1 and beyond (1 cycle = 6 weeks)				Notes
	Day 1[a]	Day 15[a]	Day 29[a]	Day 42[a]	
Admission to Clinical Facility	x				For the purpose of PK sample collection, participants will be admitted to the clinical facility prior to dosing (Day -1) on Cycle 1/Day 1 and Cycle 3/ Day 1, and will remain in the clinical facility until 24 hrs after study drug administration.
Safety Assessments					
Targeted PE	X	x	x		Targeted examination must include at a minimum the following body systems: • Cardiovascular • Gastrointestinal • Pulmonary • Neurological exam for participants with brain metastases Obtain prior to each dose.
Physical Measurements	X	x	X		Weight only. Dose adjustments are required to be made if there has been a > 10% percent weight change (increase or decrease) from the previous dose. Obtain prior to each dose.
Vital Signs and Oxygen Saturation	X	x	X		Includes body temperature, respiratory rate, and seated or supine blood pressure and heart rate, O2 saturation by pulse oximetry at rest. Blood pressure and heart rate should be measured after the participant has been resting quietly for at least 5 minutes. Vital signs should be taken as per institutional standard of care at visits and prior to, during, and after the infusion with nivolumab.
ECOG Performance Status	X	x	X		Obtain prior to each dose. See Appendix 2

Table 5.1-2: On-Treatment Procedural Outline (CA209672) - Part 1, Arm A: nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W combination

Procedure	Cycle 1 and beyond (1 cycle = 6 weeks)				Notes
	Day 1[a]	Day 15[a]	Day 29[a]	Day 42[a]	
Electrocardiogram (ECGs)	X				ECGs should be recorded after the participant has been supine for at least 5 minutes.
AE Assessment (including SAE Assessment)	X				Should occur at every visit throughout the study. See Sections 6.1 and 6.2. All AEs (SAEs or non-serious AEs), including those associated with SARS-CoV-2 infection, must be collected continuously during the treatment period.
Review of Concomitant Medications	X	x	X		Should occur at every visit throughout the study.
Laboratory Tests					
Laboratory Tests	X	x	X		Include CBC w/differential and platelets; Full Chemistry Panel: LDH, AST, ALT, ALP, T.Bili (Direct Bili if T.Bili > ULN), BUN (or serum urea level), creatinine, Ca+, Mg+, Na+, K+, Cl-, amylase, lipase, glucose, albumin, T.Protein To be done within 72 hours prior to dosing and results must be reviewed prior to dosing. Screening labs are acceptable if performed within the previous 72 hours and results are available.
Thyroid function testing	X				TSH, (free T3, Free T4 if TSH not within normal limits). To be done within 72 hours prior to dosing and results must be reviewed prior to dosing.
Pregnancy Test	X		X		Serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) to be done at screening visit and within 24 hours prior to first dose and then every 4 weeks (± 1 week) regardless of dosing schedule.

Table 5.1-2: On-Treatment Procedural Outline (CA209672) - Part 1, Arm A: nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W combination

Procedure	Cycle 1 and beyond (1 cycle = 6 weeks)				Notes
	Day 1[a]	Day 15[a]	Day 29[a]	Day 42[a]	
Efficacy Assessments					
Tumor assessments				X	The scans must be performed every 6 weeks (between Days 35 and 42 of the cycle) from date of first dosing for the first 24 weeks, and then every 12 weeks (between Days 35 and 42 of the cycle) thereafter until disease progression (including treatment beyond progression) or unacceptable toxicity. This schedule should be followed even if treatment delay occurs. All PR or CR evaluations must be confirmed by a second scan performed u 4 weeks later. See Section 5.4 for further details.
CT/MRI (brain)	See Notes				Participants with a history of brain metastasis should have surveillance MRI per standard of care (approximately every 12 weeks, or sooner if clinically indicated). CT of the Brain (without and with contrast) can be performed if MRI is contraindicated. See Section 5.4.
Other Imaging (eg, Bone Scan)	See Notes				As clinically indicated per local standards. See Section 5.4 for further details.
Pharmacokinetic (PK) Assessments					
Blood PK Sampling	X				Refer to Table 5.5.1-1 for specific PK sampling time points. See Section 5.5.
Immunogenicity (ADA) Assessments					
Blood ADA Sample	X				Refer to Table 5.5.1-1 for specific ADA sampling time points. See Section 5.5.

Table 5.1-2: On-Treatment Procedural Outline (CA209672) - Part 1, Arm A: nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W combination

Procedure	Cycle 1 and beyond (1 cycle = 6 weeks)				Notes
	Day 1[a]	Day 15[a]	Day 29[a]	Day 42[a]	
Clinical Drug Supplies					
Nivolumab Administration	x	x	X		Those supplied by BMS or sourced by the investigator.
Ipilimumab Administration	x				Those supplied by BMS or sourced by the investigator.

[a] To be done ± 2 days of scheduled visit. Every effort should be made to schedule visits within the timeframe stated in the protocol. In the case that the visits cannot be within the timeframe stated in protocol then the treatment period study procedures can be performed ± 2 days of the scheduled visit.

Table 5.1-3: On-Treatment Procedural Outline (CA209672) - Part 1, Arms B and C – Arm B: nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W × 4, followed by nivolumab 240 mg Q2W, Arm C: nivolumab 1 mg/kg + ipilimumab 3 mg/kg Q3W × 4, followed by nivolumab 240 mg Q2W

Procedure	Cycles 1 to 2 Q3W (1 cycle = 6 wks)			Cycle 3+ Q2W (1 cycle = 6 wks)				Notes
	Day 1[a]	Day 22[a]	Day 42[a]	Day 1[a]	Day 15[a]	Day 29[a]	Day 42[a]	
Admission to Clinical Facility	x			x				For the purpose of PK sample collection, participants will be admitted to the clinical facility prior to dosing (Day -1) on Cycle 1/Day 1 and Cycle 2/ Day 22, and will remain in the clinical facility until 24 hrs after study drug administration.
Safety Assessments								
Targeted Physical Examination	x	x		x	x	x		Targeted examination must include at a minimum the following body systems: • Cardiovascular • Gastrointestinal • Pulmonary • Neurological exam for participants with brain metastases Obtain prior to each dose.
Physical Measurements	x	x		x	x	x		Weight only. Dose adjustments are required to be made in cycles 1 and 2 if there has been a > 10% percent weight change (increase or decrease) from the previous dose. Obtain prior to each dose.
Vital Signs and Oxygen Saturation	x	x		x	x	x		Includes body temperature, respiratory rate, and seated or supine blood pressure and heart rate, O2 saturation by pulse oximetry at rest. Blood pressure and heart rate should be measured after the participant has been resting quietly for at least 5 minutes. Vital signs should be taken as per institutional standard of care at visits and prior to, during, and after the infusion with nivolumab.
ECOG Performance Status	x	x		x	x	x		Obtain prior to each dose.

Table 5.1-3: On-Treatment Procedural Outline (CA209672) - Part 1, Arms B and C – Arm B: nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W × 4, followed by nivolumab 240 mg Q2W, Arm C: nivolumab 1 mg/kg + ipilimumab 3 mg/kg Q3W × 4, followed by nivolumab 240 mg Q2W

Procedure	Cycles 1 to 2 Q3W (1 cycle = 6 wks)			Cycle 3+ Q2W (1 cycle = 6 wks)				Notes
	Day 1[a]	Day 22[a]	Day 42[a]	Day 1[a]	Day 15[a]	Day 29[a]	Day 42[a]	
								See Appendix 2
Electrocardiograms (ECGs)	x			x				ECGs should be recorded after the participant has been supine for at least 5 minutes.
AE Assessment (including SAE Assessment)	x							Should occur at every visit throughout the study. All AEs (SAEs or non-serious AEs), including those associated with SARS-CoV-2 infection, must be collected continuously during the treatment period.
Review of Concomitant Medications	x							Should occur at every visit throughout the study.
Laboratory Tests								
Laboratory Tests	x	x		x	x	x		Within 72 hours prior to dosing. Include CBC w/differential and platelets; Full Chemistry Panel: LDH, AST, ALT, ALP, T.Bili, (Direct Bili if T.Bili > ULN) , BUN (serum urea level), creatinine, Ca+, Mg+, Na+, K+, Cl-, amylase, lipase, glucose, albumin, T.Protein To be done within 72 hours prior to dosing and results must be reviewed prior to dosing. Screening labs are acceptable if performed within the previous 72 hours and results are available.
Thyroid function testing	x			x				TSH, (free T3, Free T4 if TSH not within normal limits). To be done within 72 hours prior to dosing and results must be reviewed prior to dosing.
Pregnancy Test	x			x				Serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) to be done at screening visit and within

Table 5.1-3: On-Treatment Procedural Outline (CA209672) - Part 1, Arms B and C – Arm B: nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W × 4, followed by nivolumab 240 mg Q2W, Arm C: nivolumab 1 mg/kg + ipilimumab 3 mg/kg Q3W × 4, followed by nivolumab 240 mg Q2W

Procedure	Cycles 1 to 2 Q3W (1 cycle = 6 wks)			Cycle 3+ Q2W (1 cycle = 6 wks)				Notes
	Day 1[a]	Day 22[a]	Day 42[a]	Day 1[a]	Day 15[a]	Day 29[a]	Day 42[a]	
								24 hours prior to first dose and then every 4 weeks (± 1 week) regardless of dosing schedule.
Efficacy Assessments								
Tumor assessments			x				x	The scans must be performed every 6 weeks (between Days 35 and 42 of the cycle) from date of first dosing for the first 24 weeks, and then every 12 weeks (between Days 35 and 42 of the cycle) thereafter until disease progression (including treatment beyond progression) or unacceptable toxicity. This schedule should be followed even if treatment delay occurs. All PR or CR evaluations must be confirmed by a second scan performed ⩾ 4 weeks later. See Section 5.4 for further details.
CT/MRI (brain)	See Notes							Participants with a history of brain metastasis should have surveillance MRI per standard of care (approximately every 12 weeks, or sooner if clinically indicated). CT of the Brain (without and with contrast) can be performed if MRI is contraindicated. See Section 5.4
Other Imaging (eg, Bone Scan)	See Notes							As clinically indicated per local standards. See Section 5.4 for further details.
Pharmacokinetic (PK) Assessments								
Blood PK Sampling	x							Refer to Table 5.5.1-2 for specific PK sampling time points. See Section 5.5.

Table 5.1-3: On-Treatment Procedural Outline (CA209672) - Part 1, Arms B and C – Arm B: nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W × 4, followed by nivolumab 240 mg Q2W, Arm C: nivolumab 1 mg/kg + ipilimumab 3 mg/kg Q3W × 4, followed by nivolumab 240 mg Q2W

Procedure	Cycles 1 to 2 Q3W (1 cycle = 6 wks)			Cycle 3+ Q2W (1 cycle = 6 wks)				Notes
	Day 1[a]	Day 22[a]	Day 42[a]	Day 1[a]	Day 15[a]	Day 29[a]	Day 42[a]	
Immunogenicity (ADA) Assessments								
Blood ADA Sample	x (See note)							Refer to Table 5.5.1-2 for specific ADA sampling time points. See Section 5.5.
Clinical Drug Supplies								
Nivolumab Administration	x	x		x	x	x		Those supplied by BMS or sourced by the investigator. Arm B: nivo 3 mg/kg Q3W × 4 followed by 240 mg Q2W Arm C: nivo 1 mg/kg Q3W × 4 followed by 240 mg Q2W
Ipilimumab Administration	x	x						Those supplied by BMS or sourced by the investigator. Arm B: ipi 1 mg/kg Q3W × 4 Arm C:ipi 3 mg/kg Q3W × 4

[a] To be done ± 2 days of scheduled visit. Every effort should be made to schedule visits within the timeframe stated in the protocol. In the case that the visits cannot be within the timeframe stated in protocol then the treatment period study procedures can be performed ± 2 days of the scheduled visit.

Table 5.1-4: On-Treatment Procedural Outline (CA209672) - Part 2, Arm D: nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W × 4, followed by nivolumab 240 mg Q2W

Procedure	Cycles 1 to 2 Q3W (1 cycle = 6 wks)			Cycle 3+ Q2W (1 cycle = 6 wks)				Notes
	Day 1[a]	Day 22[a]	Day 42[a]	Day 1[a]	Day 15[a]	Day 29[a]	Day 42[a]	
Safety Assessments								
Targeted Physical Examination	x	x		x	x	x		Targeted examination must include at a minimum the following body systems: • Cardiovascular • Gastrointestinal • Pulmonary • Neurological exam for participants with brain metastases Obtain prior to each dose.
Physical Measurements	x	x		x	x	x		Weight only. Dose adjustments are required to be made in cycles 1 and 2 if there has been a > 10% percent weight change (increase or decrease) from the previous dose. Obtain prior to each dose.
Vital Signs	x	x		x	x	x		Includes body temperature, respiratory rate, and seated or supine blood pressure and heart rate. Blood pressure and heart rate should be measured after the participant has been resting quietly for at least 5 minutes. Vital signs should be taken as per institutional standard of care at visits and prior to, during, and after the infusion with nivolumab.
ECOG Performance Status	x	x		x	x	x		See note in screening procedures.
AE Assessment (including SAE Assessment)	x							Should occur at every visit throughout the study. All AEs (SAEs or non-serious AEs), including those associated with SARS-CoV-2 infection, must be collected continuously during the treatment period.

Table 5.1-4: On-Treatment Procedural Outline (CA209672) - Part 2, Arm D: nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W × 4, followed by nivolumab 240 mg Q2W

Procedure	Cycles 1 to 2 Q3W (1 cycle = 6 wks)			Cycle 3+ Q2W (1 cycle = 6 wks)				Notes
	Day 1[a]	Day 22[a]	Day 42[a]	Day 1[a]	Day 15[a]	Day 29[a]	Day 42[a]	
Review of Concomitant Medications	x							Should occur at every visit throughout the study.
Laboratory Tests								
Laboratory Tests	x	x		x	x	x		Within 72 hours prior to dosing. Include CBC w/differential and platelets; Full Chemistry Panel: LDH, AST, ALT, ALP, T.Bili, (Direct Bili if T.Bili > ULN), BUN (or serum urea level), creatinine, Ca+, Mg+, Na+, K+, Cl-, amylase, lipase, glucose, albumin, T.Protein To be done within 72 hours prior to dosing and results must be reviewed prior to dosing. Screening labs are acceptable if performed within the previous 72 hours and results are available.
Thyroid function testing	x			x				TSH, (free T3, Free T4 if TSH not within normal limits). To be done within 72 hours prior to dosing and results must be reviewed prior to dosing.
Pregnancy Test	x			x				Serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) to be done at screening visit and within 24 hours prior to first dose and then every 4 weeks (± 1 week) regardless of dosing schedule.
Efficacy Assessments								
Tumor assessments[b]			x				x	The scans must be performed every 6 weeks (between Days 35 and 42 of the cycle) from date of first dosing for the first 24 weeks, and then every 12 weeks (between Days 35 and 42 of the cycle) thereafter (including treatment beyond progression) until initiation of subsequent anti-cancer treatment. This schedule should be followed even if treatment delay occurs.

