Official Title of Study:

A Phase 2 Clinical Trial of Nivolumab, or Nivolumab Combinations, in Recurrent and Metastatic Microsatellite Instability High (MSI-H) and non-MSI-H Colon Cancer

(**CheckMate 142**: **CHECK**point pathway and nivolu**MA**b clinical **T**rial **E**valuation **142**)

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CLINICAL PROTOCOL CA209142

A Phase 2 Clinical Trial of Nivolumab, or Nivolumab Combinations, in Recurrent and Metastatic Microsatellite Instability High (MSI-H) and non-MSI-H Colon Cancer

(**CheckMate 142**: **CHECK**point pathway and nivolu**MA**b clinical **T**rial **E**valuation **142**)

Protocol Amendment Number: 09

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DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Protocol Amendment 09	27-Aug-2021	Major changes: • Frequency of tumor assessments has been reduced from every 12 weeks to every 24 weeks for participants with disease control meeting specified criteria. • Re-initiated participants with CR were previously allowed to stay on treatment until PD. This was updated to a maximum of 24 months of additional treatment following re-initiation. • Added that COVID-19 vaccines that are NOT live are permitted during the study and after the last dose of IP. The efficacy and safety of vaccination in subjects who are receiving nivolumab, ipilimumab, BMS-986016, daratumumab, or combinations are unknown. • Added that study therapy should also be delayed in cases of confirmed or suspected SARS-CoV-2 infection and in the case of prior SARS-CoV-2 infection, symptoms should have resolved in order to resume study intervention. • Added clarification on study site closures and dissemination of clinical study data. • Updated exploratory endpoints to collect and report data on participants after re-initiation. • mStage 1/2 and cStage 1/2: Nivolumab monotherapy dosing has been updated from 3 mg/kg every 2 weeks to 480 mg every 4 weeks. • cStage 1/2 re-initiation: The treatment regimen for participants has been amended from nivolumab 480 mg Q4W to (240 mg nivolumab + ipilimumab 1 mg/kg) every 3 weeks for 4 doses followed by 480 mg nivolumab every 4 weeks. • Cohort 3 re-initiation: Participants with nivolumab dosing previously 240 mg every 2 weeks will now have dosing 360 mg every 3 weeks. • Participants who are treated beyond progression will be able to receive treatment for a maximum of 24 additional months following initial RECIST 1.1 defined PD. • Updated biomarker sampling schedule for re-initiation cohorts to align with updated dosing schedule. • Removed Patient Reported Outcome collection in re-initiation phase.
Revised Protocol 08	08-Jun-2020	Major changes: • Changed Medical Monitor and added Study Director (Incorporates Administrative Letter 08, 29-Aug-2019). • Increased Survival Follow-up from a maximum of 3 years to a minimum of 5 years. • Pharmacokinetic and immunogenicity sample collection

Document	Date of Issue	Summary of Change
		no longer required after 2 years of treatment or during post-treatment Follow-Up Visits 1 & 2. Applicable to Arms N, N+I, Cohort C3, and Cohort C6. • Nivolumab infusion duration reduced to 30 minutes for Arms N and N+I.
Revised Protocol 07	05-Feb-2019	Major changes: For MSI-H cohorts only: • Option to discontinue treatment when maximum clinical benefit has been achieved per Investigator assessment and additional protocol defined criteria. • Re-initiation of treatment upon progression for subjects who have discontinued at maximum clinical benefit is now an option for MSI-H subjects who meet criteria for re-initiation of treatment (See Section 3.1.4.8 and Section 4.3.9) • Time and Events schedules and biomarker assessment tables specific for MSI-H cohorts during re-initiation of treatment have been added. • PK/Immunogenicity assessments will not be collected from subjects during re-initiation. Incorporates Administrative Letters 07, 06, and 05.
Administrative Letter 07	11-Jan-2018	Correction in Section 1.5 Overall Risk/Benefit Section regarding nivolumab and daratumumab infusion sequence.
Administrative Letter 06	20-Nov-2017	Changed in Medical Monitor
Administrative Letter 05	31-May 2017	Corrected BMS number in Document History described for Amendment 09.
Revised Protocol 06	19-Apr-2017	Incorporates Amendment 09 and Administrative Letter 04.
Amendment 09	19-Apr-2017	• This purpose of this amendment is to add information to align with the daratumumab program standards and to add clarity to various sections of the protocol. • Changed the dose of BMS-986016 from 80 mg to 160 mg • Added language to provide information regarding the rationale for the combination of nivolumab and daratumumab and the overall risk benefit of this combination. • Added inclusion criteria and the exclusion of vaccination with live vaccines to align with the daratumumab program standards. • Clarified the sequence of the daratumumab, nivolumab, and pre- and post-infusion medications for daratumumab. • Added details regarding monitoring vital signs and premedications to align with the daratumumab program standards. • Minor clarifications were also added to several sections.
Administrative Letter 04	26-Jan-2017	Change in Medical Monitor and correction of an error in product description removed from Table4.1-1.

Document	Date of Issue	Summary of Change
Revised Protocol 05	28-Nov-2016	Incorporates Amendment 08
Amendment 08	28-Nov-2016	This global amendment was written primarily to address the following: • Add two new cohorts: o Cohort C5: Subjects with MSI-High colorectal cancer receiving nivolumab combined with an anti-LAG3 agent (BMS-986016) o Cohort C6: Subjects with non-MSI-High colorectal cancer receiving Nivolumab combined with daratumumab
Revised Protocol 04	10-Aug-2016	Incorporates Amendment: 05
Amendment 05	10-Aug-2016	This global amendment was written primarily to address the following: • Add one new cohort, C3: MSI-High subjects with metastatic colorectal cancer receiving nivolumab and ipilimumab in the first line setting for their metastastic disease • Add specificity and clarifications regarding MSI testing requirements throughout the protocol • Increase the volume of tumor tissue sample submitted for correlative biomarker work, and add a quality control step to ensure only subjects with quality tumor tissue samples may be treated with study drug. • Reduce infusion time durations to 30 minutes for nivolumab and ipilimumab for Cohort C3 only. • Require confirmatory scan subsequent to an initial scan interpreted as PR and/or CR at least 4 weeks after this initial scan. • Modify management algorithms for toxicities to reflect revised nivolumab IB. • Revise contraception language in the protocol and add appendix specifying acceptable methods of contraception to reflect revised nivolumab IB.
Administrative Letter 03	19-Nov-2015	• Reported change in the medical monitor for the study
Administrative Letter 02	22-Jan-2015	• Required archived tumor tissue obtained prior to the last systemic therapy received in the metastatic setting or from an unresectable site of disease in the event that the sample collected is of poor quality.
Revised Protocol 03	10-Jun-2015	Incorporates Amendment: 04
Amendment 04	10-Jun-2015	This global amendment was written primarily to address the following: • Add a biomarker collection schedule for subjects dosed with the combination of nivolumab plus ipilimumab. • Include an appendix regarding MSI testing panel descriptions (PCR and IHC), classification of MSI status, and sample

Document	Date of Issue	Summary of Change
		prioritization. • In addition to the above changes, other minor changes have been made including the following: • Added a clarification regarding imaging assessments indicating confirmation scans for progressive disease do not have to be performed. • Clarified inclusion criterion regarding prior treatments. • Clarified exclusion criterion regarding radiation therapy. • Edited information regarding pregnancy in section addressing discontinuation of subjects from treatment. • Edited language addressing weight fluctuations and dose recalculations in section addressing selection and timing of dose for subjects. • Clarified information regarding timing for determining safety laboratory results. • Removed EORTC QLQ-C30 & EQ-5D Questionnaires from the Survival Follow-up Visit. • Removed exploratory endpoints utilizing IRRC assessments.
Revised Protocol 02	23-Apr-2014	Incorporates Amendment: 03
Amendment 03	23-Apr-2014	This global amendment was written primarily to be consistent with other protocols within the nivolumab program regarding Adverse Event Management Algorithms. Accordingly, the existing Appendix 01 of the protocol has been replaced with the most up-to-date management algorithms. In addition to the above change, other minor changes have been made including: • The title of the study in the protocol title page was updated to be specific for Microsatellite Instability High (MSI-H) Colon Cancer population. • BRAF mutation status is documented at the screening visit in order to align with hypotheses that will be addressed by the biomarker plan for CA209142. • An oversight regarding a missing 'X' in the time and events schedule was corrected pertaining to concomitant medication information collection at the screening visit. • A table note describing the allowable time window pertaining to biomarker sample collections was edited. This change was made to ensure consistency with other biomarker sample collections across the nivolumab program.
Revised Protocol 01	06-Feb-2014	Incorporates Amendment(s) 01
Amendment 01	06-Feb-2014	[redacted] In addition, this amendment provides clarification on the

Document	Date of Issue	Summary of Change
		following items in the protocol: Synopsis: • Clarification of Eligibility Criteria for prior treatment for the MSI-H Population Trial Objectives: • Clarification of an exploratory endpoint to specify for patients treated with nivolumab in combination with ipilimumab in the non MSI-H population • Edited primary and secondary objectives in synopsis for consistency throughout protocol Trial Conduct: • Clarification that additional treatment after progression could include nivolumab alone or nivolumab in combination with ipilimumab • Modification regarding post study access to therapy language to correctly specify Sponsor obligations • Clarification to exclusion criterion regarding hepatitis serology testing methodologies to align with methodologies specified in the Flow Chart/Time and Events Schedule • Clarification throughout the protocol regarding pregnancy testing while on study treatment to ensure testing is performed every 4 weeks (+ or – 1 week), regardless of dosing schedule. • Clarification that baseline MRI for brain is only for suspected or known disease • Clarification regarding on-study local laboratory assessments to align with protocol visit schedule • Clarification regarding archived biopsy information in the biomarker sampling schedule table to be consistent with language specified in the protocol body • Changes to nivolumab and ipilimumab immunogenicity sampling schedule to collect samples at 6 months (24 weeks) and every 6 months thereafter (for nivolumab) as this was determined to be sufficient given the half-life of anti-drug antibodies. • Replace ECOG 1-5 scale with correct 0-5 scale to correctly assess subjects
Original Protocol	18-Nov-2013	Not applicable

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 09:

This study has been revised to simplify study related schedule of activities, including study drug administration, and to help reduce participant burden while aligning with current study objectives. The key updates include:

- Frequency of tumor assessments has been reduced from every 12 weeks to every 24 weeks for participants with disease control meeting specified criteria.
- Re-initiated participants with complete response (CR) were previously allowed to stay on treatment until progressive disease (PD). This was updated to a maximum of 24 additional months on treatment following re-initiation.
- Added that coronavirus disease 2019 (COVID-19) vaccines that are NOT live are permitted during the study and after the last dose of investigational product. The efficacy and safety of vaccination in subjects who are receiving nivolumab, ipilimumab, BMS-986016, daratumumab, or combinations are unknown.
- Added that study therapy should also be delayed in cases of confirmed or suspected severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and in the case of prior SARS-CoV-2 infection, symptoms should have resolved in order to resume study intervention.
- Added clarification on study site closures and dissemination of clinical study data.
- Updated exploratory endpoints to collect and report data on participants after re-initiation.
- mStage 1/2 and cStage 1/2: Nivolumab monotherapy dosing has been updated from 3 mg/kg every 2 weeks (Q2W) to 480 mg every 4 weeks (Q4W).
- cStage 1/2 re-initiation: The treatment regimen for participants has been amended from nivolumab 480 mg Q4W to (240 mg nivolumab + ipilimumab 1 mg/kg) every 3 weeks (Q3W) for 4 doses followed by 480 mg nivolumab Q4W.
- Cohort 3 re-initiation: Participants with nivolumab dosing previously 240 mg Q2W will now have dosing 360 mg Q3W.
- Participants who are treated beyond progression will be able to receive treatment for a maximum of 24 additional months following initial Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1) defined PD.
- Updated biomarker sampling schedule for re-initiation cohorts to align with updated dosing schedule.
- Removed Patient Reported Outcome collection in re-initiation phase.
- Appendices have been updated to align with nivolumab program level updates.
- Minor editorial changes were incorporated throughout this protocol to provide clarity and consistency.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 09		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	Updated Medical Monitor contact information The following change was made in the Document History table for Revised Protocol 08: • Nivolumab infusion duration reduced to 30 minutes for Arms N and N+I ~~all cohorts and 30-minute ipilimumab infusion duration will be implemented in Cohort C4~~.	Updated to new clinical scientist contact information. This was an error in the previous revision description of change section as only N and N+I infusion duration were updated during Revised Protocol 08.
Synopsis	Updated the synopsis to accommodate for the changes made throughout the body of the protocol.	Updated for consistency across protocol.
Section 1.1.4.8 Rationale for Shorter Nivolumab and Ipilimumab Infusion Times	Updated "Shortened nivolumab infusion times will be implemented in all cohorts. Shortened ipilimumab infusions will be implemented in Cohorts C3 and C4 only" to "Therefore, shortened infusion times apply to all cohorts receiving nivolumab and ipilimumab."	To clarify that all cohorts receiving nivolumab and ipilimumab should have shortened infusion times.
Section 1.1.4.9 Rationale for Nivolumab Flat Dosing	Updated text to justify nivolumab dosing and switching of nivolumab dosing and frequency.	Provides justification and background for nivolumab flat dosing.
Section 1.1.4.10 Rationale for Nivolumab Dose: 240 mg Q3W (cStage 1/2), 480 mg Q4W (mStage 1/2 and cStage 1/2), and 360 mg Q3W (Cohort 3) During Re-initiation Treatment Section 3.1.4.2 MSI-H Nivolumab Monotherapy (Arm N): mStage 1 and 2 Section 3.1.4.3 MSI-H Nivolumab + Ipilimumab (Arm N+I): cStage 1 and 2	Updated section title to include all nivolumab doses and added text for rationale of nivolumab 360 mg Q3W treatment for Cohort 3 and clarified that nivolumab 480 mg Q4W is for mStage 1/2 and cStage 1/2.	Reduces frequency of treatment to help mitigate participant burden and provides rationale for flat dosing used in treatment re-initiation.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 09		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 1.5 Overall Risk/Benefit Assessment Section 3.1.5 Review of Safety	Changed "medical safety team (MST)" to "safety management team (SMT)."	To align with current BMS nomenclature.
Section 3.1 Study Design and Duration	Removed "On-treatment tumor imaging assessments will occur, starting 6 weeks after first dose, every 6 weeks (±1 week) for the first 24 weeks, then every 12 weeks (± 1 week) until disease progression or treatment is discontinued (whichever occurs later)."	To streamline protocol and reduce repetition as this is already stated in Sections 3.1.9.1, 5.4, and Table 5.1-14.
Section 3.1.4.2 MSI-H Nivolumab Monotherapy (Arm N): mStage 1 and 2 Section 3.1.4.3 MSI-H Nivolumab + Ipilimumab (Arm N+I): cStage 1 and 2 Section 3.1.4.4 Non-MSI-H Safety Cohort (Nivolumab + Ipilimumab) Section 3.1.4.5 MSI-H C3 Cohort (No Prior Treatment in Metastatic Setting, Nivolumab + Ipilimumab) Section 3.1.4.6 MSI-H C5 Cohort (2L in Metastatic Setting, Nivolumab + BMS-986016) Section 3.1.4.7 non-MSI-H C6 Cohort (Nivolumab + Daratumumab)	Removed RECIST 1.1 evaluation of response bullets.	To streamline protocol language and reduce repetition as this is already stated in multiple sections.
Section 3.1.4.3 MSI-H Nivolumab + Ipilimumab (Arm N+I): cStage 1 and 2	Clarified that questionnaires will be completed for all subjects except for those enrolled in the non-Microsatellite Instability High (MSI-H) Safety Cohort.	Updated for clarification.
Section 3.1.4.8 Treatment Options Upon Progression after Treatment	Added "inclusive of treatment beyond progression" and removed exception for re-initiated subjects	Accumulating data suggest that 24 months of programmed death