Table 5.1-4: On-Treatment Procedural Outline (CA209672) - Part 2, Arm D: nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W × 4, followed by nivolumab 240 mg Q2W

Procedure	Cycles 1 to 2 Q3W (1 cycle = 6 wks)			Cycle 3+ Q2W (1 cycle = 6 wks)				Notes
	Day 1[a]	Day 22[a]	Day 42[a]	Day 1[a]	Day 15[a]	Day 29[a]	Day 42[a]	
								All PR or CR evaluations must be confirmed by a second scan performed u 4 weeks later. All imaging scans should be submitted to a third party for BICR assessment until initiation of subsequent anti-cancer treatment. See Section 5.4 for further details.
CT/MRI (brain)	See Notes							Participants with a history of brain metastasis should have surveillance MRI per standard of care (approximately every 12 weeks, or sooner if clinically indicated). CT of the Brain (without and with contrast) can be performed if MRI is contraindicated. See Section 5.4
Other Imaging (eg, Bone Scan)	See Notes							As clinically indicated per local standards. See Section 5.4 for further details.
Pharmacokinetic (PK) Assessments[b]								
Blood PK Sampling	x							Refer to Table 5.5.1-3 for specific PK sampling time points. See Section 5.5.
Immunogenicity (ADA) Assessments[b]								
Blood ADA Sampling	x							Refer to Table 5.5.1-3 for specific ADA sampling time points. See Section 5.5.
Outcomes Research Assessments								
QLQ-C30 Questionnaire	x			x				Assessed prior to dosing every 6 weeks. Questionnaires to be administered at the start of the clinic visit before the participant sees the physician and before any study-

Table 5.1-4: On-Treatment Procedural Outline (CA209672) - Part 2, Arm D: nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W × 4, followed by nivolumab 240 mg Q2W

Procedure	Cycles 1 to 2 Q3W (1 cycle = 6 wks)			Cycle 3+ Q2W (1 cycle = 6 wks)				Notes
	Day 1[a]	Day 22[a]	Day 42[a]	Day 1[a]	Day 15[a]	Day 29[a]	Day 42[a]	
								related procedures are done (with the exception of procedures completed 72 hours prior to visit). If a dose is delayed, the administration of the participant-reported outcome measures scheduled for that same time point should also be delayed to coincide with when that time point's dosing actually occurs.
EQ-5D-3L Questionnaire	x			x				Assessed prior to dosing every 6 weeks. Questionnaires to be administered at the start of the clinic visit before the participant sees the physician and before any study-related procedures are done (with the exception of procedures completed 72 hours prior to visit). If a dose is delayed, the administration of the participant-reported outcome measures scheduled for that same time point should also be delayed to coincide with when that time point's dosing actually occurs.
Clinical Drug Supplies								
Nivolumab Administration	x	x		x	x	x		Those supplied by BMS or sourced by the investigator.
Ipilimumab Administration	x	x						Those supplied by BMS or sourced by the investigator.

[a] To be done ± 2 days of scheduled visit. Every effort should be made to schedule visits within the timeframe stated in the protocol. In the case that the visits cannot be within the timeframe stated in protocol then the treatment period study procedures can be performed ± 2 days of the scheduled visit.

[b] As of Protocol Amendment 07: Assessments necessary for monitoring safety will continue per protocol until the follow-up visit 2 or 100 days after study drug discontinuation, whichever occurs later. Collection of PK and immunogenicity data is not applicable. Analyses of PK and immunogenicity will be based on the samples analyzed before implementation of protocol amendment 07.

Table 5.1-5: Follow-Up Period (CA209672) –Part 1, Arm A and C

Procedure	Follow-Up Visit 1[a] Last Visit + 30 days (±7 days)	Follow-Up Visit 2 Previous Follow-up Visit + 70 Days (± 7 days)	Notes
Safety Assessments			
Targeted Physical Examination, Measurements, Vital Signs, Oxygen Saturation and Performance Status	x	x	To assess for potential late emergent study drug related issues. Weight, BP, HR, temperature, oxygen saturation and ECOG status. Targeted physical examination to be performed only as clinically indicated.
Adverse Events Assessment (Including SAE)	x	x	All AEs to be collected for 100 days after last dose of nivolumab treatment. Participants will be followed for all SAEs, non-serious AEs of special interest, and all AEs associated with confirmed or suspected SARS-CoV-2 infection until resolution, the condition stabilizes, the event is otherwise explained, the event is deemed irreversible, the participant is lost to follow-up, or for suspected cases, until SARS-CoV-2 infections is ruled out.
Review of Concomitant Medications	x	x	
ECG	x		As clinically indicated or for study drug related toxicities.
Laboratory Tests	See Notes		On site/local laboratory testing. To be performed at FU1. To be repeated at FU2 if study drug related toxicity persists. CBC w/differential; Full Chemistry Panel: LDH, AST, ALT, ALP, T.Bili, (Direct Bili if T.Bili > ULN), BUN (or serum urea level), creatinine, Ca+, Mg+, Na+, K+, Cl-, glucose, albumin, T.Protein
Thyroid function	See Notes		On site/local laboratory testing. To be performed at FU1. To be repeated at FU2 if study drug related toxicity persists. TSH, (free T3, Free T4 if TSH not within normal limits)

Table 5.1-5: Follow-Up Period (CA209672) –Part 1, Arm A and C

Procedure	Follow-Up Visit 1[a] Last Visit + 30 days (±7 days)	Follow-Up Visit 2 Previous Follow-up Visit + 70 Days (± 7 days)	Notes
Pregnancy Test	x	x	Serum or urine
Pharmacokinetic (PK) Assessments[b]			
Blood PK Sampling	Refer to Table 5.5.1-2 for specific PK sampling time points.		
Immunogenicity (ADA) Assessments[b]			
Blood ADA Sample	Refer to Table 5.5.1-1 for specific ADA sampling time points. See Section 5.5.		

[a] When a participant discontinues study drug treatment, all remaining visits of that treatment cycle should be completed (without infusion and with only a single pharmacokinetic sample taken at applicable visits), and the participant should enter the Follow-up Period (Follow-up 1 and then Follow-up 2). When a participant is withdrawn from the study (during the Treatment or Follow-up Period), all evaluations associated with that study visit should be performed and the date and reason for study discontinuation should be documented on the CRF. Follow-up visit #1 (FU1) occurs approximately 30 days after the last dose (± 7 days) or coincides 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 70 days (± 7 days) after FU1. Both Follow Up visits should be conducted in person.

[b] As of Protocol Amendment 07: Assessments necessary for monitoring safety will continue per protocol until FU2 or 100 days after study drug discontinuation, whichever occurs later. Collection of PK and immunogenicity data is not applicable. Analyses of PK and immunogenicity will be based on the samples analyzed before implementation of protocol amendment 07.

Table 5.1-6: Follow-Up Period (CA209672) –Part 1, Arm B

Procedure	Follow-Up Visit 1[a] Last Visit + 30 days (±7 days)	Follow-Up Visit 2 Previous Follow-up Visit + 70 Days (± 7 days)	Notes
Safety Assessments[b]			
Targeted Physical Examination, Measurements, Vital Signs, Oxygen Saturation and Performance Status	x	x	To assess for potential late emergent study drug related issues. Weight, BP, HR, temperature, oxygen saturation and ECOG status. Targeted physical examination to be performed only as clinically indicated.
Adverse Events Assessment (Including SAE)	x	x	All AEs to be collected for 100 days after last dose of nivolumab treatment.
Review of Concomitant Medications	x	x	
ECG	x		As clinically indicated or for study drug related toxicities.
Laboratory Tests	See Notes		On site/local laboratory testing. To be performed at FU1. To be repeated at FU2 if study drug related toxicity persists. CBC w/differential; Full Chemistry Panel: LDH, AST, ALT, ALP, T.Bili, (Direct Bili if T.Bili > ULN), BUN (or serum urea level), creatinine, Ca+, Mg+, Na+, K+, Cl-, glucose, albumin, T.Protein
Thyroid function	See Notes		On site/local laboratory testing. To be performed at FU1. To be repeated at FU2 if study drug related toxicity persists. TSH, (free T3, Free T4 if TSH not within normal limits)
Pregnancy Test	x	x	Serum or urine

Table 5.1-6: Follow-Up Period (CA209672) –Part 1, Arm B

Procedure	Follow-Up Visit 1[a] Last Visit + 30 days (±7 days)	Follow-Up Visit 2 Previous Follow-up Visit + 70 Days (± 7 days)	Notes
Participant Status			
Survival Status and Subsequent Therapy Information	x	x	May be accomplished by visit, phone contact, or email.
Pharmacokinetic (PK) Assessments[b]			
Blood PK Sampling	Refer to Table 5.5.1-2 for specific PK sampling time points.		
Immunogenicity (ADA) Assessments[b]			
Blood ADA Sample	Refer to Table 5.5.1-1 for specific ADA sampling time points. See Section 5.5.		

[a] When a participant discontinues study drug treatment, all remaining visits of that treatment cycle should be completed (without infusion and with only a single pharmacokinetic sample taken at applicable visits), and the participant should enter the Follow-up Period (Follow-up 1 and then Follow-up 2). When a participant is withdrawn from the study (during the Treatment or Follow-up Period), all evaluations associated with that study visit should be performed and the date and reason for study discontinuation should be documented on the CRF. Follow-up visit #1 (FU1) occurs approximately 30 days after the last dose (± 7 days) or coincides 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 70 days (± 7 days) after FU1. Both Follow Up visits should be conducted in person.

[b] As of Protocol Amendment 07: Assessments necessary for monitoring safety will continue per protocol until FU2 or 100 days after study drug discontinuation, whichever occurs later. Collection of PK and immunogenicity data is not applicable. Analyses of PK and immunogenicity will be based on the samples analyzed before implementation of protocol amendment 07.

Table 5.1-7: Follow-Up Period (CA209672) –Part 2, Arm D

Procedure	Follow-Up Visit 1[a] Last Visit + 30 days (±7 days)	Follow-Up Visit 2 Previous Follow-up Visit + 70 Days (± 7 days)	Notes
Safety Assessments[b]			
Targeted Physical Examination, Measurements, Vital Signs, and Performance Status	x	x	To assess for potential late emergent study drug related issues. Weight, BP, HR, temperature, and ECOG status. Targeted physical examination to be performed only as clinically indicated.
Adverse Events Assessment (Including SAE)	x	x	All AEs to be collected for 100 days after last dose of nivolumab treatment. For participants assigned to treatment and never treated with study drug, SAEs should be collected for 30 days from the date of treatment assignment.
Review of Concomitant Medications	x	x	
ECG	x		As clinically indicated or for study drug related toxicities.
Laboratory Tests	See Notes		On site/local laboratory testing. To be performed at FU1. To be repeated at FU2 if study drug related toxicity persists. CBC w/differential; Full Chemistry Panel: LDH, AST, ALT, ALP, T.Bili, (Direct Bili if T.Bili > ULN), BUN (or serum urea level), creatinine, Ca+, Mg+, Na+, K+, Cl-, glucose, albumin, T.Protein
Thyroid function	See Notes		On site/local laboratory testing. To be performed at FU1. To be repeated at FU2 if study drug related toxicity persists. TSH, (free T3, Free T4 if TSH not within normal limits)
Pregnancy Test	x	x	Serum or urine

Table 5.1-7: Follow-Up Period (CA209672) –Part 2, Arm D

Procedure	Follow-Up Visit 1[a] Last Visit + 30 days (±7 days)	Follow-Up Visit 2 Previous Follow-up Visit + 70 Days (± 7 days)	Notes
Efficacy Assessments			
Tumor assessments[b]	Participants who enter the follow-up period will continue to have tumor imaging assessments by investigators and BICR as per on-treatment schedule: every 6 weeks from date of first dosing for the first 24 weeks, and then every 12 weeks thereafter until initiation of subsequent anti-cancer treatment or until 100 days post study drug discontinuation. See Section 5.4 for details on methodology.		
Brain Imaging	Participants with a history of brain metastasis or symptoms should have surveillance MRI per standard of care (approximately every 12 weeks) or sooner if clinically indicated. See Section 5.4 for further details. No brain imaging beyond 100 days post study drug discontinuation is necessary.		
Other Imaging (eg., Bone Scan)	As clinically indicated per local standards. See Section 5.4 for further details. No other imaging beyond 100 days post study drug discontinuation is necessary.		
Outcomes Research Assessments			
QLQ-C30 Questionnaire	x	x	No collection beyond 100 days post study drug discontinuation is necessary.
EQ-5D-3L Questionnaire	x	x	Can be collected either during a clinic visit or by telephone. No collection beyond 100 days post study drug discontinuation is necessary.
Participant Status			
Survival Status and Subsequent Therapy Information	x	x	May be accomplished by visit, phone contact, or email. No collection beyond 100 days post study drug discontinuation is necessary.

[a] When a participant discontinues study drug treatment, all remaining visits of that treatment cycle should be completed (without infusion and with only a single pharmacokinetic sample taken at applicable visits), and the participant should enter the Follow-up Period (Follow-up 1 and then Follow-up 2). When a participant is withdrawn from the study (during the Treatment or Follow-up Period), all evaluations associated with that study visit should be performed and the date and reason for study discontinuation should be documented on the CRF. Follow-Up Visit #1 (FU1) occurs approximately 30 days (± 7 days) after last dose or coinciding

with the date of discontinuation (± 7 days) if date of discontinuation is greater than 35 days after last dose. Follow-Up Visit #2 (FU2) occurs approximately 70 days (± 7 days) after FU1. Both Follow Up visits should be conducted in person.

[b] As of Protocol Amendment 07: Assessments necessary for monitoring safety and tumor assessments will continue per protocol until FU2 or 100 days after study drug discontinuation, whichever occurs later.

5.1.1 Retesting During Screening or Lead-in Period

This study is not actively enrolling participants.

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

Any new result will override the previous result (ie, the most current result prior to dosing) and 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 5.1-1, 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.

5.2 Study Materials

The following materials will be provided at study start:

- NCI CTCAE version 4.0
- Nivolumab/ipilimumab IBs
- Laboratory manuals for collection and handling of blood (including PK, biomarker, and immunogenicity) and tissue specimens
- Site manual for operation of IVRS
- Enrollment worksheets
- Serious Adverse Event (or eSAE) CRF pages
- Pregnancy Surveillance Forms

The site will provide all materials required for accurate source documentation of study activities and for housing the participants during the study. The site will source marketed product from a single commercial lot.

BMS will provide a BMS-approved protocol and any amendments or administrative letters (if required). Case report forms (electronic) will be provided by BMS. The central laboratory will provide labels and tubes for the collection of blood samples for PK analysis.

5.3 Safety Assessments

At baseline, a medical history will be obtained to capture relevant underlying conditions. Baseline signs and symptoms are those that are assessed within 2 weeks prior to dosing. The baseline physical examination should include weight, height, BP, HR, and temperature. These should be performed within 28 days of treatment. Concomitant medications will be collected from within 2 weeks prior to treatment assignment through the study treatment period.

Testing for asymptomatic SARS-CoV-2 infection, for example by reverse transcription polymerase chain reaction (RT-PCR) or viral antigen, is not required. However, some participants may develop suspected or confirmed symptomatic SARS-CoV-2 infection or be discovered to

have asymptomatic SARS-CoV-2 infection during the screening period. In such cases, participants may be eligible for the study after recovery from infection or completion of quarantine period in case of asymptomatic infection/potential exposure.

Toxicity assessments will be continuous during the treatment phase until 100 days (equal to approximately 5 half-lives of nivolumab) after the last dose of nivolumab.

Adverse events and laboratory values will be graded according to the NCI CTCAE version 4.0.

Vital signs should be taken as per institutional standard of care at visits and prior to, during, and after the infusion with nivolumab. The start and stop time of the study drug infusion should be documented. If there are any new or worsening clinically significant changes since the last exam, report these changes on the appropriate AE or SAE page.

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

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

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

5.3.1 Laboratory Test Assessments

A central/local laboratory will perform the analyses and will provide reference ranges for these tests.

Results of clinical laboratory tests performed on Day -1 visit must be available prior to dosing.

Results of all laboratory tests required by this protocol must be provided to BMS, either recorded on the laboratory pages of the CRF or by another mechanism as agreed upon between the investigator and BMS (eg, provided electronically). If the units of a test result differ from those printed on the CRF, the recorded laboratory values must specify the correct units. Any abnormal laboratory test result considered clinically significant by the investigator must be recorded on the appropriate AE page of the CRF (see Section 6.3).

Please refer to Table 5.1-1, Table 5.1-2, Table 5.1-3, Table 5.1-4, Table 5.1-5, Table 5.1-6, and Table 5.1-7 for required laboratory tests and schedule.

5.4 Efficacy Assessments

5.4.1 Imaging and Clinical Assessment

Change in tumor measurements and tumor response will be assessed by investigators (Part 1) or by both BICR and investigators (Part 2) using the RECIST 1.1 criteria (Appendix 1).

Study evaluations will take place in accordance with Table 5.1-1, Table 5.1-2, Table 5.1-3, Table 5.1-4, Table 5.1-5, Table 5.1-6, and Table 5.1-7.

Baseline assessments should be performed within 28 days before date of first dosing. Chest, abdomen, pelvis and any clinically indicated sites determined by the investigator should be assessed at baseline. Subsequent assessments should utilize the same imaging modality. For Part 1, tumor response should be evaluated every 6 weeks from date of first dosing for the first 24 weeks (between days 35 and 42 of the cycle), and then every 12 weeks (between days 35 and 42 of the cycle) thereafter until disease progression (including treatment beyond progression) or unacceptable toxicities. For Part 2, tumor response should be evaluated every 6 weeks (between days 35 and 42 of the cycle) from date of first dosing for the first 24 weeks and then every 12 weeks (between days 35 and 42 of the cycle) thereafter until initiation of subsequent anti-cancer treatment.

Tumor assessments for all participants should continue as per protocol even if dosing is delayed or discontinued. Changes in tumor measurements and tumor responses will be assessed by the same investigator per study design using RECIST 1.1 criteria. Investigators will also report the number and size of new lesions that appear while on study. The time point of tumor assessments will be reported on the eCRF based on the investigator's assessment using RECIST 1.1 criteria (See Appendix 1). 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 35 days on study from date of first dosing to the date of the first imaging assessment.

Tumor assessments at other time points may be performed if clinically indicated, and should be submitted to the central imaging vendor as soon as possible for Part 2. Unscheduled CT/MRI should be submitted to central imaging vendor. X-Ray and bone scans that clearly demonstrate interval progression of disease, most commonly as unequivocal lesions that are unmistakably new since the prior CT/MRI, should be submitted to central imaging vendor. Otherwise, radiographs do not need to be submitted centrally.

5.4.2 Imaging Assessment by BICR for Part 2

For Part 2, images will be submitted to a central imaging vendor for blinded independent central review (BICR) at any time during the study. Sites should be qualified prior to scanning the first study participant and understand the image acquisition guidelines and submission process as outlined in the CA209-672 Imaging Manual to be provided by the vendor.

Sites should submit all scans to a BICR, preferably within 7 days of scan acquisition, throughout the duration of the study. BICR will review scans, and remain blinded to treatment arm and investigator assessment of submitted scans.

Participants should undergo tumor assessments by both investigators and BICR continuously according to the protocol-specified (Section 5.1) schedule, or sooner if clinically indicated. Scans should be submitted to BICR until initiation of subsequent anti-cancer therapy. Collect any additional imaging that may demonstrate tumor response or progression (including scans performed at unscheduled timepoints and/or at an outside institution) for RECIST 1.1 tumor assessment and submit to the BICR.

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

5.4.3 Methods of Measurement

CT with contrast of the chest, abdomen, pelvis, and any clinically indicated sites are to be performed for tumor assessments at the time points outlined in Table 5.1-1, Table 5.1-2, Table 5.1-3, Table 5.1-4, Table 5.1-5, Table 5.1-6 and Table 5.1-7.

CT scans should be acquired with ≤5 mm slices with no intervening gap (contiguous). Should a participant have a contraindication for CT IV contrast, a non-contrast CT of the chest and a contrast enhanced MRI of the abdomen and pelvis may be obtained. MRI's should be acquired with slice thickness of ≤ 5 mm and < 2 mm gap (preferably no gap/contiguous). Every attempt should be made to image each participant using an identical acquisition protocol on the same scanner for all imaging time points.

MRI brain scans during on-study treatment and follow up periods are required only if there is a prior history of lesions present at Screening, or as clinically indicated for new signs and symptoms that suggest CNS involvement.

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 investigator as per standard medical/clinical judgment.

5.5 Pharmacokinetic and Immunogenicity Assessments

Collection of PK and immunogenicity data is not applicable per Protocol Amendment 07. Analyses will be based on the samples analyzed before implementation of protocol amendment 07. The following information refers to the original study design and is not applicable per Protocol Amendment 07.

5.5.1 Pharmacokinetic and Immunogenicity Collection & Processing

Table 5.5.1-1 (Part 1, Arm A), Table 5.5.1-2 (Part 1, Arms B and C), and Table 5.5.1-3 (Part 2, Arm D) list the sampling schedule to be followed to assess the PK and immunogenicity of nivolumab and ipilimumab. Blood samples should be drawn from a site other than the infusion site (ie, contralateral arm) on days of infusion. All predose samples should be collected just prior to the start of infusion administration, and end-of-infusion (EOI) samples should be collected as close to EOI as possible (preferably within 2 minutes prior to EOI) from the contralateral arm (ie, the arm not for the infusion). On-treatment PK samples are intended to be drawn relative to actual dosing days; if a dose occurs on a different day within the cycle due to delays or minor schedule adjustments, PK and ADA samples should be adjusted accordingly. 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. If the infusion was interrupted, the reason for interruption should also be documented on the CRF. Blood samples will be processed to collect serum. The serum samples will be analyzed for nivolumab and ipilimumab by validated methods. Further

details of blood collection, labeling, processing, storage and shipping will be provided to the site in the procedure manual.

Table 5.5.1-1: Pharmacokinetics and Immunogenicity Sampling Schedule for Nivolumab and Ipilimumab (Part 1, Arm A)

CYCLE (1 CYCLE = 6 WEEKS)	Study Day of Sample Collection[a]	Event	Time (Relative To Start of Infusion of Nivolumab) Hour: Min	PK Blood Sample for nivo[b]	PK Blood Sample for ipi[b]	ADA Blood Sample for nivo[b]	ADA Blood Sample for ipi[b]
Cycle 1 Week 1	1	Predose[c]	00:00	X	X	X	X
		EOI of ipi[d]	01:30	X	X		
			08:00	X	X		
	2		24:00	X	X		
	3		48:00	X	X		
	5		96:00	X	X		
Cycle 1 Week 2	8		168:00	X	X		
Cycle 1 Week 3	15	predose[c]	00:00	X	X	X	X
Cycle 2 Week 3	15	predose[c]	00:00	X	X	X	X
Cycle 3 Week 1	1	predose[c]	00:00	X	X		
		EOI of ipi[d]	01:30	X	X		
			08:00	X	X		
	2		24:00	X	X		
	3		48:00	X	X		
	5		96:00	X	X		
Cycle 3 Week 2	8		168:00	X	X		
Cycle 3 Week 3	15	predose[c]	00:00	X	X		
Cycle 4 Week 3	15	predose[c]	00:00	X	X	X	X
Day 15 of every 3rd cycle after cycle 4 week 3 until discontinuation of Study Treatment	15	predose[c]	00:00	X	X	X	X

Table 5.5.1-1: Pharmacokinetics and Immunogenicity Sampling Schedule for Nivolumab and Ipilimumab (Part 1, Arm A)

CYCLE (1 CYCLE = 6 WEEKS)	Study Day of Sample Collection[a]	Event	Time (Relative To Start of Infusion of Nivolumab) Hour: Min	PK Blood Sample for nivo[b]	PK Blood Sample for ipi[b]	ADA Blood Sample for nivo[b]	ADA Blood Sample for ipi[b]
Follow-Up Visits 1 & 2 (EXCEPT for participants that WITHDRAW CONSENT)				X	X	X	X

[a] If a participant permanently discontinues both nivolumab and ipilimumab study drug treatment during the sampling period, they will move to sampling at follow-up visits.

[b] If ipilimumab is discontinued and nivolumab continues, then nivolumab PK and ADA samples are continued to be collected, and ipilimumab PK and ADA should be collected only for the next 2 predose time points corresponding to nivolumab collection.

[c] Predose samples should be collected on the day of dosing just prior to the start of the infusion (preferably within 30 minutes). For combination dosing, predose samples for both nivolumab and ipilimumab should be collected prior to the start of nivo infusion. 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.

[d] EOI: End of Infusion. This sample should be collected immediately prior to stopping the infusion. For combination dosing, both nivo and ipi EOI samples should be collected immediately prior to stopping the ipilimumab infusion (preferably within 2 minutes prior to the end of ipi infusion). In the event of a delay in ipi infusion administration beyond 30 min, the EOI samples should be collected immediately prior to the actual END of the infusion. Ipilimumab infusion should be started no less than 30 min after stopping the nivolumab infusion.

Table 5.5.1-2: Pharmacokinetics and Immunogenicity Sampling Schedule for Nivolumab and Ipilimumab (Part 1, Arms B and C)

CYCLE (1 CYCLE =6 WEEKS)	Study Day of Sample Collection[a]	Event	Time (Relative To Start of Infusion of Nivolumab) Hour: Min	PK Blood Sample for nivo	PK Blood Sample for ipi	ADA Blood Sample for nivo	ADA Blood Sample for ipi
Cycle 1 Week 1	1	Predose[b]	00:00	X	X	X	X
		EOI of ipi[c]	01:30	X	X		
			08:00	X	X		
	2		24:00	X	X		
	3		48:00	X	X		
	5		96:00	X	X		

Table 5.5.1-2: Pharmacokinetics and Immunogenicity Sampling Schedule for Nivolumab and Ipilimumab (Part 1, Arms B and C)

CYCLE (1 CYCLE =6 WEEKS)	Study Day of Sample Collection[a]	Event	Time (Relative To Start of Infusion of Nivolumab) Hour: Min	PK Blood Sample for nivo	PK Blood Sample for ipi	ADA Blood Sample for nivo	ADA Blood Sample for ipi
Cycle 1 Week 2	8		168:00	X	X		
Cycle 1 Week 3	15		336:00	X	X		
Cycle 1 Week 4	22	predose[b]	00:00	X	X		
Cycle 2 Week 1	1	predose[b]	00:00	X	X	X	X
Cycle 2 Week 4	22	predose[b]	00:00	X	X		
		EOI of ipi[c]	01:30	X	X		
			08:00	X	X		
	23		24:00	X	X		
	24		48:00	X	X		
	26		96:00	X	X		
Cycle 2 Week 5	29		168:00	X	X		
Cycle 2 Week 6	36		336:00	X	X		
Cycle 3 Week 1	1	predose[b]	00:00	X	X	X	X
Cycle 5 Week 1[d]	1	predose[b]	00:00	X		X	
Day 1 of every 3rd cycle (18 weeks) after C5 until discontinuation of Study Treatment[d]	1	predose[b]	00:00	X		X	
Follow-Up Visits 1 & 2 (EXCEPT for participants who WITHDRAW CONSENT)[d]				X		X	

[a] If a participant permanently discontinues study drug treatment during the sampling period, they will move to sampling at follow-up visits.

[b] Predose samples should be collected on the day of dosing just prior to the start of the infusion (preferably within 30 minutes). For combination dosing, predose samples for both nivo and ipi should be collected prior to the start of nivo infusion. 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

[c] EOI: End of Infusion. This sample should be taken immediately prior to stopping the infusion. For combination dosing, both nivo and ipi EOI samples should be collected immediately prior to stopping the ipilimumab infusion (preferably within 2 minutes prior to the end of ipi infusion). In the event of a delay in ipi infusion administration beyond 30 min, the EOI samples should be collected immediately prior to the actual END of the infusion. Ipilimumab infusion should be started no less than 30 min after stopping the nivolumab infusion.

[d] Only nivolumab PK and ADA blood samples will be collected from Cycle 5 and beyond. Samples are not required to be collected for follow-up visits.

Table 5.5.1-3: Pharmacokinetics and Immunogenicity Sampling Schedule for Nivolumab and Ipilimumab (Part 2, Arm D)

CYCLE (1 CYCLE = 6 WEEKS)	Study Day of Sample Collection	Event	Time (Relative to Start of Infusion of Nivolumab) Hour: Min	PK Blood Sample for Nivo	PK Blood Sample for Ipi	ADA Blood Sample for Nivo	ADA Blood Sample for Ipi
Cycle 1 Week 1	1	Predose[a]	00:00	X	X	X	X
Cycle 1 Week 4	22	Predose[a]	00:00	X	X		
Cycle 2 Week	1	Predose[a]	00:00	X	X	X	X
Cycle 3 Week 1	1	Predose[a]	00:00	X	X	X	X
Cycle 5 Week 1	1	Predose[a]	00:00	X	X	X	X
Week 1 Day 1 of every 4th cycle (24 weeks) after C5 until discontinuation of study treatment	1	Predose[a]	00:00	X		X	

Note: Samples are not required to be collected for Arm D per Protocol Amendment 07.

[a] Predose samples should be collected on the day of dosing just prior to the start of the infusion (preferably within 30 minutes). For combination dosing, predose samples for both nivo and ipi should be collected prior to the start of nivo infusion. 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.