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 09		
Section Number & Title	**Description of Change**	**Brief Rationale**
Discontinuation At Maximum Clinical Benefit Section 4.3.1 Re-initiation Dose Schedules	with CR to be able to stay on treatment until PD.	receptor-1 checkpoint inhibitor treatment is sufficient for long-term benefit.
Section 3.1 Study Design and Duration	Updated Figure 3.1-1 Study Design Schematic (Arm N and Arm N+I) and Non-MSI-H Safety Cohort to include updated language of "Survival Follow-up" to "Follow-up For Survival."	Updated to clarify that follow-up for participants will continue for a minimum of 5 years from first treatment.
Section 3.1.9.1 Follow-up for all Cohorts After Initial Study Treatment	Added instructions for the investigators to reduce scan frequency for participants having disease control 3 years after the first dose. Removed duration and frequency of survival follow-up.	Added to reduce participant burden. To maintain clarity and consistency.
Section 3.1.10 End of Study Definition	Updated study conclusion definition to include a minimum of 5 years of follow-up from first treatment for the last participant, or until survival follow-up is concluded for all subjects, whichever occurs first. Added language on study completion and study site closure, reasons for early site closure, and what to do in the case of premature study termination or suspension.	Added to clarify that follow-up for participants will continue for a minimum of 5 years from first treatment. Added to clarify site closure and align with current standard BMS policies regarding site closure and end of study definition.
Section 3.4.1 Prohibited and/or Restricted Treatments	Added information regarding COVID-19 vaccines.	To explain which COVID-19 vaccines are permitted.
Section 3.6.2 Lost to Follow-Up	Modified text in this section with instructions for when a participant fails to return to the clinic for a required study visit.	Updated based on current BMS policies regarding lost to follow-up.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 09		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 4.1.3.2 Ipilimumab	Updated text for ipilimumab infusion time to approximately 30 minutes.	To align with current ipilimumab standard infusion times.
Section 4.3 Selection and Timing of Dose for Each Subject Section 5.1 Flow Chart/Time and Events Schedule	Updated dosing windows for Q2W, Q3W, Q4W, and Q6W dosing cycles. Updated doses and dosing schedules in respective tables.	The efficacy dose (cStage 1/2) was determined to be 3 mg/kg nivolumab + 1 mg/kg ipilimumab Q3W for 4 doses. Reduced dosing frequency to reduce participant burden. Dosing windows were updated to align with dosing frequencies.
Section 4.3.1 Re-initiation Dose Schedules	Updated treatments and treatment schedules upon re-initiation in Table 4.3.1-1.	To reduce unnecessary participant burden and to allow cStage 1/2 participants to reinitiate treatment with combination regimen.
Section 4.3.3 Dose Delay Criteria	Added “Study therapy should also be delayed in cases of confirmed or suspected SARS-CoV-2 infection, regardless of the severity.”	Standard SARS-CoV-2 requirement.
Section 4.3.5 Criteria to Resume Treatment	Added “In the case of prior SARS-CoV-2 infection, symptoms should have resolved in order to resume study treatment and there should be no sequelae that would place the participant at a higher risk of receiving study intervention.”	Standard SARS-CoV-2 requirement.
Section 4.3.8 Treatment Beyond Disease Progression	Added that subjects will be permitted to continue treatment for up to 24 months beyond initial RECIST 1.1 defined PD, as assessed by the investigator, and clarified that subjects who progress following re-initiation of treatment have the option to be treated beyond	For consistency with 24-month maximum treatment duration allowed for subjects who re-initiate treatment and alignment with nivolumab essential

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 09		
Section Number & Title	**Description of Change**	**Brief Rationale**
	progression for a cumulative maximum of 24 months from re-initiation dose. Added that treatment beyond progression may be administered during or after localized interventions. Added "For subjects with time point response of progression being treated beyond progression, scans should be repeated every 12 weeks or earlier, as clinically indicated, to assess further disease progression."	protocol elements (EPE). Updated to clarify when treatment beyond progression may be administered. To clarify that Investigator has flexibility to monitor progression with earlier scans if clinically indicated
Section 4.3.9 Treatment Re-initiation Inclusion Criteria: MSI-H Cohorts	Added "Inclusion Criteria" to section title.	Added to clarify that the section lists inclusion criteria for subjects in order to re-initiate treatment.
Section 5.1 Flow Chart/Time and Events Schedule	Removed "For MSI-H subjects only" and added "except for those enrolled in the non-MSI-H Safety Cohort" from EORTC QLQ-C30 and EQ-5D Questionnaires row of Table 5.1-2 and Table 5.1-3. Removed "through Week 23 visit and every alternate dose thereafter" from laboratory tests row of Table 5.1-2 and Table 5.1-3. Added troponin testing for Cohort C5 only in Table 5.1-7 and Table 5.1-13. Added "To Be Performed at Each Dosing Visit" to header in Table 5.1-9 and Table 5.1-10.	Fixing previous mistake. Every alternate dose was removed as planned sampling timelines are now aligned with dosing schedule. Consistency with relatlimab EPE. Added to clarify when assessments will be performed and for consistency across tables.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 09		
Section Number & Title	**Description of Change**	**Brief Rationale**
	Removed stool sample rows from Table 5.1-9 through Table 5.1-12.	Removed to correct previous error and align with current biomarker schedules.
	Removed "Note: Only Nivolumab will be administered during Re-initiation" from title of Table 5.1-10. Removed Nivolumab 480 mg Q4W treatment heading and footnote from Table 5.1-10.	Not applicable as re-initiation regimen for cStage 1/2 was updated.
	Updated dosing regimens and schedules in Tables 5.1-2, 5.1-3, 5.1-10, 5.1-11, and 5.1-12.	Updated to monotherapy flat dosing 480 mg Q4W schedule for mStage 1/2 and cStage 1/2. Updated nivolumab dosing from 240 mg Q2W to 360 mg Q3W for re-initiation of Cohort 3 to help reduce visits/mitigate participant burden.
	Removed table note and added reference to Table 5.1-14 in Tables 5.1-2 through 5.1-5, Table 5.1-7, and Tables 5.1-9 through 5.1-13 for clarity, as further tumor imaging assessment is required for all participants who go off treatment without having progressed.	Added reduction in scan frequency to reduce participant burden and help optimize participant safety.
	Removed the outcomes research assessment questionnaires from the re-initiation tables, Table 5.1-9 through Table 5.1-13.	Removed to reduce participant burden.
	Removed "MSI-H Cohorts at" from title of Table 5.1-13.	There are only re-initiation participants in MSI-H cohorts so all re-initiated participants are MSI-H.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 09		
Section Number & Title	**Description of Change**	**Brief Rationale**
	Added Table 5.1-14a Standard Tumor Imaging Assessment and Table 5.1-14b Reduced Tumor Imaging Assessment.	Added table to help streamline protocol. Table 5.1-14b was added to decrease participant burden and help improve safety.
Section 5.3.1 Imaging Assessment for the Study	Added "Collect any additional imaging that may demonstrate tumor response or progression (including scans performed at unscheduled time points and/or at an outside institution) for RECIST 1.1 tumor assessment and submit to the BICR."	Align with nivolumab EPE and clarify current unscheduled scan collection requirement, thereby helping to ensure accuracy of tumor response assessments.
Section 5.4 Efficacy Assessments	Added "Subjects with a history of brain metastasis should have surveillance MRI approximately every 12 weeks, or sooner if clinically indicated." Added "Confirmation of PR and/or CR is required after at least 4 weeks from the initial scan reporting response. Confirmation of progression is not required." Added rationale and criteria for subjects to qualify for reduced scan frequency.	Removed repetitive language from Section 3.1 and added to appropriate section for clarity and consolidation. Reduce participant burden and help optimize participant safety
Section 5.6.8 Tumor Samples	Removed biomarker sampling schedules for subjects in cStage 1/2 and Cohort 3 from Table 5.6.8-4. Changed biomarker sampling schedules for subjects in Cohort 5 to subjects in cStage 1/2 and Cohort 3 who re-initiate treatment in Table 5.6.8-5. Added Table 5.6.8-6 for biomarker sampling schedule for subjects in Cohort 5 who re-initiate treatment.	Due to the changes in dosing schedules, subjects in cStage 1/2 and Cohort 3 moved from Day 1 Week 5 biomarker sampling to Day 1 Week 4 biomarker sampling, so the tables were split into 2 different tables to accommodate this change.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 09		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.7 Outcomes Research Assessments	Removed "and for those subjects who re-initiate treatment in Cohorts N, N+I, and Cohorts 3 and 5." Added "If exceptional circumstances preclude the continued administration of measures using planned modalities, then alternate administration methods may be required, after consultation with Sponsor or the Sponsor's representative."	Removed to reduce participant burden. Added to allow collection of data on patient-reported outcomes via alternative administration methods.
Section 6.4 Pregnancy	Removed text on reporting pregnancy for female partners of male study subjects.	To align with the removal of contraceptive requirements for male subjects, no longer necessitating reporting of pregnancy for female partner of male study subject.
Section 8.3.3 Exploratory Endpoint(s)	Updated BOR2, ORR2, TTR2, DOR2, and PFS2 to BOR-R, ORR-R, TTR-R, DOR-R and PFS-R.	To align with language in the statistical analysis plan.
Section 9.1.2 Monitoring	Added language explaining that monitoring details describing strategy are provided in the monitoring plan.	Added to clarify remote monitoring and align with current standard BMS policies regarding remote monitoring.
Section 9.4 Dissemination of Clinical Study Data	Added language about BMS making information available to the public and where study information may be posted.	Added to align with current BMS policy on prevision of study results.
Appendix 3 Response Evaluation Criteria in Solid Tumors Guidelines (Version 1.1) with BMS Modifications	Updated to current RECIST 1.1 language.	Updated to accommodate BMS-specific RECIST 1.1 criteria.
Appendix 5 Women of Childbearing Potential	Definition of "woman of childbearing potential" was added.	Changes were made to be consistent with

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 09		
Section Number & Title	**Description of Change**	**Brief Rationale**
Definitions and Methods of Contraception	End of relevant systemic exposure time point was updated. Methods of Contraception section was updated with more details for the following sections: • Highly Effective Contraceptive Methods That Are User Dependent • Highly Effective Methods That Are User Independent • Sexual Abstinence • Less than Highly Effective Contraceptive Methods That Are User Dependent	current BMS protocol standards and policies.
Throughout	Removed BMS-936558 from all nivolumab references except the first mention. Minor editorial and typographical changes were made.	Updated for consistency when referring to nivolumab. Updated for editorial and grammatical purposes to provide clarity and consistency.

SYNOPSIS

Clinical Protocol CA209142

Protocol Title: A Phase 2 Clinical Trial of Nivolumab, or Nivolumab Combinations, in Recurrent and Metastatic Microsatellite Instability High (MSI-H) and non-MSI-H Colon Cancer

(**CheckMate 142: CHECK**point pathway and nivolu**MA**b clinical **T**rial **E**valuation **142**)

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

- Nivolumab monotherapy administered IV over 30 minutes at 3 mg/kg every 2 weeks until discontinuation of study therapy for reasons described in Section 3.1.4.1 Study Treatment Discontinuation.
- Nivolumab administered IV over 30 minutes at 1 mg/kg combined with ipilimumab administered IV over 90 minutes at 3 mg/kg every 3 weeks for 4 doses followed by nivolumab administered IV over 30 minutes at 3 mg/kg every 2 weeks until progression
- Nivolumab administered IV over 30 minutes at 3 mg/kg combined with ipilimumab administered IV over 90 minutes at 1 mg/kg every 3 weeks for 4 doses followed by nivolumab administered IV over 30 minutes at 3 mg/kg every 2 weeks until discontinuation of study therapy for reasons described in Section 3.1.4.1 Study Treatment Discontinuation.
- 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 until discontinuation of study therapy for reasons described in Section 3.1.4.1 Study Treatment Discontinuation. (Cohort C3)
- Nivolumab administered IV over 30 minutes at 240 mg every 2 weeks combined with BMS-986016 160 mg administered IV every two weeks until discontinuation of study therapy for reasons described in Section 3.1.4.1 Study Treatment Discontinuation. (Cohort C5)
- Nivolumab 240 mg every two weeks starting on Week 3, and 480 mg every four weeks starting from Week 25; combined with daratumumab 16 mg/kg weekly from Week 1-8, every two weeks from Week 9-24, and every four weeks starting on Week 25 (Cohort C6)
- Nivolumab 480 mg every 4 weeks administered IV over 30 minutes until discontinuation of study therapy for reasons described in Section 3.1.4.1 (mStage 1/2 and cStage 1/2)
- Nivolumab 360 mg every 3 weeks and ipilimumab 1 mg/kg every 6 weeks

Treatment for maximum clinical benefit subjects in MSI-H cohorts who meet criteria for re-initiation (Section 3.1.4.8) is presented below:

Cohort	Treatment upon Re-initiation
mStage 1/2	Nivolumab 480 mg Q4W
cStage 1/2	Nivo 240 mg + Ipi 1 mg/kg Q3W for 4 doses followed by Nivo 480 mg Q4W
C3 (1L)	Nivo 360 mg Q3W + Ipi 1 mg/kg Q6W
C5 (BMS-986016 /anti-LAG3)	Nivo 240 mg Q2W + BMS-986016 (LAG3) 160 mg Q2W

Abbreviations: Ipi = ipilimumab; LAG3 = lymphocyte activation gene-3; Nivo = nivolumab; Q2W = every 2 weeks; Q3W = every 3 weeks; Q4W = every 4 weeks; Q6W = every 6 weeks.

Treatment duration after re-initiation, inclusive of treatment beyond progression, will be a maximum of 24 months. Time and events schedules for study procedures during re-initiation screening, treatment and follow-up are presented in Section 5.1. PK and immunogenicity samples will not be collected at any time during re-initiated treatment.

Study Phase: 2

Research Hypothesis: Treatment with nivolumab monotherapy, nivolumab combined with ipilimumab, nivolumab combined with anti-LAG-3 antibody (BMS-986016), or nivolumab combined with daratumumab will have clinical activity in subjects with recurrent or metastatic CRC.

Objectives:

Primary Objective

To evaluate the investigator-assessed objective response rate (ORR) of nivolumab monotherapy and nivolumab in combination with either ipilimumab, or anti-LAG-3 antibody (BMS-986016) in dMMR/ microsatellite instability high (MSI-H) mCRC; the ORR of nivolumab combined with ipilimumab in subjects with metastatic non-MSI-H (pMMR) CRC; and, the ORR of nivolumab combined with daratumumab therapy in subjects with metastatic non-MSI-H (pMMR) mCRC.

Secondary Objectives

To evaluate the IRRC-assessed objective response rate (ORR) of nivolumab monotherapy and nivolumab in combination with either ipilimumab or anti-LAG-3 antibody (BMS-986016) in dMMR/MSI-H mCRC; the ORR of nivolumab combined with ipilimumab in subjects with metastatic non-MSI-H (pMMR) CRC; and, the IRRC ORR of nivolumab combined with daratumumab therapy in subjects with metastatic non-MSI-H (pMMR) mCRC.

To evaluate the disease control rate (DCR) of nivolumab monotherapy or combined with the above agents in subjects with metastatic mCRC.

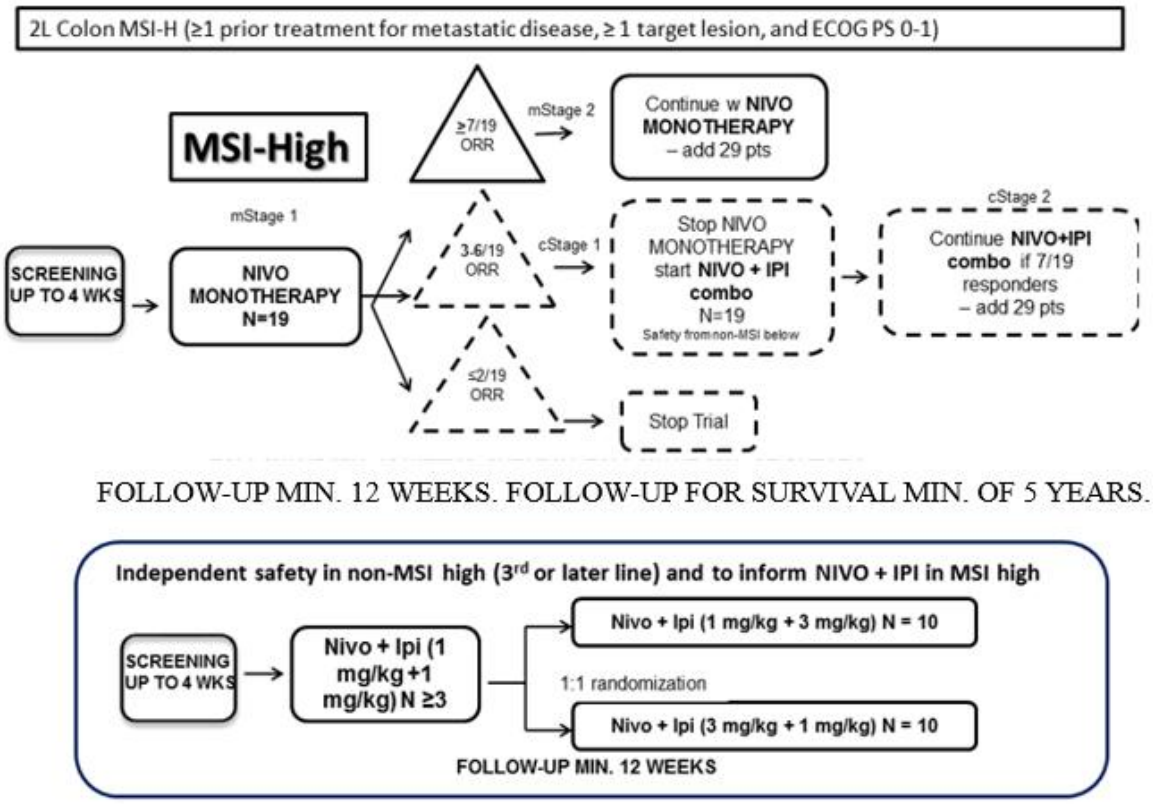
Exploratory Objectives

Listed in protocol Section 1.3.3.