5.5.2 Pharmacokinetic Sample Analyses

The serum samples will be analyzed for nivolumab and ipilimumab by validated methods.

5.5.3 Labeling and Shipping of Biological Samples

Detailed instructions for the pharmacokinetic blood collection, labeling, processing, storage, and shipping will be provided to the site in the procedure manual.

5.6 Biomarker Assessments

5.6.1 Part 1

Arms A, B, and C: Not applicable.

5.6.2 Part 2

Tumor biopsy specimens will be obtained from consenting participants prior to treatment with nivolumab combined with ipilimumab to confirm MSI/MMR status in central lab.

Fresh biopsies is preferred for biomarker analysis if accessible and deemed safe by the investigator. The fresh biopsies submitted to central lab must be the same tissue sample as was used for local MSI/MMR testing.

If fresh biopsy cannot be obtained, archived tumor tissue (a block or 10 slides) prior to therapy is acceptable only if the archived tissue is the same tissue that was used for local MSI/MMR testing.

Central lab must confirm receipt of evaluable tumor tissue prior to vial assignment.

NOTE: Exceptions to above requirements need to be discussed with the medical monitor and will be handled in a case-by-case basis. An additional source of tumor tissue must be available if the tissue obtained adhering to the above guidelines can't be tested due to poor quality or quantity.

5.7 Exploratory Biomarker Assessments

Not applicable.

5.8 Outcomes Research Assessments

5.8.1 Part 1

Not applicable.

5.8.2 Part 2

Outcomes research data including health-related quality of life and participant-reported symptom burden provide a more complete understanding of the impact of treatment by incorporating the patients' perspective. These data offer insights into the patient experience that may not be captured through physician reporting. The EQ-5D (EQ-5D-3L) will be collected in order to assess the impact of nivolumab on generic health-related quality of life, and the data will be used for populating health economic models, most notably, cost effectiveness analysis. The QLQ-C30 will be collected in order to assess cancer-specific, health-related quality of life. The combination of the generic scale for general health status and economic evaluation and the cancer specific scale will provide a robust outcomes research package.

The QLQ-C30 is a 30-item instrument comprising six functional scales (physical functioning, cognitive functioning, emotional functioning, role functioning, social functioning, and global quality of life) as well as nine symptom scales (fatigue, pain, nausea/vomiting, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Except for the overall health status

and global quality of life items, responses for all items are 4-point categorical scales ranging from 1 (Not at all) to 4 (Very much). The overall health status/quality of life responses are 7-point Likert scales. It has gone through appropriate psychometric testing and is available in over 81 languages.

General health status will be measured using the EQ-5D. The EQ-5D is a standardized instrument for use as a measure of self-reported general health status. The EQ-5D comprises five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety) and a visual analog scale (VAS). The utility data generated from the EQ-5D is recommended for and commonly used in cost effectiveness analysis. 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.

Please refer to procedural tables found in Section 5.1 for information regarding the timing of outcomes research assessments using the EQ-5D-3L and QLQ-C30.

5.9 Other Assessments

5.9.1 Immunogenicity Assessment

Collection of immunogenicity data is not applicable per Protocol Amendment 07. Analyses will be based on the samples analyzed before implementation of protocol amendment 07. The following information refers to the original study design and is not applicable per Protocol Amendment 07.

Blood samples for immunogenicity analysis will be collected from all participants at time points specified in Table 5.5.1-1, Table 5.5.1-2, and Table 5.5.1-3. Serum will be analyzed by validated immunogenicity assays. All on-treatment immunogenicity sampling time points are intended to align with days on which study drug is administered, if dosing occurs on a different day, the sampling should be adjusted accordingly. Samples may be analyzed for neutralizing antibodies by a validated method. The corresponding serum samples designated for either PK, immunogenicity, or biomarker assessments may also be used for any of those analyses, if required (eg, insufficient sample volume to complete testing, follow up on suspected immunogenicity related AE, etc.).

Detailed instructions for the immunogenicity blood collection, labeling, processing, storage, and shipping will be provided to the site in the procedure manual.

5.10 Additional Research Collection

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.

6 ADVERSE EVENTS

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a clinical investigation participant administered study drug 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 drug, whether or not considered related to the study drug.

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

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The causal relationship can be one of the following:

Related: There is a reasonable causal relationship between study drug administration and the AE.

Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination or evaluation of a participant. (In order to prevent reporting bias, participants should not be questioned regarding the specific occurrence of one or more AEs.)

BMS will be reporting AEs to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/EC and Code of Federal Regulations 21 CFR Parts 312 and 320.

6.1 Serious Adverse Events

A ***Serious Adverse Event (SAE)*** is 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)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm, 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 6.6 for the definition of potential DILI.)

Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy, overdose, cancer, and potential DILI are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 6.1.1 for reporting pregnancies.)

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 (eg, routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)
- Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)

6.1.1 Serious Adverse Event Collection and Reporting

Sections 5.6.1 and 5.6.2 in the IB represent the Reference Safety Information to determine expectedness of SAEs 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 must be collected that occur during the screening period and within days of discontinuation of dosing. However, any SAE occurring after the start of a new treatment that is suspected to be related to study treatment by the investigator will be reported.
- For participants assigned to treatment and never treated with study drug, SAEs should be collected for 30 days from the date of treatment assignment.
- 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.

- The investigator will submit any updated SAE data to the sponsor or designee within 24 hours of updated information being available.

An SAE report must be completed for any event where doubt exists regarding its seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship must be specified in the narrative section of the SAE Report Form.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS or designee within 24 hours of awareness of the event. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). The preferred method for SAE data reporting collection is through the eCRF. The paper SAE/pregnancy surveillance forms are only intended as a back-up option when the eCRF system is not functioning. In this case, the paper forms are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

For studies capturing SAEs through electronic data capture (EDC), electronic submission is the required method for reporting. In the event the electronic system is unavailable for transmission, paper forms must be used and submitted immediately. When paper forms are used, the original paper forms are to remain on site.

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

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 drug 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.

6.2 Nonserious Adverse Events

A ***nonserious adverse event*** is an AE not classified as an SAE.

6.2.1 Nonserious Adverse Event Collection and Reporting

The collection of non-serious AE (with the exception of non-serious AEs related to SARS-CoV-2 infection) information should begin at initiation of study treatment and continue during the treatment period and for a minimum of 100 days following discontinuation of study treatment. . Non-serious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the participants. All AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection must

be collected from the date of the participant's written consent until 100 days following discontinuation of dosing.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest and AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, until the event is deemed irreversible, or until the participant is lost to follow-up (as defined in Section 3.6.2), or for suspected cases, until SARS-CoV-2 infection is ruled out. All identified non-serious AEs must be recorded and described on the non-serious AE page of the CRF (paper or electronic).

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

6.3 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 drug 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).

6.3.1 Clinical Safety Laboratory Assessments

Hematology - CBC	
Hemoglobin	
Hematocrit	
Total leukocyte count, including differential	
Platelet count	
Chemistry	
Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Total bilirubin (Direct Bili if T.Bili > ULN) Alkaline phosphatase (ALP) Lactate dehydrogenase (LDH) Creatinine Blood Urea Nitrogen (BUN) or serum UREA Glucose	Albumin Total protein Sodium Potassium Chloride Calcium Magnesium

Amylase, Lipase - on treatment	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 HIV1/2 antibody-screening only	
Other Analyses	
Pregnancy test (WOCBP only: minimum sensitivity 25 IU/L or equivalent units of HCG).	
Follicle stimulating hormone (FSH) screening - only required to confirm menopause in women < age 55)	

Abbreviations: CBC = complete blood count; HBVsAG = hepatitis B surface antigen; HCG = human chorionic gonadotropin; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IU = international unit; L = liter; RNA = ribonucleic acid; fT3 = free triiodothyronine; fT4 = free thyroxine; TSH = thyroid-stimulating hormone; ULN = upper limit normal; WOCBP = women of childbearing potential.

6.4 Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study 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 the BMS designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Section 6.1.1.

In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). Please call the BMS Medical Monitor within 24 hours of awareness of the pregnancy.

The investigator must immediately notify the BMS medical monitor or designee of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Section 6.1.1.

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

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

6.5 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section 6.1.1 for reporting details.).

6.6 Potential Drug Induced Liver Injury

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 6.1.1 for reporting details).

Potential DILI is defined as:

1. Aminotransaminases (AT) (ALT or AST) elevation > 3 times ULN

AND

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

AND

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

6.7 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiogram, x-ray filming, or 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.

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

For part 2, a BICR will be used for determination of BICR-assessed ORR and other efficacy endpoints. Details of BICR responsibilities and procedures will be specified in the BICR charter. Images will be submitted to an imaging third-party vendor for central review. Sites will be trained prior to enrolling the first study patient. Imaging acquisition guidelines and submission process will be outlined in the Study Imaging Manual to be provided by the vendors. Refer to Section 5.4 Imaging Assessment for the Study for further details.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

8.1.1 Part 1

With 9 participants in each arm, if 0, 1, 2, or 3 participants experienced DLTs, the upper limit of the one-sided exact 90% CI for the true DLT rate will be less than 23%, 37%, 49%, and 60% respectively. The calculations are based on the Clopper-Pearson method for the exact confidence intervals.

8.1.2 Part 2

With an estimated discrepancy rate of 25% between local and repeating testing in central lab for MSI/MMR status, it is expected that approximately 33 participants with MSI-H/dMMR mCRC

determined by local testing will be treated in the study. A sample size of 33 will allow the lower bound of one-sided 95% CI excluding 35% when the observed ORR is 50% in the nivolumab/ipilimumab combination arm. The 35% ORR is expected for local diagnosed MSI-H/dMMR mCRC patients treated with PD-1 inhibitor monotherapy. This sample size will also provide at least 90% power to demonstrate statistical difference with historical ORR of 5% for TKI monotherapy in a similar setting at a two-sided alpha of 0.05.

Based on the estimated discrepancy rate between local and central MSI/MMR testing, of 33 treated participants, approximately 25 participants will have their MSI-H/dMMR status confirmed by repeating central lab testing. During the study, the discrepancy rate will be monitored in an ongoing basis, and study accrual may continue beyond 33 if the discrepancy rate exceeds 25%.

Due to challenges with enrollment, the enrollment for Part 2 was closed after 9 participants were treated, out of the 33 participants planned.

8.2 Populations for Analyses

The following participant populations will be used in the study:

- All enrolled participants: All participants who signed an ICF and were registered into the IVRS;
- All treated participants: All participants who received at least one dose of study medication;
- Pharmacokinetic Population: All participants who received any study drug and have available concentration time data;
- Immunogenicity Population: All participants who received any study drug and have at least one post treatment immunogenicity measurement;
- Biomarker Population: All MSI-H/dMMR CRC centrally confirmed participants who received any study drug unless otherwise stated

8.3 Endpoints

8.3.1 Primary Endpoint(s)

8.3.1.1 Part 1

The primary objective of Part 1 is to characterize the safety and tolerability of nivolumab plus ipilimumab in Chinese participants. The primary objective will be measured by:

- Number and percent of all treated participants that experience AEs occurring up to 100 days after the last dose of study drug (time frame - on a continuous basis up to 100 days after the last dose of study drug)
- Number and percent of all treated participants that experience SAEs occurring up to 100 days after the last dose of study drug (time frame - on a continuous basis up to 100 days after the last dose of study drug)
- Number and percent of all treated participants that experience AEs leading to discontinuation occurring up to 100 days after the last dose of study drug (time frame - on a continuous basis up to 100 days after the last dose of study drug)

- Number and percent of all treated participants that experience AEs leading to death occurring up to 100 days after the last dose of study drug (time frame - on a continuous basis up to 100 days after the last dose of study drug)
- Number and percent of participants with clinical laboratory abnormalities by worst toxicity grade by NCI CTCAE version 4.0 (as assessed at the planned times listed in Table 5.1-1, Table 5.1-2, Table 5.1-3, Table 5.1-4, Table 5.1-5, Table 5.1-6 and Table 5.1-7) (time frame - on a continuous basis up to 100 days after the last dose of study drug)

8.3.1.2 Part 2

The primary objective of Part 2 will be measured by the primary endpoint of BICR-assessed ORR. It is defined as the number of participants with a BOR of confirmed CR or PR, according to RECIST 1.1 criteria, divided by the number of treated participants. The final analysis of the primary endpoint will occur at least 6 months after the last participant's first dose of study therapy. The BOR is defined as the best response designation recorded between the date of first dose and the date of initial objectively documented progression per RECIST 1.1 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 purposes of analysis, if a participant receives one dose and discontinues the study without assessment or receives subsequent therapy prior to assessment, this participant will be counted in the denominator (as non-respondent).

The BICR-assessed ORR will be further characterized by rate of CR and PR.

8.3.2 Secondary Endpoint(s)

8.3.2.1 Part 1

Pharmacokinetics

The Part 1 secondary objective of characterizing the PK of nivolumab and ipilimumab in Chinese participants will be measured by PK parameters derived from serum concentration versus time data by non-compartmental analysis method. Details of PK sample collection are provided in Section 5.5. All individual PK parameters will be listed and summarized for each analyte, including any exclusions and reasons for exclusion from summaries. The PK parameters to be assessed for nivolumab and ipilimumab, if data permits, include

- Cmax - Maximum observed serum concentration
- Tmax - Time of maximum observed serum concentration
- AUC(0-T) - Area under the plasma concentration-time curve from time zero to the last time of the last quantifiable concentration.
- AUC(TAU) - Area under the concentration-time curve in one dosing interval
- Ceoinf - Serum concentration achieved at the end of study drug infusion
- Ctrough - Trough observed serum concentration at the end of dosing interval
- Ctau - Concentration at the end of dosing interval

- CLT - Total body clearance
- Css-avg - Average concentration over a dosing interval (AUC(TAU)/tau)
- AI - Accumulation index; ratio of an exposure measure at steady-state to that after the first dose (exposure measure includes AUC (TAU), Cmax, or Ctau).
- T-HALFeff - Effective elimination half-life that explains the degree of accumulation observed for a specific exposure measure (exposure measure includes AUC(TAU), Cmax, or Ctau)

The serum concentration may also be pooled with other datasets for population PK analysis, which will be presented in a separate report.

Immunogenicity

The Part 1 secondary objective relating to immunogenicity will be measured by the ADA status both at the sample level and at the participant level, and Nab if data permits. At the sample level a sample is characterized as baseline ADA-positive and ADA- persistent positive or ADA-negative to each study drug. At the participant level, relevant ADA endpoints include proportion of participants with a baseline ADA-positive sample, and proportion of ADA- persistent positive participants for each study drug. Time points for collection are specified in Table 5.5.1-1 and Table 5.5.1-2. Additional details will be presented in the statistical analysis plan.