Study Design: CA209142 is a Phase 2 open-label, multi-center trial of nivolumab monotherapy (Cohort N) or in combination therapy (Cohort N + I) to estimate the response rate in MSI-H CRC and non-MSI-H CRC. CA209142 completed a safety cohort of subjects with non-MSI-H CRC to assess the safety and tolerability of nivolumab in combination with ipilimumab in subjects with non-MSI-H CRC in preparation for an analogous 2-stage assessment of the response rate for the combination in MSI-H CRC.

As described in **Figure 1**, subjects with recurrent or metastatic CRC received nivolumab or nivolumab with ipilimumab, depending on the response rate in the monotherapy MSI-H cohort and tolerability of the nivolumab combined with ipilimumab combination in the non-MSI safety cohort.

Figure 1: **Study Design Schematic**



mStage = monotherapy Stage; cStage = combination Stage; Arm N = Nivolumab monotherapy; Arm N+I = nivolumab in combination with ipilimumab; nMSI-H N+I = non-MSI-H nivolumab in combination with ipilimumab

Two Stage Design: Both Arms N and N+I will follow a two-stage design to test whether nivolumab monotherapy or nivolumab combined with ipilimumab yields an objective response rate (ORR) that is of clinical interest in MSI-H metastatic colorectal cancer mCRC. On treatment stages that meet an ORR threshold will proceed from Stage 1 to Stage 2 (same for both m and cStage). **Table 1** contains the efficacy criteria decisions.

Table 1: **Efficacy Criteria to Proceed from Stage 1 to Stage 2**

mStage 1 Efficacy Criteria	**Next Step**
≥ 7/19 subjects have confirmed CR or PR	Go into mStage 2
3-6/19 subjects have confirmed CR or PR	Close mStage 1 & open cStage 1
≤ 2/19 subjects have confirmed CR or PR	Close Trial
cStage 1 Efficacy Criteria	
≥ 7/19 subjects have confirmed CR or PR	Go into cStage 2
< 7/19 subjects have confirmed CR or PR	Close Trial

Note: Confirmed responses are documented by a second scan performed ≥ 4 weeks after first scan reporting response

The decision to enter cStage 1 will be based not only on the activity of the mStage 1, but the safety seen in the non-MSI Independent Safety Sub-Trial; thus the decision to start the combo in MSI-H will take into account both efficacy and safety. If ≤ 2/19 subjects in mStage 1 (ie, an approximate ORR of 10%), the absolute lower bound indicating "no activity" will be declared and the protocol will close to further enrollment.

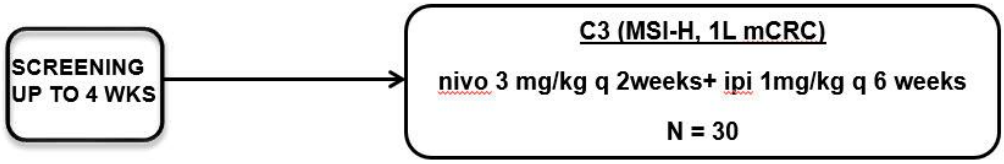
Dose-escalating Safety Evaluation Phase for Combination Arm: Although the regimen currently used in the Phase 3 melanoma study, nivolumab 1 mg/kg IV + ipilimumab 3 mg/kg, is expected to also be tolerable in mCRC, an initial dose-escalating safety evaluation for the combination arms will be conducted.

Enrollment to mStage 1 for Arm N will occur in parallel to the safety evaluation for Arm N+I.

Per Revised Protocol 07, for the monotherapy mStage 1/2 and the combination therapy cStage 1/2, the option to discontinue treatment at maximum clinical benefit as assessed by the Investigator and defined in Sections 3.1.4.1 has been incorporated. Re-initiation of treatment upon progression after discontinuation at maximum clinical benefit is an option for eligible MSI-H subjects as described in Section 3.1.4.8.

The CA209-142 study also includes the C3 cohort as described below in **Figure 2**. The C3 cohort will enroll 30 MSI-H subjects who have not had prior therapy for their metastatic disease. Per Revised Protocol 07, for Cohort C3, the option to discontinue treatment at maximum clinical benefit as assessed by the Investigator and defined in Sections 3.1.4.1 has been incorporated. Re-initiation of treatment upon progression after discontinuation at maximum clinical benefit is an option for eligible MSI-H subjects as described in Section 3.1.4.8.

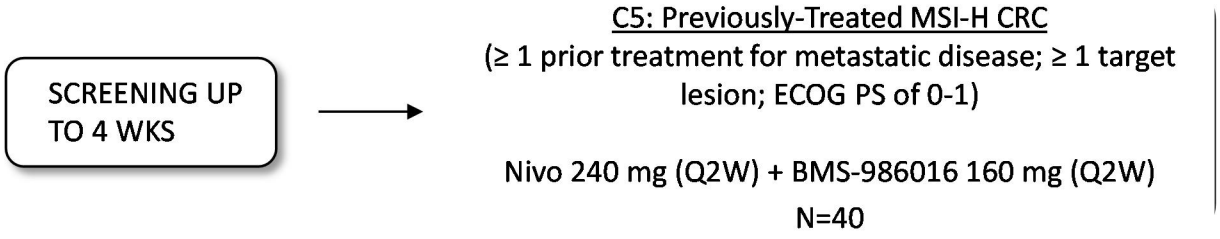
Figure 2: **Study Schematic for Cohort 3**



The CA209-142 study includes a C5 cohort as described below in **Figure 3**. The C5 cohort will enroll 40 previously-treated MSI-H subjects who have not had prior anti-PD-1 therapy for their metastatic CRC disease.

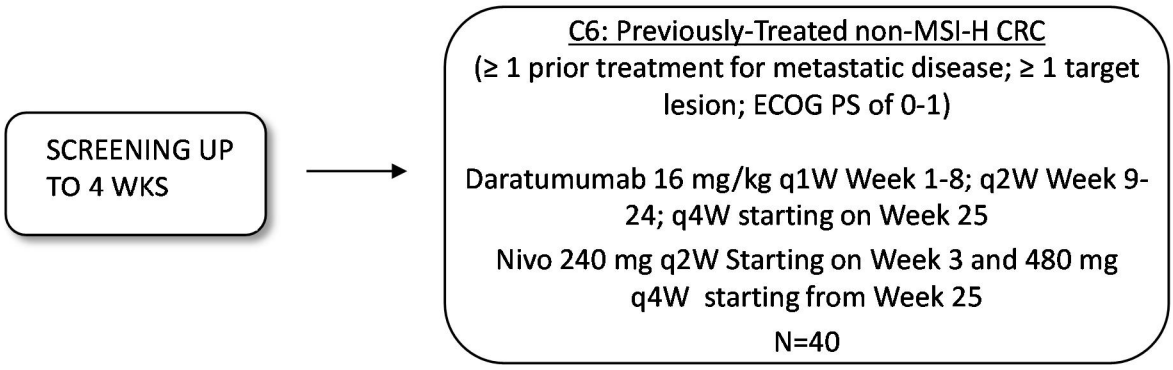
Per Revised Protocol 07, for Cohort C5, the option to discontinue treatment at maximum clinical benefit as assessed by the Investigator and defined in Sections 3.1.4.1 has been incorporated. Re-initiation of treatment upon progression after discontinuation at maximum clinical benefit is an option for eligible MSI-H subjects as described in Section 3.1.4.8.

Figure 3: **Study Schematic for Cohort 5**



The CA209142 study includes a C6 cohort as described below in **Figure 4**. The C6 cohort will enroll 40 previously-treated non-MSI-H subjects.

Figure 4: Study Schematic for Cohort 6



Study Population:

Key Inclusion Criteria (See protocol Section 3.3.1 for full list of criteria)

1. Men and women ≥ 18 years of age with an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1
2. Subjects with histologically confirmed, recurrent or metastatic CRC
3. Microsatellite instability expression detected by an accredited laboratory per local regulations.
   a. Subjects with MSI-H tumors will enroll in the MSI-H Cohort (Cohort N and Cohort N+ I) (mStage and cStage groups), the C3 Cohort, and the C5 Cohort.
   b. Subjects with phenotypes that are non-microsatellite instability high (non-MSI-H) will enroll in the non-MSI-H Safety Cohort and the C6 Cohort.
4. For subjects with recurrent or metastatic MSI-H CRC in the MSI-H Cohort (mStage and cStage groups):
   a. Progression during, after, or have been intolerant to ≥ 1 line treatment(s) for their metastatic disease, which must include at least
      i. A fluoropyrimidine, and
      ii. Oxaliplatin or irinotecan,
         1. Subjects who received 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

         OR

         2. Subject actively refuses chemotherapy for the treatment of metastatic (Stage IV) or locally advanced disease considered as standard treatment for this disease stage, despite being informed by the investigator about the treatment options. The subject's refusal must be thoroughly documented. The investigator will discuss each individual subject refusing chemotherapy with the sponsor's medical monitor to confirm eligibility.
5. For subjects with non-MSI-H colon cancer for the non-MSI-H Safety Cohort:
   a. Progression during, after, or been intolerant following the last administration of approved standard therapies, which must include at minimum a fluoropyrimidine and oxaliplatin or irinotecan, as well as at least one of the following agents, if approved or in standard national guidelines, bevacizumab, cetuximab or panitumumab (if KRAS wild type), and regorafenib.

OR

b. Subject actively refuses chemotherapy (including drugs or biologics) for the treatment of metastatic (Stage IV) or locally advanced disease considered as standard treatment for this disease stage, despite being informed by the investigator about the treatment options. The subject's refusal must be thoroughly documented. The investigator will discuss each individual subject refusing chemotherapy with the sponsor's medical monitor to confirm eligibility.

6. For subjects with metastatic or recurrent CRC in the MSI-H C3 Cohort, subjects must not have had treatment for their metastatic disease.
7. For subjects with metastatic or recurrent CRC in the C6 Cohort: Progression during, after, or been intolerant following the last administration of approved standard therapies, which must include at minimum a fluoropyrimidine, and oxaliplatin or irinotecan
8. Subjects must have measurable disease per RECIST 1.1 criteria for response assessment. Subjects 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.

Key Exclusion Criteria (See protocol Section 3.3.2 for full list of criteria)

1. Active brain metastases or leptomeningeal metastases are not allowed.
2. 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.
3. Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast.
4. Subjects with active, known or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
5. Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.

Re-initiation of Treatment for MSI-H Cohorts

Subjects in MSI-H cohorts who discontinue study treatment at Maximal Clinical Benefit, (Section 3.1.4.1) are permitted to re-initiate treatment, if disease progression defined by RECIST criteria occurs within 1 year (≤52 weeks) and protocol-defined criteria (Section 4.3.9) are met.

Study Assessments: The primary endpoint of this study is ORR which is based on tumor assessments at baseline and then at 6 weeks from first dose which continue every 6 weeks for the first 24 weeks and every 12 weeks thereafter until disease progression (investigator-assessed RECIST 1.1-defined progression) or treatment discontinuation, whichever occurs later.

Statistical Considerations:

Sample Size: This study will consist of 5 cohorts: non-MSI-H safety cohort, MSI-H cohort (Cohort N and Cohort N+I), Cohort C3 (MSI-H subjects who have not had prior therapy for their metastatic disease), MSI-H Cohort C5 Cohort and non-MSI-H Cohort C6. It is expected to treat up to approximately 96 central-pathology-lab-confirmed subjects (up to 29 non-MSI-H and up to 67 MSI-H) for the initial non-MSI-H and MSI-H cohorts. It is expected to treat approximately 30 subjects in cohort C3. It is expected to treat approximately 40 MSI-H subjects in C5 Cohort and 40 non-MSI-H subjects C6 Cohort.

Sample size determination for non-MSI-H and MSI-H cohorts:

The MSI-H cohort will include subjects who are defined as MSI-H based on standard diagnostic testing documented in the subject's medical history and prospectively confirmed in the current study by repeat testing using a polymerase chain reaction (PCR) test.

The non-MSI-H safety cohort will include all subjects testing non-MSI-H by the repeat PCR test, including those who were MSI-H by medical history but not confirmed by repeat testing.

For the non-MSI-H safety cohort, sample size is not based on power considerations and will depend on the observed toxicity.

For the MSI-H cohort, a Simon optimal two-stage design will be used to test the null hypothesis that the true ORR is ≤ 30% (not considered clinically compelling) with either nivolumab monotherapy or the combination of nivolumab/ipilimumab. In the first stage (mStage 1), 19 subjects will be treated with nivolumab monotherapy. If there are 2 or fewer responses in these first 19 treated subjects, the protocol will be closed to further enrollment. If there are more than 2 but less than 7 responses in the first 19 treated subjects, accrual to the monotherapy arm will be stopped, and the combination arm will be opened for accrual. Otherwise, if there are 7 or more responses in the first 19 treated subjects, approximately 29 additional subjects will be accrued to the monotherapy arm (mStage 2) to target a total of 48 treated subjects.

If accrual to the combination arm is opened to the MSI-H cohort as specified above, stage I of the Simon two-stage design will be initiated in the combination arm with 19 treated subjects (cStage 1). If there are 6 or fewer responses in these first 19 treated subjects, accrual to the combination arm will be stopped. Otherwise, approximately 29 additional subjects will be accrued to the combination arm (cStage 2) to target a total of 48 subjects treated with combination therapy.

Subjects whose repeat testing does not confirm MSI-H status will be replaced in order to obtain the required number of subjects in each stage of the Simon design. Note that because of the delay in obtaining the centrally evaluated MSI status, more than 48 subjects may be treated with monotherapy and combination therapy in these initial cohorts.

The null hypothesis will be rejected if 20 or more responses are observed in 48 treated subjects in the remaining open arm (nivolumab monotherapy or nivolumab/ipilimumab combination).

Within a given treatment arm, this design yields a one-sided type I error rate of 5% and power of 90% when the true response rate is 52%

Sample size determination for Cohort C3:

The sample size determination for Cohort C3 was not based on power consideration but to provide precision on estimation of ORR. Saltz et al[1] reported ORR of 49% and 38% to in chemotherapy group, per investigator assessment and per independent response review committee assessment, respectively in this patient population. **Table 2** presents the 95% CI for ORR ranging from 45% to 65%, which are considered meaningful clinical outcome, with a sample size of 30 subjects.

Table 2: Interval Estimation and Coverage Probability, Clopper-Pearson Method, 95% Confidence Interval

Sample size	Number of responses	Response rate	Confidence interval
30	13	0.43333	(0.2546, 0.6257)
30	14	0.46667	(0.2834, 0.6567)
30	15	0.50000	(0.3130, 0.6870)
30	16	0.53333	(0.3433, 0.7166)
30	17	0.56667	(0.3743, 0.7454)

Table 2: Interval Estimation and Coverage Probability, Clopper-Pearson Method, 95% Confidence Interval

Sample size	Number of responses	Response rate	Confidence interval
30	18	0.60000	(0.4060, 0.7734)
30	19	0.63333	(0.4386, 0.8007)
30	20	0.66667	(0.4719, 0.8271)

Sample size determination for Cohort C5:

The sample size determination for Cohort C5 was not based on power consideration but to provide precision on estimation of ORR. The table below shows the precision of the estimation of ORR based on the two sided 95% exact CI using Clopper Pearson methods based on 4, 8, 12, 16 and 20 responders out of 40 subjects. With 40 subjects, the 95% CI of observed 16 responders will be (24.9%, 56.7%), which has the lower bound excluding the 23% background ORR from previous interim results.