8.3.2.2 Part 2

The secondary endpoint for Part 2 will be measured by:

- Investigator-assessed ORR, defined as the proportion of all treated participants whose BOR is either confirmed complete response (CR) or confirmed partial response (PR).
- Investigator-assessed and BICR-assessed disease control rate (DCR), defined as the proportion of participants whose BOR is confirmed CR or confirmed PR or stable disease (SD) for at least 12 weeks.
- Investigator-assessed and BICR-assessed duration of response (DOR), defined as the time between the date of first confirmed response to the date of the first documented tumor progression (per RECIST 1.1), or death due to any cause, whichever occurs first
- Investigator-assessed and BICR-assessed progression-free survival (PFS), defined as the time from the first dosing date to the date of first objectively documented disease progression per RECIST 1.1 (ie, radiologic) or death due to any cause, whichever occurs first.

8.3.3 Exploratory Endpoint(s)

8.3.3.1 Part 1

The Part 1 exploratory objective of assessing the anti-tumor response of nivolumab will be measured by the following endpoints at participant level:

- BOR by investigators using Response Evaluation Criteria in Solid Tumor RECIST 1.1

The following endpoints will be summarized by arm and/or across arm:

- ORR is defined as the proportion of all treated participants whose BOR is either a CR or PR by investigators using RECIST 1.1

1. PFS Rate (PFSR) at 6 months, as defined as the proportion of treated participants remaining progression free and surviving at 6 months since the first dosing date. The proportion will be calculated by the Kaplan-Meier estimate which takes into account censored data.
2. Overall Survival (OS) for Arm B participants, defined as the time from the first dosing date to the date of death due to any cause. A participant who has not died will be censored at last known date alive.

8.3.3.2 Part 2

Part 2 exploratory objectives include the following:

- Safety and tolerability of nivolumab in combination with ipilimumab in participants with recurrent or metastatic MSI-H/dMMR CRC, as measured by the incidence of AEs and specific laboratory abnormalities (worst grade). Toxicities will be graded using the NCI CTCAE version 4.0.
- PK, which will be measured using serum concentration-time data.
- OS is defined as the time from first dosing date to the date of death due to any cause. A participant who has not died will be censored at last known date alive.

Other exploratory endpoints for immunogenicity and outcomes research are discussed in detail in Section 5.5 and Section 5.8, respectively.

8.4 Analyses

8.4.1 Demographics and Baseline Characteristics

Frequency distributions of gender, race, and other categorical demographic variables will be tabulated by arm. Summary statistics for age, body weight, height, body mass index (BMI), and other categorical demographic variables will be tabulated by arm.

8.4.2 Efficacy Analyses

8.4.2.1 Part 1

Individual participant's BOR will be listed by arm and/or across arm based on RECIST 1.1. BOR outcomes will be tabulated by arm and/or across arms for all treated participants.

ORR will be calculated and corresponding two-sided 95% exact CIs using Clopper-Pearson method will be provided by arm and/or across arms for all treated participants.

PFS will be calculated by the Kaplan-Meier estimate for all treated participants.

8.4.2.2 Part 2

Primary Endpoint Methods

The BICR-assessed ORR will be summarized. A response-rate estimate and corresponding two-sided exact 95% CI using the Clopper-Pearson method will be provided. BICR-assessed ORR will be further characterized by the rate of CR and PR.

Secondary and Exploratory Endpoint Methods

ORR based on Investigators' assessment will be summarized and further characterized by rate of CR and PR as above.

BICR-assessed and Investigator-assessed DCR will be summarized and corresponding two-sided exact 95% CI using the Clopper-Pearson method will be provided.

BICR-assessed and Investigator-assessed DOR will be listed for participants who achieve confirmed PR or CR.

PFS and OS will be listed.

8.4.3 Safety Analyses

Part 1

All recorded AEs will be listed and tabulated by system organ class, preferred term and treatment. Vital signs and clinical laboratory test results will be listed and summarized by treatment. Any significant physical examination findings, and clinical laboratory results will be listed. ECG readings will be evaluated by the investigator and abnormalities, if present, will be listed.

Part 2

Safety analyses will be performed in all treated participants. Descriptive statistics of safety will be presented using NCI CTCAE version 4.0. On-study AEs will be tabulated using worst grade per NCI CTCAE v4.0 criteria by system organ class and Medical Dictionary for Regulatory Activities (MedDRA) preferred term. On-study lab parameters including hematology, chemistry, liver function, thyroid function, and renal function will be summarized using worst grade per NCI CTCAE v4.0 criteria. Vital signs, physical examination abnormality findings, and ECG readings will be listed.

8.4.4 Pharmacokinetic Analyses

Part 1

Summary statistics will be tabulated for PK parameters of nivolumab and ipilimumab as specified in Section 8.3.2.1 by treatment, dose, and cycle as appropriate. Geometric means and coefficients of variation will be presented for Cmax, Ceoinf, AUC(0-T), AUC(TAU), Ctrough, Ctau, CLT, and AI. Median, minimum, and maximum will be presented for Tmax. Means and %CV will be provided for the remaining PK parameters. To assess attainment of steady state, plots of geometric mean Ctrough versus time will be provided. Pharmacokinetic concentrations of nivolumab and ipilimumab from all participants will be listed and summary statistics will be tabulated by

treatment (arm), cycle, study day and nominal time, and may be used in combination with other studies for exposure-response or population PK modeling, which will be part of a separate report.

Part 2

Pharmacokinetic concentrations of nivolumab and ipilimumab from all participants will be listed, and may be used in combination with other studies for exposure-response or population PK modeling, which will be part of a separate report.

8.4.5 Biomarker Analyses

Biomarker analyses are not applicable for Part 1 Arms A, B and C.

For Part 2 Arm D, baseline MSI/MMR status, both central and local testing, will be listed.

8.4.6 Exploratory Biomarker Analyses

Not applicable.

8.4.7 Outcomes Research Analyses

8.4.7.1 European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (QLQ-C30)

The analysis of European Organization for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30) will be performed in all treated participants. The questionnaire completion rate, defined as the proportion of questionnaires actually received out of the expected number, will be calculated and summarized at each assessment point.

All scales and single items are scored on a categorical scale and linearly transformed to 0 to 100 scales with higher scores for a functional scale representing higher levels of functioning, higher scores for the global health status/quality of life representing higher levels of global health status/quality of life, and higher scores for a symptom scale representing higher level of symptoms. Baseline, each post baseline assessment, and change from baseline in EORTC QLQ-C30 global health status/quality of life composite scale data and the remaining EORTC QLQ-C30 scale data will be summarized by time point using descriptive statistics for each cohort (N, mean with SD and 95% CI, median, first and third quartiles, minimum, maximum). In addition, the percentage of participants demonstrating a clinically meaningful deterioration (defined as a 10-point change from baseline) will be presented for each scale at each assessment time point. Percentages will be based on number of participants assessed at assessment time point.

8.4.7.2 EQ-5D-3L

The analysis of EQ-5D-3L will be performed in all treated participants. Participant's overall health state on a visual analog scale (EQ-VAS) and utility index scores (based on UK weighting algorithm), at each assessment time point will be summarized using descriptive statistics (N, mean, with SD and 95% CI, median, first and third quartiles, minimum, maximum). The proportion of participants reporting no, moderate, or extreme problems will be presented for each of the 5 EQ-5D-3L dimensions at each assessment time point. Percentages will be based on number participants assessed at assessment time point.

The questionnaire completion rate, defined as the proportion of questionnaires actually received out of the expected number, will be calculated and summarized at each assessment point.

A by-participant listing of EQ-5D-3L with the problem levels for each of the 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), health state (5 dimensions digits combined in a 5-digit number), utility index and EQ-VAS will be provided.

8.4.8 Other Analyses

Immunogenicity Analyses

Data from the assessment of immunogenicity markers will be listed by participant. Number and frequency of ADA response classifications will be summarized by arm, as appropriate. The details of the ADA response classifications will be provided in the study statistical analysis plan.

8.5 Interim Analyses

Part 1

Administrative interim analyses may be performed at several times prior to completion of the study in order to facilitate program decisions and to support presentations or publications.

Part 2

The final analysis of the primary endpoint ORR will occur at least 6 months after the last participant's first dose of study therapy.

In addition, other interim analyses may be conducted to seek initial efficacy signal or for external data disclosure for this cohort.

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, BMS. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study participants.

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

- IRB/IEC for review and approval/favorable opinion
- BMS
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) 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 participants currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new participants prior to enrollment.

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

9.1.2 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.

In addition, the study may be evaluated by BMS 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 BMS.

9.1.2.1 Source Documentation

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), AE 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.

9.1.3 Investigational Site Training

Bristol-Myers Squibb will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent, and enrollment of WOCBP.

9.2 Records

9.2.1 Records Retention

The investigator 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, whichever is longer. The investigator must contact BMS prior to destroying any records associated with the study and BMS will notify the investigator when the study records are no longer needed.

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

9.2.2 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of study drug (inventoried and dispensed) is maintained at the study site to include the following investigational product. Records or logs must comply with applicable regulations and guidelines and should include:

- amount received and placed in storage area
- amount currently in storage area
- label identification number or batch number
- amount dispensed to and returned by each participant, including unique participant identifiers
- amount transferred to another area/site for dispensing or storage
- nonstudy disposition (eg, lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to BMS
- retained samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

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

9.2.3 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 BMS 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 or 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 BMS.

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

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

The completed CRF, SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a sub-investigator and who is delegated this task on the Delegation of Authority Form. 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 BMS training requirements and must only access the BMS electronic data capture tool using the unique user account provided by BMS. User accounts are not to be shared or reassigned to other individuals.

9.3 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 (eg, among the top quartile of enrollers)
- Involvement in trial design
- Other criteria (as determined by the study team)

The data collected during this study are confidential and proprietary to BMS. Any publications or abstracts arising from this study require approval by BMS prior to publication or presentation and must adhere to BMS's publication requirements as set forth in the approved clinical trial agreement (CTA). All draft publications, including abstracts or detailed summaries of any proposed presentations, must be submitted to BMS at the earliest practicable time for review, but at any

event not less than 30 days before submission or presentation unless otherwise set forth in the CTA. BMS shall have the right to delete any confidential or proprietary information contained in any proposed presentation or abstract and may delay publication for up to 60 days for purposes of filing a patent application.

9.4 Dissemination of Clinical Study Data

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

9.5 Data Protection, Data Privacy, and Data Security

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

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

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

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

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

10 GLOSSARY OF TERMS

Term	Definition
Complete Abstinence	Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. This also means that abstinence is the preferred and usual lifestyle of the participant. This does not mean periodic abstinence (eg, calendar, ovulation, symptothermal, profession of abstinence for entry into a clinical trial, post-ovulation methods) and withdrawal, which are not acceptable methods of contraception. Women must continue to have pregnancy tests. Acceptable alternate methods of highly or less effective contraception must be discussed in the event that the participant chooses to forego complete abstinence.
Additional Research	Those scientific activities which cannot be reasonably anticipated at the time of trial design, for which we would like to collect and/or retain samples from study participants. Examples of additional research include, but are not limited to, new assay development and validation, companion diagnostic development, new hypotheses in the interaction of drug and the human body, and exploration of emerging science in the understanding of disease.

11 LIST OF ABBREVIATIONS

Term	Definition
ADA	anti-drug antibody
AE	adverse event
AI	accumulation index
AI_AUC	AUC Accumulation Index; ratio of AUC(TAU) at steady state to AUC(TAU) after the first dose
AI_Cmax	Cmax Accumulation Index; ratio of Cmax at steady state to Cmax after the first dose
AI_Ctau	Ctau Accumulation Index; ratio of Ctau at steady state to Ctau after the first dose
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AT	aminotransaminases
AUC	area under the concentration-time curve
AUC(0-T)	area under the concentration-time curve from time zero to the time of the last quantifiable concentration
AUC(TAU)	area under the concentration-time curve in one dosing interval
BICR	blinded independent central review
BMI	body mass index
BMS	Bristol-Myers Squibb
BOR	best overall response
BP	blood pressure
BUN	blood urea nitrogen
Cavg28	average serum concentration at Day 28
CBC	complete blood count
CD	cluster of differentiation
Cexpected-tau	expected concentration in a dosing interval
CFR	Code of Federal Regulations
cHL	classical Hodgkin lymphoma
CI	confidence interval
CL	clearance

Term	Definition
CLss	clearance at steady state
CLT	total body clearance
Cmax	maximum observed concentration
CNS	Central nervous system
COVID-19	coronavirus disease 2019
CR	complete response
CRC	Colorectal cancer
CrCl	creatinine clearance
CRF	Case Report Form, paper or electronic
CRR	complete response rate
CT	computed tomography
CTA	clinical trial agreement
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte–associated antigen 4
Ctau	Concentration in a dosing interval (eg, concentration at 24 hours, concentration at 12 hours, etc.)
Ctrough	Trough observed plasma concentration
CV%	% coefficient of variation
DBL	data base lock
DCR	disease control rate
DILI	drug-induced liver injury
DLTs	dose-limiting-toxicities
dMMR	DNA mismatch repair deficient
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eGFR	estimated glomerular filtration rate
EMRs/EHRs	electronic medical/health records

Term	Definition
EOI	end-of-infusion
EORTC	European Organisation for Research and Treatment of Care
EQ-5D-3L	EuroQol 5 Dimensions questionnaire
E-R	exposure-response
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer quality of life questionnaire
FSH	follicle stimulating hormone
FU2	follow-up visit 2
GC	gastric cancer
GCP	Good Clinical Practice
GI	gastrointestinal
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCG	human chorionic gonadotrophin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HNPCC	hereditary non-polyposis colorectal cancer
HR	heart rate
HRT	hormone replacement therapy
HuMAb	human monoclonal antibody
IB	investigator brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IgG	immunoglobulin G
IHC	immunohistochemistry
IMAE	immune mediated adverse events
IO	immuno-oncology
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IRT	Interactive Response Technology
IUDs	intrauterine devices

Term	Definition
IV	intravenous
IVRS	Interactive Voice Response System
LDH	lactate dehydrogenase
LFTs	liver function tests
mAb	monoclonal antibody
mCRC	metastatic CRC
MedDRA	Medical Dictionary for Regulatory Activities
MMR	mismatch repair deficient
MRI	magnetic resonance imaging
MSI-H	microsatellite instability high
MSI-L	MSI-Low
MST	medical safety team
MTD	maximum tolerated dose
NCI	National Cancer Institute
NPC	nasopharyngeal cancer
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed death 1
PD-L1	programmed death–ligands 1
PD-L2	programmed death–ligands 2
PFS	progression-free survival
PID	patient identification number
PK	pharmacokinetics
PPK	population PK
PR	partial response
PTs	preferred terms
Q2W	every 2 weeks

Term	Definition
Q3W	every 3 weeks
Q4W	every 4 weeks
QLQ-C30	Quality of Life Questionnaire Core-30
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RTPCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCCHN	Squamous Cell Cancer of the Head and Neck
SCLC	small cell lung cancer
SD	stable disease
SOP	Standard Operating Procedures
SmPC	Summary of Product Characteristics
TB	tuberculosis
TEN	toxic epidermal necrolysis
T-HALFeff_AUC	Effective elimination half-life that explains the degree of AUC accumulation observed
Tmax	time of maximum observed concentration
ULN	upper limit of normal
USPI	United States Package Insert
VAS	visual analog scale
Vc	Volume of central
Vss	volume of distribution at steady state
WBC	white blood cell
WOCBP	women of childbearing potential

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APPENDIX 1 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

Abbreviations: 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

Abbreviations: 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

Abbreviations: 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 2 ECOG PERFORMANCE STATUS

ECOG PERFORMANCE STATUS	
Grade	**ECOG**
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 self-care 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

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5: 649 - 655, 1982.

APPENDIX 3 MANAGEMENT ALGORITHMS FOR STUDIES UNDER CTCAE VERSION 4.0

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 therapeutic procedure, is recommended.

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

GI Adverse Event Management Algorithm

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

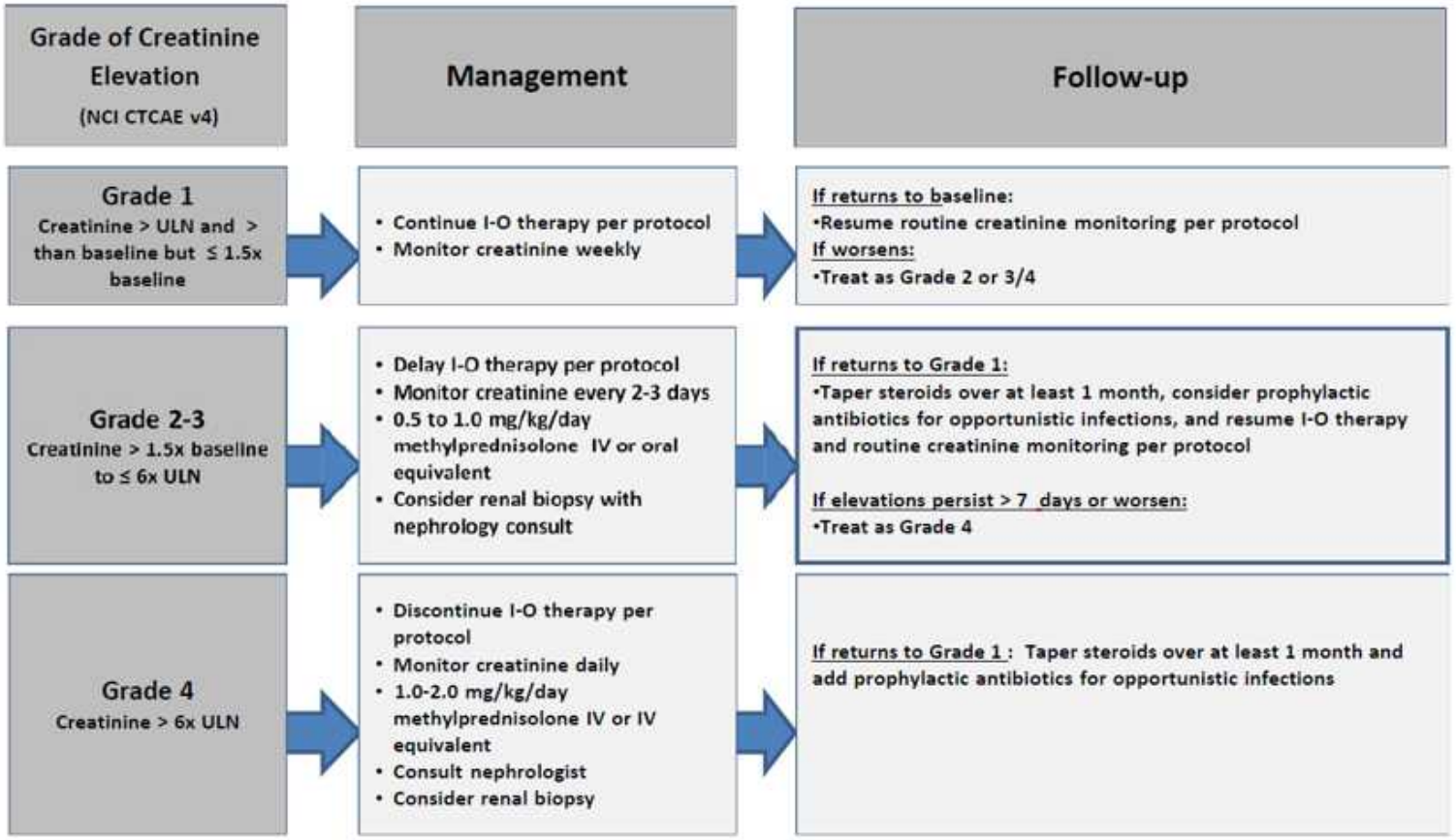
Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea: < 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hrs; not interfering with ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recur: • 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as grade 3/4
Grade 3-4 Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with ADL Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation	• Discontinue I-O therapy per protocol • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis

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

28-Sep-2020

Renal Adverse Event Management Algorithm

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

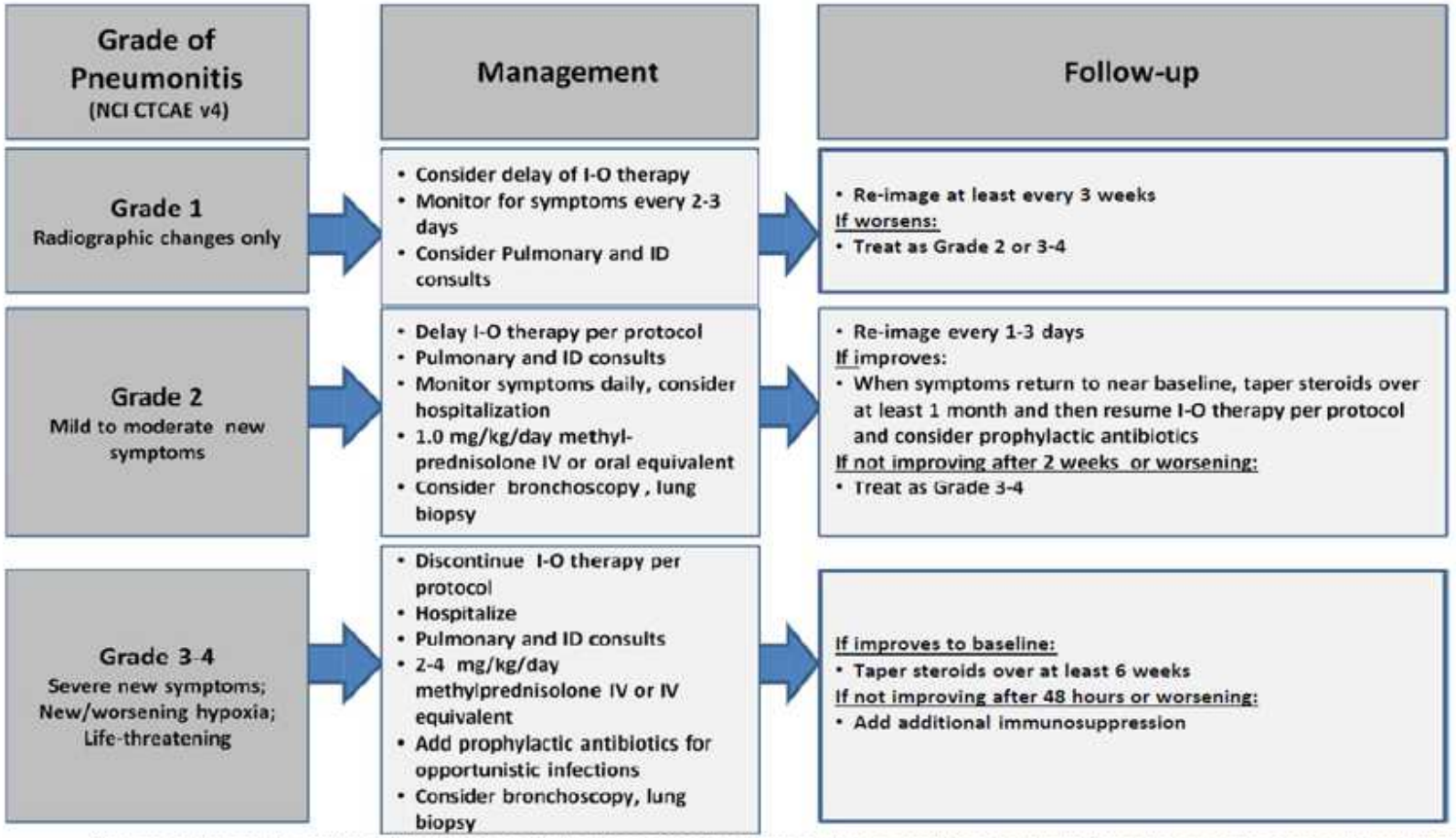


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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 (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids

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.

Grade of Liver Test Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 AST or ALT > ULN to 3.0 x ULN and/or T. bili > ULN to 1.5 x ULN	• Continue I-O therapy per protocol	• Continue LFT monitoring per protocol If worsens: • Treat as Grade 2 or 3-4
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and/or T. bili > 1.5 to ≤ 3 x ULN	• Delay I-O therapy per protocol • Increase frequency of monitoring to every 3 days	If returns to baseline: •Resume routine monitoring, resume I-O therapy per protocol If elevations persist > 5-7 days or worsen : • 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol
Grade 3-4 AST or ALT > 5 x ULN or T.bili >3 x ULN	• Discontinue I-O therapy* • Increase frequency of monitoring to every 1-2 days • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent* • Add prophylactic antibiotics for opportunistic infections • Consult gastroenterologist	If returns to grade 2: • Taper steroids over at least 1 month If does not improve in >3-5 days, worsens or rebounds: • Add mycophenolate mofetil 1 g BID • If no response within an additional 3-5 days, consider other immunosuppressants per local guidelines

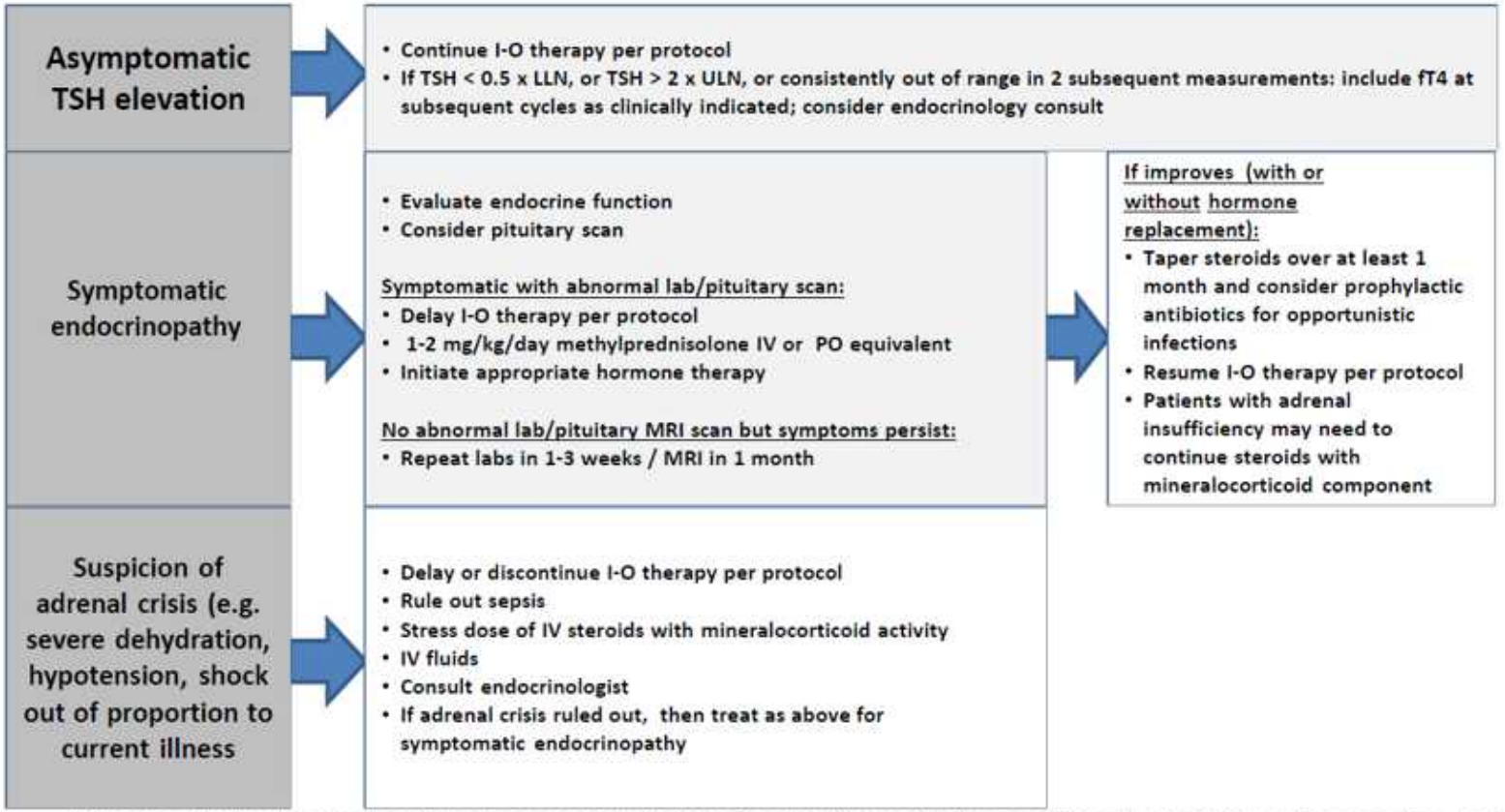
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

*The recommended starting dose for grade 4 hepatitis 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.