Table 3: Two-sided 95% exact CI using Clopper-Pearson method based on the number of observed responses out of 40 subjects (For C5 Cohort)

The number of observed responses	4	8	12	16	20
Observed Response Rate	4/40 (10.0%)	8/40 (20.0%)	12/40 (30.0%)	16/40 (40.0%)	20/40 (50.0%)
95% exact CI	(2.8%, 23.7%)	(9.1%, 35.6%)	(16.6%, 46.5%)	(24.9%, 56.7%)	(33.8%, 66.2%)

Sample size determination for Cohort C6:

The sample size determination for Cohort C6 was not based on power consideration but to provide precision on estimation of ORR. The table below shows the precision of the estimation of ORR based on the two sided 95% exact CI using Clopper Pearson methods based on 6, 7, 8, 9, and 12 responders out of 40 subjects. With 40 subjects, the 95% CI of observed 6 responders will be (5.7%, 29.8%), which has the lower bound excluding the 5% background ORR.

Table 4: Two-sided 95% exact CI using Clopper-Pearson method based on the number of observed responses out of 40 subjects (For C6 Cohort)

The number of observed responses	6	7	8	9	12
Observed Response Rate	6/40 (15.0%)	7/40 (17.5%)	8/40 (20.0%)	9/40 (22.5%)	12/40 (30.0%)
95% exact CI	(5.7%, 29.8%)	(7.3%, 32.8%)	(9.1%, 35.6%)	(10.8%, 38.5%)	(16.6%, 46.5%)

Endpoints:

The primary endpoint is investigator-assessed ORR in each cohort. It is defined as the number of subjects with a best overall response (BOR) of confirmed CR or PR, according to RECIST 1.1 criteria, divided by the number of treated subjects in the related cohort. The secondary endpoint is IRRC-assessed ORR in each cohort. It is defined as the

number of subjects with a best overall response (BOR) of confirmed CR or PR, according to RECIST 1.1 criteria, divided by the number of treated subjects in the related cohort.

Analyses:

In each cohort, the investigator-assessed ORR will be further characterized by the investigator assessed duration of response (DOR) and rate of complete response (CR). A response rate estimate and corresponding two-sided 95% exact CI will be provided. The method proposed by Atkinson and Brown will be used to estimate the CI. This confidence interval takes into account the group sequential nature of the two-stage Simon design, where applicable. The method of Clopper-Pearson will be used otherwise if more subjects were treated beyond the sample size per the original Simon's 2-stage design. Within each cohort, ORR will be further characterized by the duration of response (DOR) and rate of complete response (CR). DOR will be summarized for subjects who achieve confirmed PR or CR using the Kaplan-Meier (KM) product-limit method. Median values of DOR, along with two-sided 95% CI (based on the log-log transformation), will also be calculated. Investigator-assessed CR will be summarized by cohort and by treatment (monotherapy and combination therapy, if applicable). An estimate of complete response rate (CRR) and corresponding two-sided 95% exact CI will be provided using Clopper-Pearson method.

ORR based on IRRC assessment will be summarized similarly as above and will be characterized by IRRC-assessed DOR and IRRC-assessed CRR similarly as above.

Safety analyses will be performed in all treated subjects by cohort (MSI-H, non-MSI-H, and C3) and treatment (monotherapy and combination therapy, if applicable). 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.

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[1] Saltz LB, Clarke S, Díaz-Rubio E, et al: Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. J Clin Oncol. 2008;26:2013-2019.

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1 INTRODUCTION AND STUDY RATIONALE

1.1 Study Rationale

CA209142 (CheckMate 142: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 142) is a Phase 2 open-label, multi-center trial of BMS-936558 (nivolumab) monotherapy and nivolumab in combination with ipilimumab, BMS-986016, or daratumumab to estimate the response rate in subjects whose colorectal tumors have defects in the DNA mismatch repair system (dMMR/MSI-H) or in subjects whose colorectal tumors have proficient MMR (pMMR/non-MSI-H). Tumors with the MMR defect are referred to as having high-level microsatellite instability (MSI-H). The central objective of the study will be to determine if nivolumab alone or nivolumab in combination therapy demonstrates a clinically meaningful objective response rate (ORR) > 30% in distinct patient populations. Well-established tests to identify patients with MSI-H colorectal cancer (CRC) include immunohistochemistry (IHC) for MMR protein expression, polymerase chain reaction (PCR)-based analysis for the molecular signature of microsatellite instability, and next-gen sequencing (NGS) for the corresponding genomic defects in the genes coding for MMR or microsatellite instability signature. These tests will allow for identification of potential subjects. Patients with MSI-H CRC have a distinctly recognizable clinicopathological profile and the MSI-H status serves both as a prognostic and predictive factor when compared to non-MSI-H CRC patients. Part of the clinicopathologic profile of MSI-H CRC includes a local and systemic anti-tumoral immune response to evade the control of the immune system. This initial control of the MSI-H tumor by immune surveillance gives a strong rationale that nivolumab or nivolumab combination therapy, with its mechanism of action that abrogates immune tolerance, will have significant clinical activity in advanced MSI-H CRC or non-MSI-H CRC.

1.1.1 Colon Cancer Background and Treatment Options

Worldwide, colon cancer (including rectal cancer) is the third most common form of cancer in men with 663,000 cases (10% of the total), and second most common in women with 571,000 cases (9.4% of the total) per year.[1] This disease predominately occurs in developed regions with the highest rates being found in Australia/New Zealand and Western Europe and to a lower extent in Africa and South-Central Asia. There is a higher incidence in men vs women with a ratio of 1.4:1. Each year, there are about 608,000 deaths from colon cancer, which is approximately 8% of all cancer deaths, making colon cancer the fourth most common cause of cancer death. In 2013 in the United States (US), an estimated 142,820 new cases will be diagnosed with 50,830 deaths.[2]

Treatment options for patients with metastatic colon or rectal cancer (mCRC) are predominantly 5-fluorouracil (5-FU) and leucovorin containing regimens in combination with either oxaliplatin or irinotecan (FOLFOX or FOLFIRI) with a biologic agent such as bevacizumab. Cetuximab is also an option if KRAS status is non-mutated.[3] Both regimens are considered to be equivalent, with a median first-line progression-free survival (PFS) of 8.5 months for FOLFIRI and 8 months for FOLFOX.[4] In second-line for those patients who had first-line therapy with FOLFOX or another 5-FU containing therapy, the median PFS for patients receiving FOLFIRI is approximately

4.5 months.[5,6] Bevacizumab, ramucirumab, and ziv-afilbercept have indications for second-line treatment in combination with chemotherapy and have demonstrated improvement in median OS (mOS); for both biologic agents, the improvement in mOS is less than 2 months: 13.5 months vs 12.06 months for bevacizumab,[7] 13.3 months vs 11.7 months for ramucirumab,[8] and 11.2 months vs 9.8 month for ziv-aflibercept.[9] Cetuximab also has demonstrated an improvement in mOS of less than 2 months in patients who have previous received chemotherapy, 6.1 months vs 4.6 months, when compared to best supportive care (BSC).[10] Lastly, regorafenib, in patients who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy, has demonstrated an improvement in mOS of less than 2 months, 6.4 months vs 5 months, when compared to BSC.[11] Similar results were demonstrated for triflurdine/tipiracil HCl.[12] Despite the numerous treatment options for mCRC, the benefit of these therapies after first-line therapy is modest, and complete radiographical responses are rare, highlighting the need for more effective therapies.

1.1.2 Microsatellite Instability

Microsatellite instability (MSI) is the molecular fingerprint of a deficient mismatch repair system (MMR). The term MSI is widely accepted as a surrogate for both dMMR and MSI-H tumors. Approximately 15% of CRCs display MSI-High (MSI-H), owing either to epigenetic silencing of MLH1 or a germline mutation in one of the mismatch repair genes MLH1, MSH2, MSH6 or PMS2.[13] There are well established methods to detect dMMR/MSI-H that are incorporated into clinical practice. A clinical and molecular profile of MSI tumors has been described, leading to the concept of an MSI phenotype in CRC. Studies have confirmed that MSI identification can be prognostic in that MSI tumors have a better prognosis[14] than microsatellite stable CRC, but MSI status can also be predictive in that MSI-H cancers do not necessarily have the same response to the chemotherapeutic strategies used to treat microsatellite stable tumors. Specifically, Stage II MSI tumors might not benefit from 5‑fluorouracil‑based adjuvant chemotherapy regimens.[15,16] In the metastatic setting, however, there are conflicting data regarding MSI status and response to chemotherapy[17] including association with better,[18] worse,[19] or differential (5-fluorouracil compared to capecitabine)[20] chemosensitivity, with no randomized trial comparing chemotherapy regimens in subjects with MSI-H mCRC or comparing MSI-H and non-high MSI (nMSI-H) subjects with mCRC.

Characterization of the molecular basis of MSI in CRC is underway and initial results show that mutations in genes encoding kinases and candidate genes with microsatellite tracts are over‑represented in MSI tumors.[17] Hypermethylation of *MLH1* can cause *BRAF* mutations in CRC and are more frequent in sporadic MSI-H cases compared to hereditary cases.[21,22] The strong local immune reaction observed in MSI-H CRC is characterized by peritumoral lymphoid nodules (Crohn's-like reaction) and a dense overall infiltration of the tumor with lymphocytes,[23] part of which are activated and cytotoxic.[24,25] Frameshift mutations encountered in MSI-H CRC might lead to the generation of tumor-specific antigens.[26] In addition, it is known that antigens expressed

in a noninflamed environment may induce tolerance rather than eliciting an antitumoral immune response[27]; however, the existence of T cell responses directed against a multiple tumor antigens in individuals with MSI-H CRC has been demonstrated in patients.[28,29] This observation strongly suggests that antigenic structures are generated from coding DNA sequences carrying frameshift mutations in sufficient amounts to trigger antigen-specific T cell responses. The cytokine milieu encountered at the MSI-H tumor site initially tends to be proinflammatory and favoring T-cell response rather than contributing to tolerance induction.[30,31] The mechanism by which immune tolerance is induced is not completely understood. This initial control of the MSI-H tumor by immune surveillance makes it hopeful that nivolumab, with its mechanism of action that abrogates immune tolerance, will have significant clinical activity in MSI-H CRC. In study CA209003, a Phase 1 trial of subjects with solid tumors, one trial subject with MSI-H metastatic CRC (mCRC) had a long-term complete response, suggesting the immune-modulatory approach warrants further evaluation.[32]

1.1.3 MSI Testing

The National Comprehensive Cancer Network (NCCN) recommends MSI testing for all patients with CRC.[33] There are several options for testing. The IHC MMR testing consists of staining of tumor tissue for loss of expression of the four mismatch repair proteins known to be mutated in Lynch syndrome, *MLH1*, *MSH2*, *MSH6*, and *PMS2*.[34] If at least one of these is not normally expressed, then the testing indicates the dMMR (MSI) phenotype. PCR amplification of a set of mono-and/or di-nucleotide repeats on tumor and normal DNA, followed by comparison of the peak patterns by capillary electrophoresis, can also assess for MSI. In 2009, the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group evaluated IHC and PCR testing methods in patients with Lynch Syndrome and found that:

- the sensitivity of MSI testing is about 89% for mutations in MLH1 and MSH2, with a lower sensitivity of about 77% for mutations in MSH6 (and PMS2), while sensitivity is higher when three or more mononucleotide markers are included in the panel; specificity is estimated to be 90.2%, with an adequate level of evidence;
- sensitivity of IHC testing is 83%, regardless of the underlying MMR gene mutation with specificity is more variable, and central estimate is 88.8%;
- inadequate evidence is available to determine the distribution of mutations in the MMR genes, but preliminary estimates are 32% MLH1, 39% MSH2, 14% MSH6, and 14% PMS2.[35]

Many recommendations for MSI testing include recommendations for *BRAF* testing for the V600E mutation when *MLH1* expression is absent in the tumor by ICH analysis. The significance of this *BRAF* mutation often indicates that *MLH1* expression is down-regulated by somatic methylation of the promoter region of the gene and not a germline mutation.[36] Testing for *BRAF* may be useful for determination of a heritable condition, ie, Lynch Syndrome, but is likely more important as a prognostic factor as two recent reports have demonstrated worse survival in MSI-H subjects with *BRAF* mutations, which can occur in up to 50% of patients with MSI-H tumors.[37,38]

1.1.4 Rationale for CA209142 Study Design

1.1.4.1 Rationale for Nivolumab Monotherapy

Nivolumab monotherapy at 3 mg/kg was chosen to be tested in a 2-stage Simon design estimating the response rate in MSI-H CRC because of a favorable risk-benefit ratio in multiple other tumor types in the large Phase 1 CA209003. The dose and schedule of nivolumab in this study will be 3 mg/kg every two weeks, based upon the analyses of safety, efficacy, and exposure-response data from the ongoing Phase 1 study CA209003. Anti-tumor activity was observed at dose levels ranging from 1 to 10 mg/kg in melanoma, non-small cell lung cancer (NSCLC), and renal cell carcinoma (RCC), as well as at dose levels of 0.1 and 0.3 mg/kg in melanoma. The anti-tumor activity of nivolumab in RCC was investigated at dose levels 1 and 10 mg/kg, with the higher activity observed at 10 mg/kg.

The observed anti-tumor activity in melanoma and NSCLC was highest at 3 mg/kg, suggesting that anti-tumor activity approaches a plateau at dose levels of 3 mg/kg and above. Consistent with these observations, the results of the exposure-response analyses for these tumor types show that the probability of a tumor response tended to approach a plateau for trough concentrations produced by 3 and 10 mg/kg every 2 week dosing.

Nivolumab was adequately tolerated up to 10 mg/kg, the highest dose level tested, and no maximum tolerated dose (MTD) was identified. Although the spectrum, frequency, and severity of nivolumab-related AEs were generally similar across the dose levels tested, the 10 mg/kg doses level had numerically higher Grade 3-4 drug-related SAEs and AEs leading to discontinuation. Based upon the totality of the safety, efficacy, and exposure-response data, a dose of 3 mg/kg every 2 weeks (Q2W) was selected as the dose anticipated to achieve an appropriate balance of efficacy and risk.

1.1.4.2 Rationale for Nivolumab Combined with Ipilimumab

The combination of nivolumab and ipilimumab was chosen as an experimental arm because of preclinical and preliminary clinical evidence suggesting synergy between nivolumab and ipilimumab. While PD-1 and CTLA-4 are both co-inhibitory molecules, evidence suggests that they use distinct mechanisms to limit T cell activation. Preliminary indirect data from peripheral T cell assessments suggest that a given T-cell checkpoint inhibitor may modulate host immune cell phenotype rendering them more susceptible to alternate checkpoint inhibitors and thereby enhancing anti-tumor activity. Specifically, nivolumab increased peripheral CTLA-4+ and regulatory T cells in subjects without clinical response in CA209006. In a preclinical melanoma model, anti-CTLA-4 therapy increased PD-1+, PD-L1+ and CTLA-4+ tumor infiltrating T cells. CTLA-4 knockout mice suffer from a fatal lymphocyte proliferative disorder. CTLA-4 is expressed on T_{reg} cells and transiently on activated T cells. CTLA-4 interaction with its ligands B7-1 (CD80) and B7-2 (CD86), results in cell cycle arrest, with G1 inhibition particularly evident in CD4 cells on secondary antigen exposure. In vivo blockade of CTLA-4, utilizing anti-CTLA-4 mAb, induces regression of established tumors and enhanced antitumor immune responses in several immunogenic murine tumor models. Moreover, when anti-CTLA-4 mAb is used in conjunction with granulocyte macrophage colony stimulating factor (GM-CSF)-secreting tumor

vaccines, poorly immunogenic cancers in mice are rejected. Tumor infiltration with activated lymphocytes, associated inflammation, and increased resistance to Treg activity as well as microenvironmental changes in tumor vasculature, are the hallmark of the anti-tumor effect of ipilimumab. These findings suggest that CTLA-4 blockade, alone or in combination with another immunological agent, can induce a potent antitumor response. In addition, in the Phase 2 ipilimumab monotherapy study CA184004, increases in tumor infiltrating lymphocytes (TILs) and interferon-inducible genes were observed following treatment with ipilimumab, and PD-L1 positive tumor cells co-localize with both TILs and interferon expression in metastatic melanoma. The preliminary clinical evidence has demonstrated a higher frequency of patients with substantial tumor burden reduction for the combination of nivolumab and ipilimumab. Improved OS associated with substantial tumor burden reduction has been noted with immunotherapies. For instance, improved OS has been noted in metastatic melanoma subjects obtaining a complete response to IL-2. If this observation is also applicable to treatment with nivolumab combined with ipilimumab then there could also be the potential for large improvements in overall survival compared to other targeted therapies or to chemotherapy.

1.1.4.3 Rationale for Nivolumab and Ipilimumab in Treatment-Naive dMMR mCRC: Cohort C3

Immune responses to combination therapy with nivolumab and ipilimumab may be more robust in patients who are chemotherapy-naive.[39] This observation, taken together with the decreased benefit from cytotoxic chemotherapy in the dMMR/MSI-H mCRC population,[40] suggest that a rational approach would be to offer combined immunotherapy to dMMR/MSI-H patients earlier in the course of their disease.

Standard of care therapy for mCRC is cytotoxic chemotherapy with response rates >40% in the first-line setting, but toxicities reported such Grade 3-4 neutropenia or diarrhea exceed 40%.[41] The median time to disease progression is reported as almost 8 months for combination chemotherapy without bevacizumab [42,43] and up to 9.4 months with bevacizumab.[42]

Cytotoxic chemotherapy is the standard of care in the first-line treatment of all patients with mCRC,[43] including the elderly[44] and those with dMMR/MSI-H.[16] However, it has been demonstrated that earlier stage dMMR/MSI-H patients get no survival benefit from adjuvant cytotoxic chemotherapy. In order to spare early-stage dMMR/MSI-H from treatment-related toxicities, expense, and reduced quality of life during chemotherapy, many experts recommend against adjuvant 5-FU based chemotherapy for their disease, and these patients are managed with post-resection observation.[16] In the metastatic setting, there is a strong suggestion that dMMR/MSI-H patients may have worse prognosis and PFS when treated with cytotoxic chemotherapy.[45] Approximately 30% all of mCRC patients will discontinue first-line chemotherapy due to toxicity.[42]

There is potential for a first-line immunotherapy approach to be particularly beneficial for the elderly. Methylation in normal colon tissue is correlated with aging,[46] and sporadic MLH1 hypermethylation in tumors is much more common in older patients. dMMR/MSI can result from

increased frequencies of promoter methylation (the CpG island methylator phenotype, or CIMP). CIMP-positive cancers tend to occur in older patients.[47] Given ongoing concerns that the elderly may be more vulnerable to toxicities of chemotherapy,[48] an immuno-oncology approach in the first-line would address an unmet need in the elderly mCRC population. Given the clinically meaningful and durable responses to combined immunotherapy, research has continued to focus on expanding the benefit of PD-1 blockade in mCRC.

Analysis of results from multiple studies across tumor types (melanoma, RCC, lung cancer, gastric cancer, and hematologic malignancies) has demonstrated enhanced antitumor activity and response rates for the combination of nivolumab plus ipilimumab when compared to nivolumab alone. The efficacy of this combination is anticipated to be equal if not greater to that of nivolumab monotherapy, and the safety profile for nivolumab as monotherapy is expected to be comparable to that for the combination with ipilimumab. Hence, it is considered not necessary to have a staged enrollment for Cohort C3. To further build on the hypothesis that a combined immunotherapy approach may offer prolonged benefit and be well-tolerated in this patient population, Cohort C3 will enroll patients with treatment-naive dMMR/MSI-H mCRC in a 1-stage approach to the combination of nivolumab and ipilimumab.[39,49,50]

1.1.4.4 LAG-3 and T Cell Exhaustion

Like PD-1, lymphocyte activation gene-3 (LAG-3; CD223) is also a type I transmembrane protein that is expressed on the cell surface of activated CD4+ and CD8+ T cells and subsets of NK and dendritic cells.[51] LAG-3 is closely related to CD4, which is a co-receptor for T helper cell activation. Both molecules have 4 extracellular Ig-like domains and require binding to their ligand, major histocompatibility complex (MHC) class II, for their functional activity. In contrast to CD4, LAG-3 is only expressed on the cell surface of activated T cells and its cleavage from the cell surface terminates LAG-3 signaling. LAG-3 can also be found as a soluble protein, but it does not bind to MHC class II, and its function is unknown.

It has been reported that LAG-3 plays an important role in promoting regulatory T cell (Treg) activity and in negatively regulating T cell activation and proliferation.[52] Both natural and induced Treg express increased LAG-3, which is required for their maximal suppressive function.[53,54] Furthermore, ectopic expression of LAG-3 on CD4+ effector T cells reduced their proliferative capacity and conferred on them regulatory potential against third-party T cells.[54] Recent studies have also shown that high LAG-3 expression on exhausted lymphocytic choriomeningitis virus (LCMV)-specific CD8+ T cells contributes to their unresponsive state and limits CD8+ T cell antitumor responses.[55] In fact, LAG-3 maintained tolerance to self and tumor antigens via direct effects on CD8+ T cells in 2 murine models.

1.1.4.5 Rationale for Combination Nivolumab/Anti-LAG-3 Antibody (BMS-986016) Therapy in MSI-H mCRC (Cohort C5)

BMS-986016 is a fully human antibody specific for human LAG-3 that was isolated from immunized transgenic mice expressing human immunoglobulin genes. It is expressed as an IgG4 isotype antibody that includes a stabilizing hinge mutation (S228P) for attenuated Fc receptor

binding in order to reduce or eliminate the possibility of antibody- or complement-mediated target T cell killing. BMS-986016 binds to a defined epitope on LAG-3 with high affinity (Kd, 0.25-0.5 nM) and specificity and potently blocks the interaction of LAG-3 with its ligand, MHC class II (IC50, 0.7 nM). The antibody exhibits potent in vitro functional activity in reversing LAG-3-mediated inhibition of an antigen-specific murine T-cell hybridoma overexpressing human LAG-3 (IC50, 1 nM). In addition, BMS-986016 enhances activation of human T cells in superantigen stimulation assays when added alone or in combination with nivolumab (anti-PD-1 antibody).

Immune tolerance observed in the setting of tumor development and tumor recurrence, however, seems to be mediated by the co-expression of various T cell negative regulatory receptors, not solely from LAG-3. Data from chronic viral infection models,[54,55,56] knock-out mice,[57,58,59] tumor recurrence models,[60] and, to a more limited extent, human cancer patients[60,61,62] support a model wherein T cells that are continuously exposed to an antigen become progressively inactivated through a process termed "exhaustion." Exhausted T cells are characterized by the expression of T cell negative regulatory receptors, predominantly CTLA-4, PD-1, and LAG-3, whose action is to limit the cell's ability to proliferate, produce cytokines, and kill target cells and/or to increase Treg activity. However, the timing and sequence of expression of these molecules in the development and recurrence of tumors have not been fully characterized.

It is hypothesized that CTLA-4 acts as the dominant off-switch for tolerance, but it is the strong synergy between the PD-1 and LAG-3 inhibitory pathways that seems to mediate tolerance to both self and tumor antigens.[57,58,60] Whereas CTLA-4 knockout (KO) mice die prematurely from multiorgan inflammation,[63] PD-1 and LAG-3 single knockout mice present minimal immunopathologic sequelae.[58] In contrast, dual knock-out mice (LAG3-/-PD1-/-) abrogates self-tolerance with resultant autoimmune infiltrates in multiple organs and even lethality.[57,58] These dual knock-out mice also show markedly increased survival from and clearance of multiple transplantable tumors.[57]

Conversely, extensive co-expression of PD-1 and LAG-3 on tumor-infiltrating CD4+ and CD8+ T cells has been shown in distinct transplantable tumors and samples from melanoma, RCC, head and neck, NSCLC, and ovarian cancer patients.[60,64,65,66,77,79,80] Blockade of PD-1/PD-L1 interactions has been successfully used to restore antitumor immunity in preclinical and clinical studies. But the simultaneous blockade of PD-1 and LAG-3 pathways on T cells may exert an even more robust antitumoral immunity in naive as well as in recurrent tumors due to the possibility of reversing LAG-3–mediated T cell exhaustion. In 2 syngeneic mice models, for example, dual anti–LAG-3/anti–PD-1 antibody therapy is able to cure most mice of established tumors that are largely resistant to single antibody treatment.[57] Furthermore, recurrent tumors from a melanoma mouse model with increased Treg cell numbers and increased expression of checkpoint inhibitors PD-1, LAG-3, TIGIT, and TIM-3 can be controlled by depletion of Tregs (via FoxP3-DTR) plus the administration of anti-PD-L1 antibody. But more importantly, tumor regression of these recurrent tumors can also be accomplished with the combination of anti-PD-L1 plus anti-LAG-3 antibodies (C9B7W mAb), which also increases T cell activity.[60] In a recent analysis, 33% to 47% of head

and neck tumors showed a T cell-inflamed phenotype (TCIP) similar to melanoma, based on a gene expression signature. Furthermore, various checkpoint molecules were universally co-expressed in these TCIP tumors, including PD1, CTLA4, LAG3, PDL-2, and IDO, as shown in gene expression analysis.[64]

Given the above literature supporting synergistic activity of nivolumab and anti–LAG-3 antibody, it is hypothesized that this combination could have antitumor effects in solid cancers such as mCRC. In a study that examined infiltrating lymphocytes from 108 colorectal tumor samples and their peritumoral tissues using immunohistochemistry, the percentage of LAG-3 expressing cells was four times higher in tumor samples than in peritumoral tissues.[65]

These data argue strongly that dual blockade of the PD-1 and LAG-3 pathways could be a promising combinatorial strategy for MSI-H mCRC and support treatment of an MSI-H mCRC population with a combination of nivolumab and anti-LAG-3 mAb BMS-986016.

1.1.4.6 Dose and Scheduling Rationale (Nivolumab and Ipilimumab)

In CA209004, the 3 mg/kg nivolumab and 3 mg/kg ipilimumab cohort exceeded the maximum tolerated dose per protocol. In CA209004, while both Cohort 2 (1 mg/kg nivolumab + 3 mg/kg ipilimumab) and Cohort 2a (3 mg/kg nivolumab + 1 mg/kg ipilimumab) had similar clinical activity, a dose of 3 mg/kg of ipilimumab every 3 weeks for a total of four doses and 1 mg/kg nivolumab every 3 weeks for four doses followed by nivolumab 3 mg/kg every 2 weeks until progression was chosen. Exposure-response analysis of nivolumab monotherapy across dose ranges of 1 mg/kg to 10 mg/kg revealed similar clinical activity while exposure-response analysis of 0.3 mg/kg, 3 mg/kg, and 10 mg/kg of ipilimumab monotherapy have demonstrated increasing activity with increase in dose in the Phase 2 study CA184022. Therefore, theoretically, the selection of 3 mg/kg of ipilimumab (Cohort 2) may be more clinically impactful than selection of 3 mg/kg of nivolumab (Cohort 2a). The combination arm in this study has a similar dose and schedule as that in CA209004 for the first 12 weeks, increasing the likelihood of replicating the clinical activity seen in the CA209004 study. Based on the clinical activity in CA209004, the majority of responses to the combination of nivolumab and ipilimumab occur in the first 12 weeks.

Given the uncertainty of whether the ipilimumab administered past week 12 contributes to the clinical benefit and the fact that the approved schedule for ipilimumab is every 3 weeks for a total of four doses in the FDA and EMA approved label dosing section, ipilimumab will administered every 3 weeks for a total of 4 doses. Nivolumab monotherapy treatment every two weeks until progression was studied in CA209003 and has been studied across the nivolumab monotherapy Phase 3 registrational trials. Refer to the current nivolumab Investigator Brochure for additional information.

Clinical activity of nivolumab and ipilimumab combination was further evaluated in patients with stage IIB-IV NSCLC as first-line treatment in CA209012, a large Phase 1, multi-arm safety study of nivolumab monotherapy and nivolumab in combination with various systemic anticancer therapies. Early combination cohorts of nivolumab 1 mg/kg + ipilimumab 3 mg/kg and nivolumab 3 mg/kg + ipilimumab 1 mg/kg, both followed by maintenance nivolumab 3 mg/kg Q2W, resulted in significant toxicity in the NSCLC population, with 39% of patients discontinuing treatment due to a treatment-related adverse events. Thus, additional combination cohorts were initiated using lower doses of both nivolumab (1 mg/kg) and ipilimumab (1 mg/kg), or the approved dose of nivolumab (3 mg/kg Q2W) with less frequent dosing of ipilimumab (Q6W or Q12W). These new regimens were better tolerated, and the safety profile was comparable to what has been observed in the nivolumab monotherapy cohort study. Clinical activity was observed in all combination cohorts, but numerically higher response rates were observed in the cohorts evaluating the approved dose of nivolumab 3 mg/kg, with confirmed response rates ≥ 30% for the ipilimumab 1 mg/kg Q12W and Q6W regimens, cohorts P and Q, respectively.[67] Given the similarity in patient profiles of advanced NSCLC and CRC, nivolumab 3 mg/kg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks will be studied in Cohorts C3 and C4 with the expectation that there will not be changes in the safety profile, as has been demonstrated in NSCLC.

1.1.4.7 Rationale for Treatment Duration and Introducing Re-Initiation in MSI-H/dMMR Cohorts

Clinical study CA209-142 was originally designed to continue nivolumab monotherapy and nivolumab combination treatments until progression in all cohorts. The optimal duration of immunotherapy still remains an important question and continues to be investigated. At the time of Revised Protocol 07, some patients with MSI-H/dMMR mCRC have experienced durable clinical benefit and have remained on study treatment for longer than 2 years. Revised Protocol 07 was developed to identify optimal treatment duration for those patients who achieve maximum clinical benefit and to allow re-initiation of study treatment within the first year of treatment discontinuation.

Few patients with MSI-H/dMMR mCRC, a distinct and often IO-sensitive subgroup of mCRC, seem to experience a unique response pattern, with few late responders and deepening of responses with long-term treatment.[68] This observation from the CA209-142 study was taken into account when defining optimal time for treatment discontinuation for maximum benefit.

Accumulating data suggest that 2 years of PD-1 checkpoint inhibitor treatment may be sufficient for long term benefit; therefore this duration was considered when modifying treatment duration

for MSI-H/dMMR Cohorts of CA209-142 study. As an example, 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 subjects with NSCLC), specified a maximum treatment duration of 2 years. Among 16 subjects with NSCLC who discontinued nivolumab after completing 2 years of treatment, 12 subjects were alive > 5 years and remained progression-free without any subsequent therapy. In the CA209003 NSCLC cohort, the OS curve begins to plateau after 2 years, with an OS rate of 25% at 2 years and 18% at 3 years.[69] These survival outcomes are similar to Phase 3 studies in previously treated NSCLC, in which nivolumab treatment was continued until progression or unacceptable toxicity (2-year OS rates of 23% and 29%, and 3 year OS rates of 16% to18% for squamous and non-squamous NSCLC, respectively).[70] Similar results have been reported in clinical studies of pembrolizumab, another PD-1 inhibitor. Keynote-010 was a randomized phase 3 trial of pembrolizumab (at either 2 mg/kg or 10 mg/kg every 3 weeks) versus docetaxel in subjects with previously treated, PD-L1-positive, advanced NSCLC which specified a maximum treatment duration of 2 years for pembrolizumab. OS was significantly longer with both pembrolizumab 2 mg/kg (HR 0.72, P = 0.00017) and pembrolizumab 10 mg/kg (HR 0.60, P < 0.00001) compared to docetaxel, with an OS plateau developing beyond 2 years in both pembrolizumab arms. Among 690 patients who received pembrolizumab, 47 patients completed 2 years of pembrolizumab and stopped treatment. Most were able to maintain their response, including those with stable disease, with only 2 patients (4%) having confirmed progression after stopping at 2 years.[71]

CA209-142 trial was originally designed to continue nivolumab monotherapy or combination treatments until progression or toxicity. Recently presented data from CA209-142 study in subjects with MSI-H mCRC tumors suggest that some subjects achieve response and deepening of response with longer treatment duration. A small number of subjects achieved response as late as second year of treatment. Moreover, some subjects who are still on treatment in earlier cohorts have already been on treatment longer than 24 months. Therefore, a strict stopping rule at 2-years was not considered ideal for CA209-142. Instead, Revised Protocol 07, incorporates the option to discontinue treatment after minimum of 24 months of treatment in subjects who have achieved maximum clinical benefit as assessed by the Investigator and described in Section 3.1.4.1. It is not yet known whether subjects with late partial response would need treatment longer than 24 months. Therefore, to minimize the potential risk of disease recurrence as a result of premature treatment discontinuation, all MSI-H subjects who achieved objective response within second year of treatment, will be required to continue to receive study therapy for additional 12 months before considering the option to discontinue for maximum clinical benefit (Section 3.1.4.1).