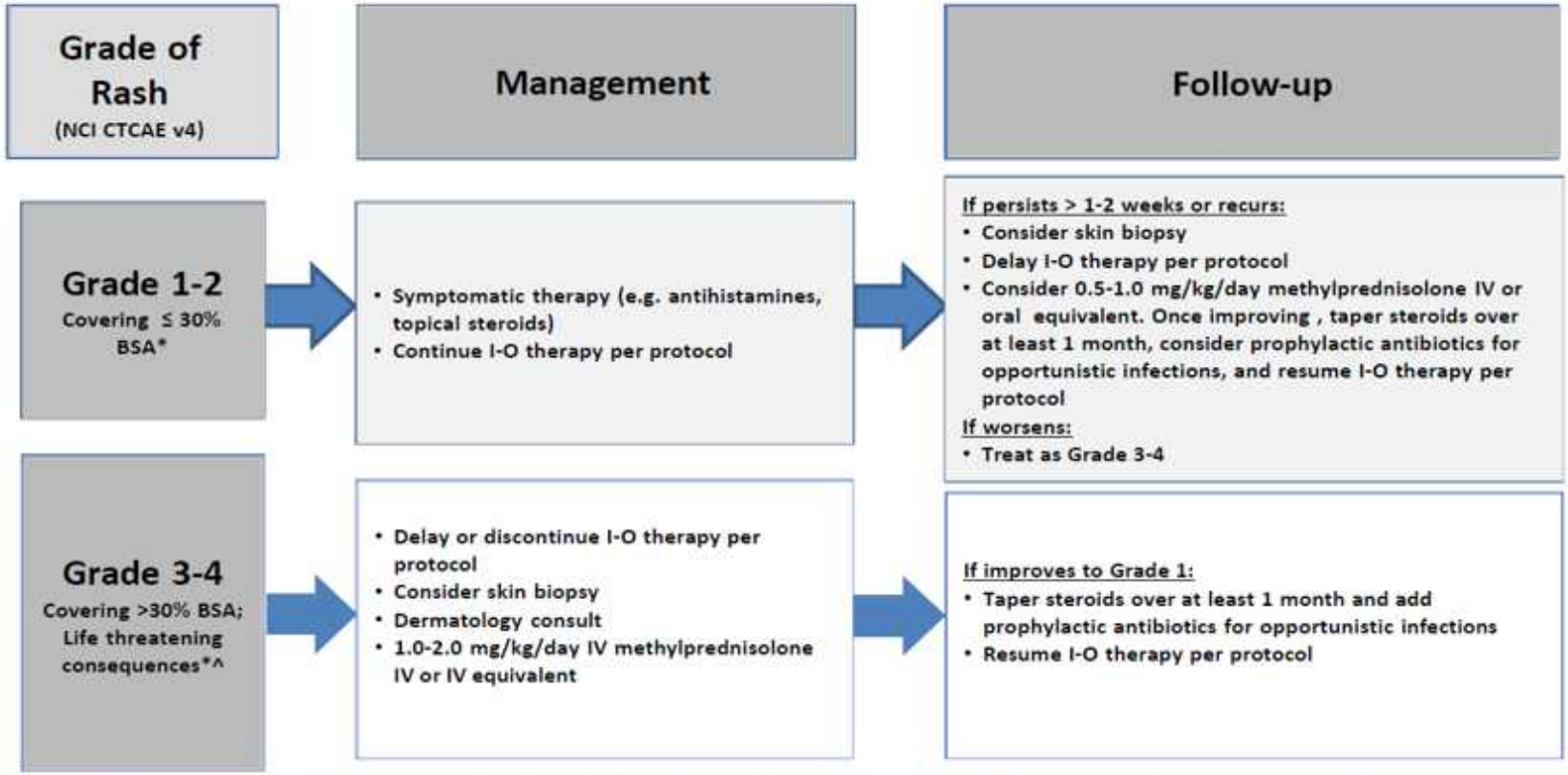


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

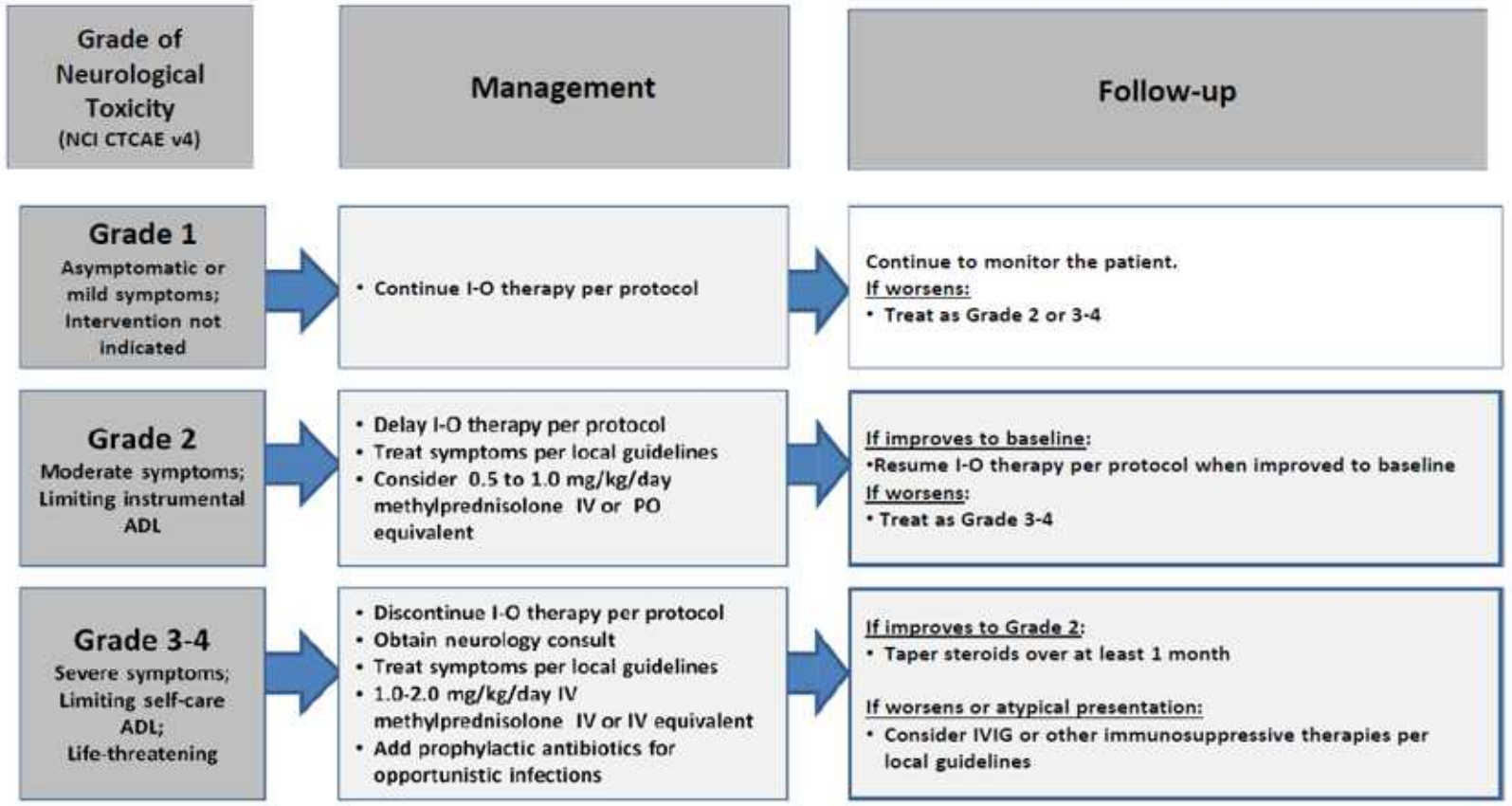
*Refer to NCI CTCAE v4 for term-specific grading criteria.

^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

28-Sep-2020

Neurological Adverse Event Management Algorithm

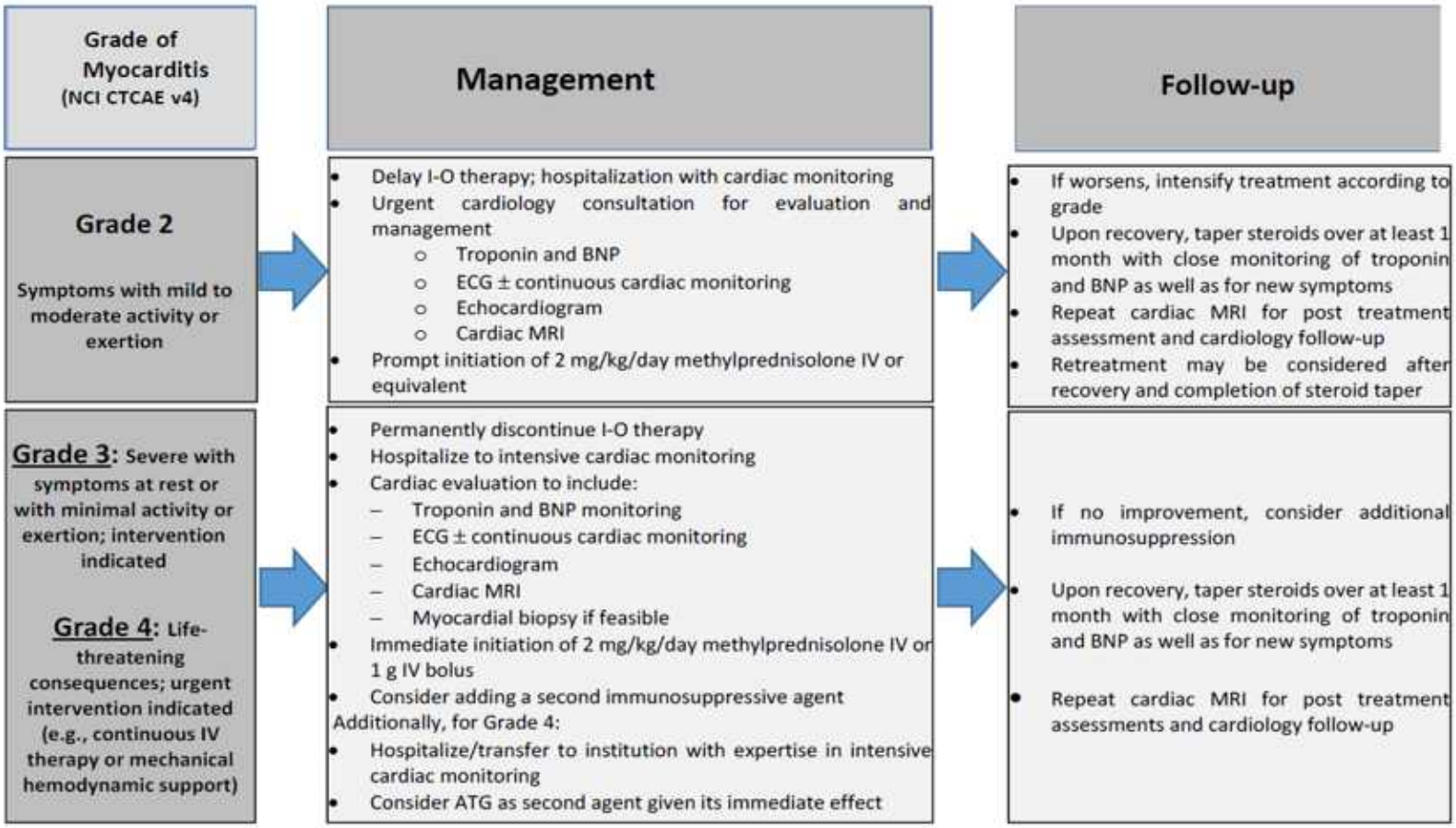
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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

28-Sep-2020

Myocarditis Adverse Event Management Algorithm



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

28-Sep-2020

APPENDIX 4 MSI STATUS TESTING

TESTING PANEL DESCRIPTIONS (PCR AND IHC)

Bethesda method and Promega MSI Multiplex System (PCR) Panel Description and Classification of MSI Status

- Reference panel:
  - BAT25 (mononucleotide)
  - BAT26 (mononucleotide)
  - D5S346 (dinucleotide)
  - D2S123 (dinucleotide)
  - D17S250 (dinucleotide)

- Alternative loci:
  - BAT40
  - BAT34C4
  - TGF-□-RII
  - ACTC (635/636)
  - NR-21
  - NR-24
  - MONO-27

- Classification:
  - **If 5 loci tested (reference panel):**
    - MSI-H: ≥ 2 markers with instability
    - MSI-L: 1 marker with instability
    - MSS or MSI-L: 0 markers with instability
  - **If > 5 loci tested (reference panel plus alternative loci):**
    - MSI-H: ≥ 30-40% markers with instability
    - MSI-L: < 30-40% markers with instability
    - MSS or MSI-L: 0 marker with instability
  - **In the case of 1 PCR amplification failure:**
    - If ≥ 3 markers of 4→MSI-H
    - If 1 marker of 4→re-amplify

IHC method Panel Description and Classification of MSI Status Panel

- hMSH2
- hMLH1
- hMSH6
- hPMS2

Classification:

- **MSI-H:** ≥1 markers with instability
- **MSS:** 0 marker with instability
- **MSI-L:** not evaluable with this technique

Prioritization of Tumor Tissue Samples for MSI Testing

1) Fresh biopsy (Preferred)
   a) For MSI status confirmation

2) Archive tissue
   a) For MSI status confirmation

If fresh biopsy cannot be obtained, archived tumor tissue prior to therapy is acceptable only if the archived tissue is the same tissue that was used for local MSI/MMR testing.

Important Reminders:

- Refer to Central Lab Flow Chart and protocol for specific sample requirements
- Central lab must confirm receipt of evaluable tumor tissue prior to vial assignment.
- Please contact BMS or The Central Lab if there are any questions

APPENDIX 5 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

Appendix 5 provides general information and definitions related to Woman of Childbearing Potential and methods of contraception that can be applied to most clinical trials. For information specific to this study regarding acceptable contraception requirements for female and male participants, refer to Section 3.3.1 of the protocol. Only the contraception methods as described in Section 3.3.1 are acceptable for this study.

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.

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

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

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

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

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

METHODS OF CONTRACEPTION

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

Highly Effective Contraceptive Methods That Are 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 and/or implantation (These methods of contraception cannot be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol)[b] – Oral (birth control pills) – Intravaginal (rings) – Transdermal • Combined (estrogen-and progestogen-containing) hormonal contraception must begin at least 30 days prior to initiation of study therapy.
• Progestogen-only hormonal contraception associated with inhibition of ovulation (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol)[b] – oral – injectable • Progestogen-only hormonal contraception must begin at least 30 days prior to initiation of study therapy.
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation and/or implantation (This method of contraception cannot be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol)[b] • Intrauterine device • Intrauterine hormone-releasing system (IUS) (This method of contraception cannot be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol) [b,c]

• Bilateral tubal occlusion
• Vasectomized partner Having a vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.* • Continuous abstinence must begin at least 30 days prior to initiation of study therapy. • It is not necessary to use any other method of contraception when complete abstinence is elected. • WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2. • Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence • Periodic abstinence (including, but not limited to, calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception for this study.
NOTES: [a] Typical use failure rates may differ from failure rates when contraceptive methods are used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies. [b] Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized. For information specific to this study regarding permissibility of hormonal contraception, refer to Sections 6.1 INCLUSION CRITERIA and 7.7.1 PROHIBITED AND/OR RESTRICTED TREATMENTS of the protocol. [c] IUSs are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness. For information specific to this study regarding permissibility of hormonal contraception, refer to Sections 3.3.1 INCLUSION CRITERIA and 3.4.1 PROHIBITED AND/OR RESTRICTED TREATMENTS of the protocol..

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

COLLECTION OF PREGNANCY INFORMATION

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

APPENDIX 6 REVISED PROTOCOL SUMMARY OF CHANGE HISTORY

Overall Rationale for Protocol Amendment 06, 02-Jul-2021

The main purpose of this amendment is to:

- update the study language for post-study access to therapy (criteria of study termination and disposition for those subjects still in study when the study terminates)
- add a section about outcome research analyses
- replace older versions of appendices (management algorithms and WOCBP) with newer versions
- align the protocol with current program-level language for nivolumab and ipilimumab including language associated with SARS-CoV-2 infection.