In addition to treatment discontinuation for maximum clinical benefit, Revised Protocol 07 brings the option to re-initiate study treatment for subjects who experience a progression during the first year (≤ 52 weeks), as long as the eligibility criteria for re-initiation are met (Section 4.3.9). MSI-H/dMMR mCRC has widely shown to be a IO-sensitive subgroup, and some patients may potentially benefit from resuming study treatment at time of progression. In advanced NSCLC, updated results from KEYNOTE-010 demonstrated that a majority of patients who completed 2 years of pembrolizumab treatment and subsequently developed confirmed progression benefited

from a second course of pembrolizumab (re-initiation).[72] 25 patients developed progression, and 14 of these patients started a second course of pembrolizumab. Among patients who underwent re-initiation, 6 (43%) had PR and 5 (36%) had SD per BICR per RECIST 1.1. Clinical activity of reinitiating study treatment with nivolumab or nivolumab combinations will be evaluated in CA209142 to shed light on this important clinical question in MSI-H/dMMR mCRC.

1.1.4.8 Rationale for Shorter Nivolumab and Ipilimumab Infusion Times

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 approximately 30 minutes duration in subjects will diminish the burden provided no change in safety profile. Previous clinical studies of nivolumab monotherapy and ipilimumab monotherapy and the combination of nivolumab and ipilimumab have used a 60-minute infusion duration for nivolumab and 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.

- Nivolumab has been administered safely over 60 minutes at doses ranging up to 10 mg/kg safely over a long treatment duration. In Study CA209010 (a Phase 2, randomized, double blinded, dose-ranging study of nivolumab in subjects with advanced/metastatic clear cell RCC), 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 approximately 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 the CA184022 study, where ipilimumab was administered up to a dose of 10 mg/kg, on-study drug-related hypersensitivity events (Grade 1-2) were reported in 1 (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 90-minute infusion in large Phase 3 studies in prostate cancer (CA184043) and as adjuvant therapy for stage 3 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 nivolumab or ipilimumab clinical studies or the combination of nivolumab and ipilimumab. 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.

Therefore, shortened infusion times apply to all cohorts receiving nivolumab and ipilimumab.

1.1.4.9 Rationale for Nivolumab Flat Dosing

The nivolumab dose of 240 mg Q2W was selected based on clinical data and modeling and simulation approaches using population PK (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 PK has been extensively studied in multiple tumor types, including melanoma, NSCLC, RCC, classical Hodgkin lymphoma (cHL), squamous cell carcinoma of the head and neck (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.[73,74] A flat dose is expected to simplify dosing and administration for re-initiation Cohort 2. A flat dose of 240 mg Q3W was equivalent to the 3 mg/kg dose at the median body weight of approximately 80 kg in patients in the nivolumab program based on modeling and simulation. As compared to body weight-corrected dosing regimen, a flat dosing regimen is expected to reduce dosing errors.[75] Nivolumab 360 mg every 3 weeks (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 [Cavgss] following administration of nivolumab 360 mg Q3W and 480 mg Q4W are predicted to be similar to those following administration of nivolumab 240 mg Q2W and nivolumab 3 mg/kg Q2W administered to patients over a wide body weight range (34-180 kg) across tumor types. 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.

Extensive exposure-response analyses of multiple PK measures (maximum serum concentration at Day 1 [Cmax1], average serum concentration at Day 28 [Cavg28], and trough serum concentration at Day 28 [Cmin28]) and efficacy and safety endpoints indicated that the efficacy of the flat-dose 480 mg IV regimen are similar to that of 3 mg/kg Q2W IV regimen. In exposure-response 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 exposure-

response 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. Based on PK modeling and simulations, administration of nivolumab 480 mg Q4W will be started after steady state is achieved with 240 mg Q2W and is predicted to provide Cavgss similar to 240 mg Q2W. While 480 mg Q4W is predicted to provide greater (approximately 20%) maximum steady state concentrations and lower (approximately 10%) steady state trough concentrations, these exposures are predicted to be within the exposure ranges observed at doses up to 10 mg/kg Q2W used in the nivolumab clinical program, and are not considered to put participants at increased risk. Similar to the nivolumab 240 mg Q2W dosing regimen, the exposures predicted following administration of nivolumab 480 mg Q4W are on the flat part of the exposure-response curves for previously investigated tumors, melanoma, and NSCLC, and are not predicted to affect efficacy. Based on these data, nivolumab 480 mg Q4W is expected to have similar efficacy and safety profiles to nivolumab 240 mg Q2W.

Based on population pharmacokinetic and exposure-response (efficacy and safety analysis) for data from the nivolumab lung program analyses as well as totality of clinical data in nivolumab program, the nivolumab 360 mg Q3W regimen is predicted to produce average exposure at steady state comparable to that of the nivolumab 3 mg/kg Q2W regimen when combined with ipilimumab 1 mg/kg Q6W. Data from the clinical sub group efficacy and safety analyses indicated that the clinical benefits/risks following nivolumab 360 mg Q3W flat dose administration is expected to be similar to that following nivolumab 3 mg/kg Q2W administration, when administered in combination with ipilimumab 1 mg/kg Q6W in subjects with unresectable mesothelioma.[76] Moreover, the dosing regimen of nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W was demonstrated to be safe and tolerable in 1L NSCLC in Study CA2099LA when combined with 2 cycles of chemotherapy. Thus, the same regimen without combination with chemotherapy is expected to be safe and may be more tolerable in 1L CRC subjects.

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

1.1.4.10 Rationale for Nivolumab Dose: 240 mg Q3W (cStage 1/2), 480 mg Q4W (mStage 1/2 and cStage 1/2), and 360 mg Q3W (Cohort 3) During Re-initiation Treatment

Nivolumab is currently approved for the treatment of various tumors, including melanoma, NSCLC, SCLC, RCC, cHL, SCCHN, UC, and MSI-H mCRC using a regimen of either nivolumab 240 mg Q2W or nivolumab 480 mg Q4W. A flat dose is expected to simplify dosing and administration for re-initiation Cohort 2. The rationale for a flat dose of 240 mg Q3W is provided above in Section 1.1.4.9.[75] Subjects in CA209142 originally enrolled to either mStage 1/2 or cStage 1/2 who are going into re-initiation will be treated with nivolumab 480 mg every 4 weeks (Q4W), which provides a more convenient dosing regimen for subjects. While 480 mg Q4W is predicted to provide greater (approximately 117%) maximum concentrations and lower (approximately 10%) steady state trough concentrations, these exposures are predicted to be lower

than the exposure ranges observed exposures at doses up to 10 mg/kg Q2W used in the nivolumab clinical program, and are not considered to put subjects at increased risk. Similar to the nivolumab 240 mg Q2W dosing regimen, the exposures predicted following administration of nivolumab 480 mg Q4W, are on the flat part of the exposure-response curves for previously investigated tumors, melanoma and NSCLC, and are not predicted to affect efficacy. Based on these data, nivolumab 480 mg Q4W is expected to have similar efficacy and safety profiles to nivolumab 240 mg Q2W.

The less frequent dosing regimen, nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W, selected as the regimen to be used for Cohort 3 subjects re-initiating treatment is expected to substantially reduce the burden on patients and health care providers while offering a favorable benefit/risk profile for 1L CRC subjects. Based on population pharmacokinetic and exposure-response (efficacy and safety analysis) for data from the nivolumab lung program analyses as well as totality of clinical data in nivolumab program, the nivolumab 360 mg Q3W regimen is predicted to produce average exposure at steady state comparable to that of the nivolumab 3 mg/kg Q2W regimen when combined with ipilimumab 1 mg/kg Q6W.[76]

1.1.5 Rationale to Support Dose/Schedule of Nivolumab Combined with BMS-986016 (Cohort C5)

The dose selection and schedule of nivolumab in combination with the BMS-986016 antibody have been determined using all available safety (clinical and laboratory) and PK/pharmacodynamic data modeling recommendations, and by incorporating toxicity profiles for nivolumab (data from the completed Study CA209003, a Phase 1 nivolumab monotherapy study in advanced solid tumors) and BMS-986016 (data from the ongoing Study CA224020).

The combination of nivolumab and BMS-986016 is currently being evaluated in Study CA224020, a Phase 1, dose escalation and cohort expansion study of the safety, tolerability, and efficacy of anti-LAG-3 antibody (BMS-986016) administered alone and in combination with anti-PD-1 mAb (nivolumab) in advanced solid tumors, and in Study CA224022 in hematologic malignancies.

Table 1.1.5-1: BMS-986016 Alone or in Combination with Nivolumab in Study CA224020 (Solid Tumors)

BMS-986016 Q2W	Nivolumab Q2W	Number of Subjects
20 mg	NA	5
80 mg	NA	4
240 mg	NA	4
800 mg	NA	10
20 mg	80 mg	7
20 mg	240 mg	9
80 mg	240 mg	129[a]
160 mg	240 mg	4
240 mg	240 mg	8

Source: Protocol CA224020 Table S.6.4A.2

[a] Eight subjects in dose escalation and 121 subjects in dose expansion.
Abbreviation: NA = not applicable.

As of 23-Jan-2017 in Study CA224020, among all subjects treated with BMS-986016 as monotherapy or in combination with nivolumab (N = 121), the median duration of therapy was 8.33 weeks (range: 2.0 to 32.7 weeks). Among the subjects treated with BMS-986016 at 160 mg and nivolumab at 240 mg (n = 4), the median duration of therapy was 9.25 weeks (range: 7.9 to 12.7 weeks).

No DLTs were observed in the BMS-986016 monotherapy cohorts up to the maximum administered dose of 800 mg Q2W. A total of 5 DLTs were observed in the combination cohorts: 1 in the BMS-986016 20 mg and nivolumab 80 mg cohort (Grade 3 mucositis); 1 in the BMS-986016 20 mg and nivolumab 240 mg cohort (Grade 4 ventricular fibrillation); 1 in the BMS-986016 80 mg and nivolumab 240 mg cohort (Grade 4 lipase elevation); and 2 in the BMS-986016 240 mg and nivolumab 240 mg cohort (1 event of Grade 3 aseptic meningitis and 1 event of Grade 5 myocarditis).

The most common AEs observed among all 157 treated subjects and those treated at the BMS-986016 160 mg and nivolumab 240 mg dose level are shown in Table 1.1.5-3. The most common SAEs are shown in Table 1.1.5-3. AEs leading to study discontinuation are shown in Table 1.1.5-4. On-study deaths through 16-Feb-2017 are shown in Table 1.1.5-5.

As of 20-Feb-2017, an additional 2 subjects have received study treatment with BMS-986016 160 mg and nivolumab 240 mg, scheduled Q2W, on Study CA224022 (subjects with hematologic malignancies). No subjects have discontinued study treatment due to AEs. There have been no treatment-related SAEs. All of the subjects are still alive and either remain on treatment or in safety follow-up. For these subjects, Table 1.1.5-2 shows the subjects' treatment exposure, AEs, and study outcome. Thus, across both Study CA224020 (solid tumors) and Study CA224022 (hematologic tumors), 6 subjects have been treated for a minimum of 60 days with the dose level of BMS-986016 160 mg and nivolumab 240 mg Q2W.

Table 1.1.5-2: Safety Results of Subjects Treated with BMS-986016 160 mg and Nivolumab 240 mg Every 2 Weeks on Study CA224022 (Hematologic Tumors)

Age	Cancer Diagnosis	Date of First Dose	Number of Treatments	Treatment-related Adverse Events	Outcome
59	Hodgkin's Lymphoma	7-Dec-16	4	None	On-treatment
23	Hodgkin's Lymphoma	14-Dec-16	5	None	On-treatment

Table 1.1.5-3: Most Common (> 10%) Adverse Events in Study CA224020

Adverse Event	BMS-986016 160 mg and Nivolumab 240 mg (N = 4)		All BMS-986016 and Nivolumab Combination Cohorts (N = 157)	
	Any Grade n (%)	Grade 3-4 n (%)	Any Grade n (%)	Grade 3-4 n (%)
Fatigue	2 (50.0)	0	34 (21.7)	1 (0.6)
Malignant neoplasm progression	0	0	25 (15.9)	2 (1.3)
Asthenia	0	0	22 (14.0)	1 (0.6)
Nausea	0	0	19 (12.1)	0
Diarrhea	0	0	16 (10.2)	2 (1.3)
Dyspnea	0	0	16 (10.2)	2 (1.3)

Source: Protocol CA224040 Table S.6.1A.2

Table 1.1.5-4: Most Common Serious Adverse Events (> 10%) in Study CA224020

Serious Adverse Event	BMS-986016 160 mg and Nivolumab 240 mg (N = 4)		All BMS-986016 and Nivolumab Combination Cohorts (N = 157)	
	Any Grade n (%)	Grade 3-4 n (%)	Any Grade n (%)	Grade 3-4 n (%)
Malignant neoplasm progression	0	0	25 (15.9)	2 (1.3)
Blindness unilateral	1 (25.0)	1 (25.0)	0	0
Intestinal obstruction	1 (25.0)	1 (25.0)	0	0

Source: Protocol CA224020 Table S.6.3A.2

Table 1.1.5-5: Adverse Events Leading to Discontinuation in Study CA224020

Adverse Event	BMS-986016 160 mg and Nivolumab 240 mg (N = 4)		All BMS-986016 and Nivolumab Combination Cohorts (N = 157)	
	Any Grade n (%)	Grade 3-4 n (%)	Any Grade n (%)	Grade 3-4 n (%)
Malignant neoplasm progression	0	0	6 (3.8)	1 (0.6)
Meningitis aseptic	0	0	2 (1.3)	2 (1.3)
Lipase increased	0	0	1 (0.6)	1 (0.6)
Mucosal inflammation	0	0	1 (0.6)	1 (0.6)
Myocarditis	0	0	1 (0.6)	0
Pneumonitis	0	0	1 (0.6)	1 (0.6)

Table 1.1.5-5: Adverse Events Leading to Discontinuation in Study CA224020

Adverse Event	BMS-986016 160 mg and Nivolumab 240 mg (N = 4)		All BMS-986016 and Nivolumab Combination Cohorts (N = 157)	
	Any Grade n (%)	Grade 3-4 n (%)	Any Grade n (%)	Grade 3-4 n (%)
Troponin I increased	0	0	1 (0.6)	1 (0.6)
Ventricular fibrillation	0	0	1 (0.6)	1 (0.6)

Source: Protocol CA224020 Table S.6.4A.2

Table 1.1.5-6: On-Study Deaths in Study CA224020

	BMS-986016 160 mg and Nivolumab 240 mg (N = 4) n (%)	All BMS-986016 and Nivolumab Combination Cohorts (N = 157) n (%)
Deaths	0	32 (20.4)
Disease	0	30 (19.1)
Study treatment toxicity (myocarditis)	0	1 (0.6)
Other	0	1 (0.6)

Source: Protocol CA224020 Table S.6.2A

Based on the safety data from Feb-2017 of 157 subjects treated with either monotherapy or in combination with nivolumab, BMS-986016 demonstrates a manageable safety profile. Excluding disease progression, the most common AEs are constitutional and GI. No DLTs were observed at the 160 mg dose of BMS-986016 combined with 240 mg of nivolumab. One death was reported as due to study treatment-related toxicity (myocarditis); however, this was with the higher 240 mg dose of BMS-986016 that will not be utilized in this study. Therefore, BMS-986016 160 mg Q2W will be administered in combination with nivolumab 240 mg Q2W in subjects with recurrent or metastatic CRC.

Additional details are provided in the current version of the BMS-986016 IB.

1.1.6 Rationale for Nivolumab plus Daratumumab Combination Therapy (Cohort C6)

This study will investigate the combination of daratumumab and nivolumab in patients with non-MSI-H CRC.

The tumor microenvironment plays an important role in determining whether a patient can mount an effective immune response to his/her tumor. Tumor cells can induce an immunosuppressive microenvironment through multiple mechanisms, resulting in evasion of the anti-tumor immune

response. Two such mechanisms include (1) upregulation of PD-L1, which following binding to PD-1 on T cells, inhibits activation and expansion of previously activated T cells; and (2) recruitment of immunosuppressive cell types such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs). Since individual tumors may use more than one means to evade the immune system, more than one method may be needed for optimal tumor regression.

Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that blocks the interaction between the inhibitory receptor, PD-1, and its ligands PD-L1 and PD-L2, thus allowing for sustained activation of T cells. Nivolumab has demonstrated single agent clinical efficacy in patients with metastatic melanoma, squamous and non-squamous NSCLC, advanced RCC, head and neck cancer, and bladder cancer and has an approved label in these indications. Nivolumab has also demonstrated significant response rates in other solid tumor malignancies including small-cell lung cancer and hepatocellular carcinoma. The combination of nivolumab with other immunomodulatory therapies, such as ipilimumab, has also demonstrated meaningful response rates and PFS in multiple solid tumor indications and is approved for the treatment of metastatic melanoma in the US. Certain tumor types, however, such as the MSS subtype of CRC, have been shown to have a poor anti-tumor immune response, suggesting that more than one method to target the immunosuppressive tumor microenvironment may be necessary to treat this tumor type. The potential for additive or synergic clinical activity when nivolumab is combined with other therapies is currently being evaluated in several trials, including CA209142.

Daratumumab is a human immunoglobulin G1 (IgG1) monoclonal antibody that targets CD38, inducing death of CD38-expressing cells through several mechanisms, including antibody-dependent cell mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and antibody-dependent cellular phagocytosis (ADCP).[77,78] The majority of malignant myeloma cells express CD38, and as such, treatment of patients with MM with daratumumab leads to a significant clinical benefit. Daratumumab has shown anti-myeloma activity in 2 clinical studies (GEN501 and SIRIUS) in patients with relapsed and refractory MM, resulting in significant response rates, including stringent complete responses (sCRs) and prolonged clinical responses in heavily pretreated patients.[79,80] Based on these data, daratumumab was approved by the US Food and Drug Administration for patients with MM who have received 3 or more prior lines of therapy.[81]

Daratumumab is an attractive therapeutic antibody in other solid tumor indications given that subsets of immunosuppressive cells such as MDSC and Tregs express CS38 and could be targeted for depletion by daratumumab.[82,83] Consistent with this hypothesis, frequencies of Tregs and MDSCs were reduced in MM patients following daratumumab administration. Furthermore, daratumumab led to changes in T cell populations including increased effector memory CD8+ T cells, increased overall T-cell clonality and increased antiviral and alloreactive T cell functionality.[82]

Preclinical studies suggest that targeting both CD38 and PD1 pathways may offer improvement in anti-tumor efficacy over each single agent alone. In mouse models of lung cancer, molecular profiling revealed increases in CD38 mRNA and protein expression in tumors with resistance to

PD1/PD-L1 blockade. While tumor growth was detected in mice deficient in PD-L1, tumor growth was not observed in mice deficient in both PD-L1 and CD38, suggesting that CD38 may be a negative regulator of the antitumor immune response.[84] Consistent with this hypothesis, treatment of mice bearing CD38-positive tumors with a combination of nivolumab and daratumumab mouse surrogate antibodies led to a significantly higher number of tumor-free mice compared to single agent treatments (BMS unpublished data). In tumor biopsies from CRC patients, there is elevated expression of CD38 mRNA and an upregulation of a regulatory T cell signature, suggesting an immunosuppressive state in CRC.[85]

In the current study, the combination of daratumumab and nivolumab is hypothesized to deplete CD38+ immunosuppressive cells from the tumor microenvironment, thus alleviating the immunosuppression so that the nivolumab activated T cells can mount an effective immune response to the tumor. This trial will test whether simultaneous blockade of PD-1 with nivolumab and the immunoregulatory effects of daratumumab will result in enhanced anti-tumor responses in patients with CRC or other solid tumors.

1.1.7 Rationale to Support Dose/Schedule of Nivolumab Combined with Daratumumab (Cohort C6)

For the nivolumab/daratumumab combination cohort, nivolumab will be administered at 240 mg Q2W, an approved nivolumab dosing regimen for NSCLC and RCC indications. Daratumumab will be administered at 16 mg/kg QW from Week 1 to 8, Q2W from Week 9 to 24, and Q4W from Week 25 and beyond until disease progression as described in the daratumumab label. As nivolumab 480 mg Q4W dosing regimen would produce similar exposures to that of 240 mg Q2W dosing regimen based on PPK modeling and simulation, nivolumab will be administered at 480 mg Q4W starting from Week 25 for the convenience to patients.

Dosing of daratumumab in subjects with multiple myeloma is recommended at 16 mg/kg (weekly for 8 weeks, then every 2 weeks for 16 weeks, then every 4 weeks thereafter) administered via IV until disease progression or unacceptable toxicity. The dose selection was based on an acceptable safety profile, maximal clinical activity, and pharmacokinetics consistent with saturation of the target. The data supporting the selection of a 16 mg/kg dose for the treatment of multiple myeloma are as follows:

- Safety: Clinical safety data demonstrated that daratumumab is well-tolerated, with clinically manageable side effects, highlighted by the fact that no subject treated with 16 mg/kg daratumumab monotherapy discontinued treatment as a result of a daratumumab related adverse event.
  - For doses above 4 mg/kg, there was no dose dependent toxicity pattern observed.
- Clinical efficacy: Clinical response data derived from Study GEN501 and Study MMY2002 show robust activity among subjects treated at 16 mg/kg with ORRs of 36% and 29%, respectively.
  - The response rates were consistently and significantly higher and deeper at the 16 mg/kg dose level as compared to various schedules at the 8 mg/kg dose level.

- Pharmacokinetics: Daratumumab exhibits target-mediated drug disposition. Daratumumab binds to CD38 receptors in the body and the complex with daratumumab is rapidly cleared. As the dose is increased or after repeated administration, CD38 becomes saturated, and the impact of target binding clearance is minimized and PK data can indicate target saturation.
  - Population pharmacokinetic and exposure-response analyses suggested that 16 mg/kg is the lowest tested dose at which the majority (approximately 80%) of subjects achieved serum concentrations above the model-predicted 99% target saturation threshold and 90% of the maximum effect on ORR threshold.
  - Lowering the dose would likely result in reduced efficacy, whereas increasing the dose may not provide further improvement of the benefit-risk profile.
  - The initial weekly dosing schedule rapidly established efficacious concentrations. The every 2 week and every 4 week dosing frequencies were sufficient to produce serum concentration levels that maintained target saturation; thus reducing the risk of disease progression.

Daratumumab is associated with infusion-related reactions requiring treatment with steroid. In GEN501 study, a Phase 1/2 study of daratumumab in relapsed/refractory MM subjects, infusion-related reactions were the most frequent adverse events, occurring in 71% of patients. The majority of these reactions included Grade 1 and 2, and characterized by rhinitis, cough, headache, pyrexia, and dyspnea. Most infusion-related reactions occurred during the first daratumumab infusion, and only few patients (<10%) had infusion-related reactions with more than one infusion. The SIRIUS (MMY2002) study confirmed the results from GEN501 study that demonstrated single agent activity of daratumumab with a favorable toxicity profile.[80] Among 106 patients who had a median of 5 prior lines of therapy (95% refractory to lenalidomide and bortezomib) and received daratumumab monotherapy at a dose of 16 mg/kg, 43% of the patients experience infusion-related reactions, which were predominantly Grade 1 and 2 and could be managed with interruption of the infusion or extra corticosteroids and antihistamines. Therefore, to mitigate the increased risk of infusion-related reactions for nivolumab/daratumumab combination cohort, nivolumab 240 mg Q2W administration will start with the third daratumumab infusion, and corticosteroids will be administered before and after treatment.

Historically, clinical trials with nivolumab have prohibited the use of high dose steroids before and during the study due to the potential interference with the immune activation mechanism of checkpoint inhibition. Specifically, in the nivolumab registrational trials, patients requiring treatment with systemic corticosteroids (greater than 10 mg daily prednisone equivalents) within 14 days of study drug administration were excluded. However, there have been exceptions to eligibility criteria for certain subjects which have not appeared to impact the efficacy of the therapy including prophylactic high-dose steroids for contrast dye allergy and non-autoimmune conditions such as delayed-type hypersensitivity reaction. Furthermore, high-dose systemic corticosteroids and other immunosuppressants are commonly used to treat immune-related adverse reactions. This concomitant steroid use to manage immune-related AEs does not appear to impair the efficacy of nivolumab, and these conclusions have been shared with the regulatory authorities. Pre-treatment with steroids has also been allowed in nivolumab trials where corticosteroids are part of standard

of care. High doses of dexamethasone have been administered with nivolumab therapy for patients with hematological malignancies where both lenalidomide and bortezomib require administration with standard doses of dexamethasone. In first-line NSCLC studies with nivolumab and pembrolizumab, steroid premedication is mandated with some chemotherapies, and this has not appeared to impact overall response rates.[39,86] In glioblastoma studies, corticosteroid treatment for symptomatic brain lesions is considered standard of care and therefore allowed in these trials. Furthermore, the inclusion of steroid treatment in the clinical trials with daratumumab did not impact the pharmacodynamic effect of expansion of activated T cells that was observed, suggesting that T cell activation and expansion still occurs in the presence of systemic steroid treatment. Taken together, the low likelihood that steroid premedication would compromise safety and the evidence that efficacy is not impacted by steroid premedication support the evaluation of the nivolumab in combination with daratumumab given with appropriate steroid premedication.

Based on the well-established safety profiles of daratumumab and nivolumab, it is not anticipated that the combination treatment will result in overlapping toxicities. The clinical experience of the combination treatment consists of 3 multiple myeloma patients treated in the CA209-039 study (Multiple Phase 1 Safety Cohorts of Nivolumab Monotherapy or Nivolumab Combination Regimens Across Relapsed/Refractory Hematologic Malignancies), that were treated with nivolumab and daratumumab at the doses that will be administered in this study. The current duration of treatment in these patients ranges from 41-53 days and all patients remain on study. No SAEs have been reported in these 3 patients. Reported AEs include the following: Grade 1 weakness and Grade 4 neutropenia for nivolumab/daratumumab/pomalidomide cohort and Grade 1 muscle cramps, cough, nasal congestion for nivolumab/daratumumab cohort. All safety data from the daratumumab/nivolumab cohort in the current study will be regularly monitored by the study physician, the protocol study team, and the BMS and Janssen medical safety teams.

1.1.8 Rationale for Objective Response Rate

Objective response rate (ORR) is the proportion of subjects with tumor size reduction of a predefined amount for a minimum time period and is a direct measure of drug antitumor activity.

The significance of ORR is assessed by its magnitude and duration and the percentage of complete responses (no detectable evidence of tumor). It is reasonable to test the hypothesis that nivolumab alone or in combination with ipilimumab will provide a response rate and depth of response (tumor shrinkage) that may translate to improved OS or provide quality of life benefits for patients with metastatic MSI-H CRC. Changes in tumor measurements and tumor responses will be assessed using standardized criteria, RECIST 1.1 (Response Evaluation Criteria in Solid Tumors).[87] Please refer to Appendix 3 for the specifics of the RECIST 1.1 criteria to be utilized in this study. In addition to investigator assessed response, the protocol contains a plan to use an independent radiology review committee (IRRC) to also assess response.

1.1.9 Rationale for Biomarker Analyses

Nivolumab and Ipilimumab

The biological basis of nivolumab and ipilimumab in the treatment of oncological disease is to modulate the immune system to generate or to restore a durable anti-tumor response leading to clearance of tumor. The clinical data generated with the monotherapy and combination therapy supports the hypothesis that blockade of PD-1 and CTLA-4 pathways results in rejection of tumor by the host immune system.

The precise mechanisms by which nivolumab and ipilimumab exert their anti-tumor activity is unclear, however, as particular cell types, such as effector T cells and regulatory T cells, are critical for the anti-tumor response. Nivolumab and ipilimumab appear to have distinct mechanisms of action, based on signaling of the PD-1 and CTLA-4 pathways, and the observations of a rise in Absolute Lymphocyte Count elevations in ipilimumab, but not nivolumab, therapy.

Retrospective analysis of advanced melanoma patients treated with ipilimumab showed that increased expression of proliferation and polarization markers in CD4+ and CD8+ cells, decreased CCR7 and IL-7R on CD4+ T cells, and upregulated Granzyme B in CD8+ T cells may serve as pharmacodynamic indicators of the effects of ipilimumab. Increased activation markers ICOS and eomesodermin (EOMES) were significantly associated with fewer AEs and less favorable outcome, respectively, but baseline elevated expression of EOMES appears to predict favorable relapse-free survival in this analysis.

ICOS potentially could be a useful marker for CD4+ T-cell responses generated after CTLA-4 blockade. Human leukocyte antigen (HLA-DR) expression could also potentially serve as a T-cell marker.

Retrospective gene expression analysis was performed on 46 primary or metastatic melanoma tumors, collected in a Phase 2 trial in advanced melanoma subjects.[88] Ipilimumab treatment was associated with downregulation of a number of melanoma-associated transcripts in the tumors within 3 weeks after administering the first dose. Expression of immune-related genes such as CD8A, GZMA, LCK, CXCL-9, -10, -11, and CXCR3 in tumors at Week 3 post-treatment was associated with the total lymphocyte infiltrate, clinical benefit, and OS. The preliminary results suggest that high pre-existing immune activity favors a clinical response to ipilimumab therapy. These analyses also provide a list of candidate biomarkers with potential predictive value for response to ipilimumab, to be explored in the proposed study.

Nivolumab and BMS-986016

For PD-L1 and biomarker research testing, tumor tissue (formalin-fixed, paraffin embedded archival or recent acquisition) must be received during the screening period. Archival tissue is accepted if it is taken < 3 months from screening, without any intervening therapies. If PD-L1 results are available, results will be collected. (Note: Fine Needle Aspiration (FNA) and bone metastases samples are not acceptable for submission.).

As LAG-3 is an immune checkpoint expressed by exhausted immune cells, the detection of LAG-3 in tumor microenvironment prior to the start of treatment may yield information on potential correlation between LAG-3 expression and clinical benefit. This may enable LAG-3 specific precision medicine, based on the biomarker analysis. Furthermore, the characterization of LAG-3,

in the context of overall tumor immune phenotyping, would provide insight on the mechanism of action in this particular disease setting.

Detailed immune and tumor phenotyping will be pursued to build clinical data to support the clinical findings. The biomarker analysis would include but are not limited to the following:

1) Examination of tumor-associated immune cells and microenvironment, through proteomics, histopathology (in particular LAG-3 expression), NGS, and expression (mRNA) profiling.
2) Genomics (NGS and/or RNA) analysis on tumor, and/or cell-free DNA, for tumor mutation burden and tumor genetics analysis

Nivolumab and Daratumumab

For PD-L1 and biomarker research testing, tumor tissue (formalin-fixed, paraffin embedded archival or recent acquisition) must be received during the screening period. (Note: Fine Needle Aspiration (FNA) and bone metastases samples are not acceptable for submission.)