In addition, personnel changes, and administrative letter 06 have been incorporated.

Summary of Key Changes for Protocol AMENDMENT 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title page	Changed Medical Monitor (MM) from [redacted] (Clinical Trial Physician-MM) and added [redacted] Clinical Scientist	To report important personnel changes
Synopsis: Study Population; Section 3.3.1, Inclusion Criteria 2. Target population j)	<u>Previously written:</u> Subjects must have shown progression during, after, or have been intolerant to ≥ 1 line treatment(s) for metastatic disease, which must include a fluoropyrimidine, oxaliplatin, and irinotecan <u>Changed to:</u> Subjects must have shown progression during, after, or have been intolerant to ≥ 1 line treatment(s) for metastatic disease, which must include at least a fluoropyrimidine, and oxaliplatin or irinotecan	To clarify that the inclusion criteria is in line with the study purpose and it is for subjects with second-line+ (2L+) recurrent/metastatic CRC

Summary of Key Changes for Protocol AMENDMENT 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
Synopsis: Study Drug for CA209672	Added information about the availability of Ipilimumab Solution for Injection, 50 mg (5 mg/mL) Added nivolumab name next to BMS-936558-01	Added a new formulation dose option for Ipilimumab Solution and nivolumab name for completeness
Synopsis: Study Design Schematic; Figure 3.1.1-1: Study Design Schematic	Added text to the note indicating that maximum treatment duration is of 24 months EXCEPT in participants with late response (during second year of treatment) who may receive treatment for up to an additional 12 months after onset of response	To clarify that the maximum treatment duration is of 24 months except for participants with late response
Section 1: Introduction and Study Rationale	Added most recent background information including mechanism of action and clinical activity for nivolumab and ipilimumab	To align with the current state of knowledge about nivolumab and ipilimumab
Section 1.1.1: Rationale to Support Dose/Schedule of Nivolumab Combined with Ipilimumab	Updated clinical data for nivolumab and ipilimumab based on the CHECKMATE-142 trial	To reflect clinical data updates from the study CHECKMATE-142
Section 1.1.2: Rationale for Nivolumab Flat Dose in Nivolumab Monotherapy Portion	Updated clinical data for nivolumab from studies in multiple tumor types and dosing schedules	To align with the current state of knowledge about nivolumab
Section 1.1.5: Rationale for Two-Year Duration of Treatment	Revised the section based on data from on-going clinical trials for nivolumab and ipilimumab and retrospective pooled analysis	To align with the current state of knowledge about nivolumab and ipilimumab
Section 1.4.4.1: Pharmacokinetics of Nivolumab; Section 1.4.4.3: Pharmacokinetics of Nivolumab with Ipilimumab	Added clinical pharmacology information for nivolumab alone and in combination with ipilimumab	Added new scientific information

Summary of Key Changes for Protocol AMENDMENT 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 1.4.4.4: Safety Summary of Nivolumab in Combination with Ipilimumab	Updated safety data for nivolumab and ipilimumab based on CHECKMATE-142 trial	To reflect safety data updates from study CHECKMATE-142
Section 3.1.3.2: Screening	Added the following text: • A complete schedule of activities for screening can be found in Table 5.1-1 • Inclusion/Exclusion Criteria are assessed during the screening period and must be confirmed prior to randomization • All medical history relevant to the disease under study should be collected	Clarified the location of screening related schedule of activities and other criteria in the protocol.
Section 3.2: Post Study Access to Therapy	Revised description of provisions for accessing study treatments by subjects after the conclusion and in the event of termination of the clinical study	Changed to clarify post-study access provisions to therapy
Section 3.3.1: Inclusion Criteria 3. Age and Reproductive Status	Edited inclusion criteria 3 to align with the program level standards	To align with program level language for nivolumab
Section 3.3.2: Exclusion Criteria 1a, 1b, 2a, 3g, 3h, 3i, 3j, 3k, and 4a	Edited 1a, 1b, 2a, 3g, 3h, 3i, 3j, 3k, and 4a to align with the program level standards	To clarify and align with program level language for nivolumab
Section 3.4.1: Prohibited and/or Restricted Treatments	Modified or added the following prohibited and/or restricted treatments: • Immunosuppressive agents including systemic corticosteroids • Any concurrent systemic antineoplastic therapy • Non-palliative radiation therapy	Clarified concomitant therapy restrictions

Summary of Key Changes for Protocol AMENDMENT 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
	• Any complementary medications • Any live / attenuated vaccine	
Section 3.6: Post Study Drug Follow up	Added text about potential collection of survival data on all treated participants outside of the protocol defined window (Table 5.1-5)	To align with program level language
Table 4-1: Study Drugs for CA209672 - Treatment Period	Added information about the availability of an Ipilimumab Solution for Injection as a 10 mL vial (50 mg [5 mg/mL], 1 vial per carton) Added nivolumab name next to BMS-936558-01	Added a new formulation dose option for Ipilimumab Solution and nivolumab name for completeness
Section 4.3: Storage and Dispensing	Added a statement saying that patients dosed with nivolumab and ipilimumab should be observed to ensure that no infusion reaction has occurred and begin study treatment within 3 calendar days of treatment assignment	To ensure patient safety
Section 4.5.3: Dose Delay Criteria	Edited dose delay criteria to conform with current standards	To align with program level language for nivolumab
Section 4.5.5: Criteria to Resume Treatment	Added conditions to resume treatment for participants with SARS-CoV-2 infection (either confirmed or suspected)	To mitigate risks to participants with known or suspected SARS-CoV-2 infection
Section 4.5.6: Treatment Discontinuation Criteria	Myocarditis was added to Grade 3 drug related adverse events	To align with the text in the Investigator Brochure
Section 4.5.7: Treatment Beyond Disease Progression	Updated statement that the decision to continue treatment beyond initial investigator-assessed progression, defined per RECIST v1.1, should	Clarified that treatment beyond progression is defined by RECIST v1.1 and needs to be agreed by the Investigator

Summary of Key Changes for Protocol AMENDMENT 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
	be discussed with and agreed by the Investigator	
Table 5.1-1: Screening Procedural Outline (CA209672)	Added a note to Informed Consent row: "Study allows for re-enrollment of a participant that has discontinued the study as a pre-treatment failure. If re-enrolled, the participant must be re-consented and assigned a new participant number from IRT." Added a note to Inclusion/Exclusion Criteria, Screening visit: "Must be confirmed prior to randomization/treatment assignment"	To align with program level language for nivolumab
Table 5.1-1: Screening Procedural Outline (CA209672)	Added a note to Monitor for Serious Adverse Events row: "All SAEs that occur during the screening period and within 100 days of discontinuation of dosing must be collected."	To correct an inconsistency, communicated previously as a part of the administrative letter 06
Table 5.1-1: Screening Procedural Outline (CA209672); Table 5.1-2: On-Treatment Procedural Outline (CA209672) - Part 1, Arm A; Table 5.1-3: On-Treatment Procedural Outline (CA209672) Part 1, Arms B and C; Table 5.1-4: On-Treatment Procedural Outline (CA209672) - Part 2, Arm D	Added text to the comment cell of SAE/AEs row: All AEs (SAEs or non-serious AEs) associated with SARS-CoV-2 infection collected from time of consent	To align with program level language for SARS-CoV-2 infection

Summary of Key Changes for Protocol AMENDMENT 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 5.1-5: Follow-Up Period (CA209672) –Part 1, Arm A and C	Added text to the comment cell of AEs row: "Participants will be followed for all SAEs, non-serious AEs of special interest, and all AEs associated with confirmed or suspected SARS-CoV-2 infection until resolution, the condition stabilizes, the event is otherwise explained, the event is deemed irreversible, the participant is lost to follow-up, or for suspected cases, until SARS-CoV-2 infections is ruled out."	To align with program level language for SARS-CoV-2 infection
Table 5.1-7: Follow-up Period (CA209672) - Part 2, Arm D	Added a note to Adverse Events Assessment (including SAE) row: "For participants assigned to treatment and never treated with study drug, SAEs should be collected for 30 days from the date of treatment assignment."	Clarified collection timelines for SAEs
Section 5.3: Safety Assessment	Added management of SARS-CoV-2 infection during the screening period. Added other measures to monitor and evaluate laboratory, cardiac, or pulmonary toxicities	To ensure patient safety
Section 5.4.2: Imaging Assessment by BICR for Part 2	Added a note saying: "Collect any additional imaging that may demonstrate tumor response or progression (including scans performed at unscheduled timepoints and/or at an outside institution) for RECIST 1.1 tumor assessment and submit to the BICR."	Clarified additional imaging collection details
Section 5.8.2: Part 2 of Outcomes Research Assessments	Added text, "If exceptional circumstances preclude the continued administration of measures using planned modalities, then alternate administration	To align with recommendations from PRC reviewers

Summary of Key Changes for Protocol AMENDMENT 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
	methods may be required, after consultation with the Sponsor or the Sponsor's representative."	
Section 5.10: Additional Research Collection	Added that: "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."	Clarified Additional Research Collection details
Section 6: Adverse Events	Added description, assessment, and collection of immune-mediated adverse events (IMAEs)	Updated AEs with respect to IMAEs
Section 6.1.1: Serious Adverse Event Collection and Reporting	Added notes stating that: • for participants assigned a treatment and never treated with study drug, collect SAEs for 30 days from the date of treatment assignment • the investigator will submit any updated SAE data to the sponsor or designee within 24 hours of updated information being available	Clarified SAE collection, submission, and reporting requirements for patients with or without study drugs
Section 6.2.1: Nonserious Adverse Event Collection and Reporting	Added details on the time period, frequency, and follow-up period for collecting AE and SAE information related to patients with or without SARS-CoV-2 infection	Clarified details regarding collecting AEs/non-serious SAE information for patients with or without SARS-CoV-2 infection
Section 6.3.1: Clinical Safety Laboratory Assessments	Listed Hematology, Chemistry, Serology, and other clinical safety laboratory analyses	Clarified to specify collection of clinical safety laboratory assessments being carried out for this study
Section 8.4.7: Outcomes Research Analyses; Section 8.4.7.1: European Organization for Research and	Created a new section and subsections describing Outcome Research Analyses	To align with recommendation from PRC reviewer regarding PRO endpoint

Summary of Key Changes for Protocol AMENDMENT 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
Treatment of Cancer Quality of Life Questionnaire (QLQ-C30); Section 8.4.7.2 EQ-5D-3L		
Section 9.1.2: Monitoring	Added text about monitoring plan	Clarified what monitoring/monitoring plan represent
Section 9.4: Dissemination of Clinical Study Data	Added a new section describing dissemination of clinical trial data and results	To conform with regulatory and BMS requirements
Appendix 3: Management Algorithms Studies Under CTCAE Version 4.0	Replaced the older version of appendix under CTCAE v4.0, 2018 with a newer version of the appendix (v4.0, 2020)	To align with the current state of knowledge about management algorithms
Appendix 4: MSI Status Testing	Removed the following under "Important Reminders: "A normal control ACD whole blood sample is required as well as tumor tissue."	To correct an inconsistency, communicated previously as a part of the administrative letter 06
Appendix 4: MSI Status Testing	Adding alternative loci NR-21, NR-24 and MONO-27 for MSI status testing applying from Promega panel Changes made to "Prioritization of Tumor Tissue Samples for MSI Testing" to clarify that fresh biopsy is preferred over archived tissue	To expand the criteria for MSI status detection according to current clinical guideline recommendations
Appendix 5: Women of Childbearing Potential Definitions and Methods of Contraception	Replaced the older appendix with a newer version of the appendix	To align with program level language for nivolumab
All	Minor formatting and typographical/editorial corrections	Minor, therefore have not been summarized

Overall Rationale for the Revised Protocol 05, 09-Jan-2020

Revised Protocol 05 will made a removal of blood sample collection as a control for MSI/MMR status confirmation as it is not necessary in the Biocartis PCR assay.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.1 Flow Chart/Time and Events Schedule Table 5.1-1	Removal of Blood sample collection in Screening as a control for MSI/MMR status confirmation	Blood sample as a control is not needed for the Biocartis assay for utilized the study
All Sections	Minor formatting and typographical corrections	Minor, therefore have not been summarized

Overall Rationale for the Revised Protocol 04, 08-Apr-2019

Colorectal cancer (CRC) DNA mismatch repair deficient (dMMR)/microsatellite instability - high (MSI-H) patients are not sensitive to chemotherapy, especially in second-line and above patients. Thus, there is significant unmet medical need for pre-treated CRC dMMR/MSI-H patients.

CA209142 study showed that total 84 pre-treated dMMR/MSI-H CRC subjects were treated with nivolumab (3 mg/kg) in combination with ipilimumab (1 mg/kg):

- NIVO + IPI provided durable responses, sustained disease control, and encouraging survival data in pretreated patients with dMMR/MSI-H mCRC
  - Objective response rate (ORR) of 55%, with 79% of patients achieving disease control for ≥ 12 weeks
  - 88% of patients alive at 9 months
- NIVO + IPI demonstrated a manageable safety profile; 29% of patients had grade 3/4 treatment-related adverse events (TRAEs)

Revised Protocol 04 will add Part 2, Arm D cohort to evaluate efficacy of nivolumab in combination with ipilimumab in recurrent or metastatic dMMR/MSI-H CRC subjects.

Reference: Thierry Andre, et al. Combination of nivolumab (NIVO) + ipilimumab (IPI) in the treatment of patients (pts) with deficient DNA mismatch repair (dMMR)/high microsatellite instability (MSI-H) metastatic colorectal cancer (mCRC): CheckMate 142 Study, 2017 ASCO Poster 3531. ClinicalTrials.gov identifier NCT02060188)

Summary of key changes for Revised Protocol 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
All Sections	Rationale, objectives, background, investigational plan, and all details have been added to account for the additional Arm D recurrent or metastatic dMMR/MSI-H CRC cohort.	To evaluate efficacy of nivolumab in combination with ipilimumab in recurrent or metastatic dMMR/MSI-H CRC subjects.
Section 3.3.1, Inclusion Criteria	Inclusion criteria 2) a) i) CRC subjects with historically documented MSI-H or dMMR status detected by local laboratory	Eligibility criteria
Section 3.3.3 Women of Childbearing Potential	Removed entire section and added Appendix 5 WOCBP	To align with the latest BMS standards.
Section 4.5 Selection and Timing of Dose for Each Subject	Entire section was updated to align with the updated BMS standards for Dose delay, Dose reduction and Criteria to Resume Treatment	To align with the latest BMS standards.
Section 7, Data Monitoring Committee and Other External Committees	A blinded independent central review (BICR) will be added to this study.	For determination of BICR-assessed ORR
All Sections	Minor formatting and typographical corrections	Minor, therefore have not been summarized
Appendix 4	Added	Added to describe MSI status testing
Appendix 5	Added	Added to provide information on contraception requirements for WOCBP