Detailed immune and tumor phenotyping may be pursued to build clinical data to support the clinical findings. The biomarker analysis would include but are not limited to the following:

1) Systemic immune monitoring on circulating immune cells and secreted cytokines, chemokines, and other related soluble factors.
2) Examination of tumor-associated immune cells and microenvironment, through proteomics, histopathology (eg, CD38, MDSC, TIL), NGS, and expression (mRNA) profiling.
3) Genomics (NGS and/or RNA) analysis on tumor, and/or cell-free DNA, for tumor mutation burden analysis

Summary

Therefore, the major hypotheses that will be addressed by the biomarker plan for CA209142 are:

- Does expression of PD-L1 on tumor cells prior to therapy correlate with clinical efficacy to monotherapy or combination therapy?
- Does the mutational status of tumor cells (ie, KRAS, Microsatellite instability, BRAF) correlate with clinical efficacy to monotherapy or combination therapy?
- Can we define distinct pharmacodynamic markers of monotherapy and combination therapy in the peripheral compartment?
- How does monotherapy or combination therapy alter the activating and negative co-stimulatory molecules on immune cells in the periphery and at the tumor site? Are there distinct mechanisms of resistance to monotherapy and combination therapy?
- Is the intratumoral or peripheral T cell repertoire predictive of response to monotherapy or combination therapy?
- Does the composition and phenotype of the tumor microenvironment, including microbiota, at baseline, or on-treatment, correlate with clinical efficacy?

1.2 Research Hypothesis

Treatment with nivolumab monotherapy, nivolumab combined with ipilimumab, nivolumab combined with anti-LAG-3 antibody (BMS-986016), or nivolumab combined with daratumumab (C6 Cohort) will have clinical activity in subjects with recurrent or metastatic CRC.

1.3 Objectives(s)

1.3.1 Primary Objectives

To evaluate the investigator-assessed ORR of nivolumab monotherapy and nivolumab in combination with either ipilimumab, or anti-LAG-3 antibody (BMS-986016) in dMMR/MSI-H mCRC; the ORR of nivolumab combined with ipilimumab in subjects with metastatic non-MSI-H (pMMR) CRC; and, the ORR of nivolumab combined with daratumumab therapy in subjects with metastatic non-MSI-H (pMMR) mCRC.

1.3.2 Secondary Objectives

- To evaluate the IRRC-assessed ORR of nivolumab monotherapy and nivolumab in combination with either ipilimumab or anti-LAG-3 antibody (BMS-986016) in dMMR/MSI-H mCRC; the ORR of nivolumab combined with ipilimumab in subjects with metastatic non-MSI-H (pMMR) CRC; and, the IRRC ORR of nivolumab combined with daratumumab therapy in subjects with metastatic non-MSI-H (pMMR) mCRC.
- To evaluate the disease control rate (DCR) of nivolumab monotherapy or combined with the above agents in subjects with metastatic mCRC.

1.3.3 Exploratory Objectives

- To determine the safety and tolerability [defined as toxicity rates (worst CTC grade per subject) of adverse events and specific laboratory tests] of nivolumab monotherapy (mStage 1 and 2), nivolumab in combination with ipilimumab (cStage 1 and 2, and C3 Cohort) in subjects with metastatic CRC, nivolumab in combination with anti-LAG-3 antibody (BMS-986016) in subjects with metastatic dMMR/MSI-H mCRC, or nivolumab in combination with daratumumab in subjects with metastatic non-MSI-H (pMMR) mCRC.
- To estimate PFS and OS for subjects with metastatic CRC who have received nivolumab monotherapy (mStage 1 and 2), nivolumab in combination with ipilimumab (cStage 1 and 2, and C3 Cohort, nivolumab in combination with anti-LAG-3 antibody (BMS-986016) in subjects with metastatic dMMR/MSI-H mCRC or nivolumab in combination with daratumumab in subjects with metastatic non-MSI-H (pMMR) mCRC.
- To evaluate the safety and tolerability of nivolumab in combination with ipilimumab in subjects with metastatic non-MSI-H CRC in the safety cohort.
- To evaluate investigator-assessed and IRRC-assessed ORR of nivolumab in combination with ipilimumab in subjects with metastatic non-MSI-H CRC in the safety cohort.
- To characterize the PK of nivolumab monotherapy, PK of nivolumab, ipilimumab, BMS-986016, and daratumumab when combined, and to explore exposure-response relationships.

- To characterize the immunogenicity of nivolumab monotherapy, immunogenicity of nivolumab, ipilimumab, BMS-986016, and daratumumab when combined.
- To evaluate the pharmacodynamic activity of nivolumab monotherapy, nivolumab in combination with ipilimumab, nivolumab in combination with anti-LAG-3 antibody (BMS-986016), and nivolumab in combination with daratumumab in subjects with metastatic CRC in the peripheral blood and tumor tissue as measured by flow cytometry, immunohistochemistry, soluble factor analysis, and gene expression (microarray technology, quantitative RT-PCR).
- To investigate the association between biomarkers in the peripheral blood and tumor tissue, such as PD-L1 expression, with safety and efficacy for subjects with advanced or metastatic tumors treated with nivolumab monotherapy, nivolumab in combination with ipilimumab, nivolumab in combination with anti-LAG-3 antibody (BMS-986016), and nivolumab in combination with daratumumab.
- To characterize the discordance rate between repeat MSI testing and prior MSI testing in subjects.
- 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.
- To evaluate clinical activity and safety of nivolumab monotherapy or combination treatment after re-initiation.

1.4 Product Development Background

Information for nivolumab (anti-PD-1 antibody), ipilimumab (YERVOY®; anti-CTLA antibody), and BMS-986016 (anti-LAG-3 antibody) is provided in the sections below; additional details are provided in the respective Investigator Brochures.

1.4.1 Nivolumab and Ipilimumab Mechanisms of Action

Cancer immunotherapy rests on the premise that tumors can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. An effective immune response in this setting is thought to rely on immune surveillance of tumor antigens expressed on cancer cells that ultimately results in an adaptive immune response and cancer cell death. The immune surveillance functions by limiting the emergence of tumors as they arise and/or causing tumor shrinkage. Tumor progression may depend upon acquisition of traits that allow cancer cells to evade immune surveillance and an effective immune response. This evasion may occur by exploiting any of the checkpoints that control the regulatory immune response, including display of antigens and control of co-stimulatory pathways that affect the proliferation of cells involved in immunity. Current immunotherapy efforts attempt to break the apparent tolerance of the immune system to tumor cells and antigens by either introducing cancer antigens by therapeutic vaccination or by modulating regulatory checkpoints of the immune system, either directly by stimulation of immune cells by antibodies directed to receptors on T and B cells or indirectly by cytokine manipulation. T-cell stimulation is a complex process involving the integration of numerous positive, as well as negative, co-stimulatory signals in addition to antigen recognition by the T-

cell receptor (TCR). Collectively, these signals govern the balance between T-cell activation and tolerance to antigens.

Programmed death receptor-1 (PD-1, CD279), a 55 kD type I transmembrane protein, is a member of the CD28 family of T-cell co-stimulary receptors that also includes CD28, CTLA-4, ICOS, and BTLA.2 PD-1 contains an intracellular membrane proximal immunoreceptor tyrosine inhibitory motif (ITIM) and a membrane distal immunoreceptor tyrosine-based switch motif (ITSM). Two ligands specific for PD-1 have been identified: PD-L1 (B7-H1/CD274) and PD-L2 (B7-DC/CD273). PD-L1 and PD-L2 have been shown to down-regulate T-cell activation upon binding to PD-1 in both murine and human systems. PD-1 delivers a negative signal by the recruitment of SHP-2 to the phosphorylated tyrosine residue in the ITSM in its cytoplasmic region. PD-1 is primarily expressed on activated T cells, B cells, and myeloid cells. Further evidence for a negative regulatory role of PD-1 comes from studies of PD-1-deficient mice. PD-1-deficient mice develop various autoimmune phenotypes, including dilated cardiomyopathy, a lupus-like syndrome with arthritis and nephritis, and accelerated diabetes mellitus. The emergence of these autoimmune phenotypes is dependent upon the genetic background of the mouse strain and many of these phenotypes emerge at different times and show variable penetrance. In addition to the phenotypes of null mutations, PD-1 inhibition by antibody-mediated blockade in several murine models has been found to play a role in the development of autoimmune diseases such as encephalomyelitis, graft-versus-host disease, and type I diabetes. Taken together, these results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self antigens.

Preclinical animal models of tumors have shown that blockade by PD-1 by monoclonal antibodies (mAbs) can enhance the anti-tumor immune response and result in tumor rejection. Antitumor activity by PD-1 blockade functions in PD-L1-positive tumors as well as in tumors that are negative for the expression of PD-L1. This suggests that host mechanisms (ie, expression of PD-L1 in antigen-presenting cells) limit the antitumor response. Consequently, both PD-L1 positive and negative tumors may be targeted using this approach. In humans, constitutive PD-L1 expression is normally limited to macrophage-lineage cells, although expression of PD-L1 can be induced on other hematologic cells as well, including activated T cells. However, aberrant expression of PD-L1 by tumor cells has been reported in a number of human malignancies. PD-L1 expressed by tumor cells has been shown to enhance apoptosis of activated tumor-specific T cells in vitro. Moreover, the expression of PD-L1 may protect the tumor cells from the induction of apoptosis by effector T cells.

Nivolumab (anti-PD-1 mAb) is a fully human monoclonal immunoglobulin (Ig) G4 antibody that binds to the programmed death-1 (PD-1) cell surface membrane receptor, a negative regulatory molecule expressed by activated T and B lymphocytes. Blockade of the PD-1 pathway by nivolumab was studied using the mixed lymphocyte reaction (MLR). PD-1 blockade resulted in a reproducible enhancement of both proliferation and interferon release in the MLR. The effect of nivolumab on antigen-specific recall response was investigated using a CMV-restimulation assay with human peripheral blood mononuclear cells (PBMCs), and was evaluated by ELISA.

Nivolumab 3 mg/kg monotherapy is currently approved for the treatment of advanced melanoma and lung cancer, metastatic renal carcinoma, and Hodgkin lymphoma, and is being studied in several phase 3 and 2 clinical trials in advanced and metastatic solid and hematologic malignancies.

Ipilimumab is a fully humanized IgG1 monoclonal antibody binding to the anti-cytotoxic T-cell lymphoma-4 antigen (CTLA-4). Ipilimumab is an approved therapy for metastatic melanoma and has demonstrated improved overall survival as monotherapy and in combination with dacarbazine.[89,90] It has been studied in combination with multiple standards of care (SOC) therapies including chemotherapy for squamous and non-squamous NSCLC and radiotherapy for hormone resistant prostate cancer.[91] Ipilimumab is currently also approved as adjuvant therapy in stage III melanoma.

1.4.2 Summary of Results from the Ipilimumab and Nivolumab Programs

Additional details are also available in the nivolumab and ipilimumab Investigator Brochures (IB).

1.4.2.1 Summary of Safety

Ipilimumab Monotherapy

In study MDX010-20, the ipilimumab monotherapy arm was administered 3 mg/kg ipilimumab every 3 weeks for four doses. In this arm, there were 79% drug related adverse events, with 21% being Grade 3/4 and 3/131 (2%) Grade 5. The most frequent adverse events of interest were rash (30%), pruritus (33%), diarrhea (33%), colitis (8%), endocrine disorders (9%), AST/ALT increased (2%), and hepatitis (1%). Any grade immune related adverse events were 60% and the Grade 3/4 immune related adverse events for the same cohort was 13% with the most frequent adverse events being diarrhea (5%), colitis (5%), rash (2%), and endocrine disorders (3%).

Comprehensive details on the safety profile of ipilimumab, including results from other clinical studies, are available in the ipilimumab product information and Investigator Brochure.

Nivolumab Monotherapy

One study has contributed most to the clinical experience with nivolumab monotherapy in subjects with melanoma and other solid malignancies. CA209003 is an ongoing Phase 1 open label, multiple dose escalation study in 306 subjects with select previously treated advanced solid tumors, including melanoma, RCC, NSCLC, colorectal cancer, and hormone-refractory prostate cancer. Subjects received nivolumab at doses of 0.1, 0.3, 1, 3 or 10 mg/kg intravenously every 2 weeks, up to a maximum of 2 years of total therapy. As of 05-Mar-2013, a total of 107 melanoma subjects were treated with nivolumab in the dose range of 0.1-10 mg/kg.

No maximal tolerated dose was identified in CA209003. The incidence, severity and relationship of AEs were generally similar across dose levels and tumor types. Nivolumab related AEs of any grade occurred in 72.4% of subjects. The most frequent nivolumab related AEs occurring in > 5% of subjects included: fatigue (25.7%), rash (13.5%), diarrhea (11.8%), pruritus (10.2%), nausea (7.9%), decreased appetite (7.9%), hemoglobin decreased (5.9%) and pyrexia (5.3%).

The majority of events were low grade, with grade 3-4 drug related AEs observed in 14.8% of subjects. The most common Grade 3-4 drug-related AEs occurring in > 1% of subjects were: fatigue (1.6%), lymphopenia (1.3%), abdominal pain (1%), diarrhea (1%), hypophosphatemia (1%) and pneumonitis (1%). At least one SAE was reported for 150 (49.3%) of the 304 subjects at all dose levels. Grade 3-4 SAEs were reported for 23 subjects (7.6%). Drug-related SAEs occurred in 11.5% of subjects. Grade 3-4 drug-related SAEs reported in at least 2 subjects included: diarrhea (3 subjects, 1.0%), pneumonitis (3 subjects, 1.0%), pneumonia (2 subjects, 0.7%) and lipase increased (2 subjects, 0.7%). Additional select treatment-related AEs have occurred with low frequency (< 5%) but are considered clinically meaningful, as they require greater vigilance for early recognition and prompt intervention. These AEs include: ALT increased (4.3%), AST increased (3.6%), pneumonitis (3.3%), hypothyroidism (3.0%), hyperthyroidism (1.3%), renal failure (1.0%), adrenal insufficiency (0.7%) and colitis (0.7%). Grade 3-4 events of pneumonitis were reported in 3 subjects (1.0%) as described above (1 event was Grade 4). Grade 3 events of colitis, ALT increased, and AST increased were reported in 2 subjects (0.7%) each. Grade 3 events of adrenal insufficiency, hyperthyroidism, and hypothyroidism were reported in 1 subject (0.3%) each. Treatment-related AEs leading to discontinuation were reported in 18 (5.9%) of the 304 treated subjects on CA209003. The only events reported in more than 1 subject were pneumonitis (4 subjects; 1.3%) and hepatitis (2 subjects; 0.7%). There were 3 (1%) drug related deaths; each occurred after development of pneumonitis.

Preliminary new non-clinical safety findings of adverse pregnancy outcomes and infant losses in the absence of overt maternal toxicity have been reported. The findings of increased late stage pregnancy loss and early infant deaths/euthanasia in nivolumab exposed pregnant monkeys suggest a potential risk to human pregnancy if there is continued treatment with nivolumab during pregnancy.

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

Nivolumab Combined with Ipilimumab

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

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

As of 15-Feb-2013, a total of 53 melanoma subjects were treated with nivolumab combined with ipilimumab in CA209004 across cohorts 1, 2, 2a, and 3, including subjects who received higher cumulative doses of the combination components than planned in the current study. At least one AE regardless of causality has been reported in 98% of subjects treated. The most common (reported at > 10% incidence) treatment-related AEs (any Grade %; Grade 3-4 %: 93; 53) are rash (55; 4), pruritus (47; 0), vitiligo (11; 0), fatigue (38; 0), pyrexia (21, 0), diarrhea (34; 6), nausea (21, 0), vomiting (11, 2), ALT increased (21; 11), AST increased (21; 13), lipase increased (19; 13), amylase increased (15, 6), headache (11, 0), and cough (13, 0).

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

Currently, the combination therapy of 3 mg/kg ipilimumab plus 1 mg/kg nivolumab is approved for the treatment of patients with BRAF V600 wild-type and BRAF V600 mutation-positive unresectable or metastatic melanoma.

1.4.2.2 Summary of Clinical Activity

There has been no clinical trial so far quantitating the clinical benefit of nivolumab or nivolumab plus ipilimumab in MSI-H CRC. One subject in clinical trial CA209001, a 67-year-old male with MSI-High CRC metastatic to intra-abdominal lymph nodes received five doses of nivolumab at 3 mg/kg and experienced a complete response by radiographical criteria persisting beyond 21 months. In clinical trial CA209003, 19 out of 306 subjects had a baseline diagnosis of colon or rectal cancer. These subjects were treated with 10 mg/kg nivolumab monotherapy and the safety experience was consistent with other solid tumor types in this study. No responses were noted in these subjects, however, the MSI status of these subjects were never confirmed.

The following summary notes the ability of nivolumab and nivolumab plus ipilimumab to induce responses at estimated rates that equal or surpass those of active controls in a spectrum of solid tumors.

Nivolumab Monotherapy

In CA209003, the clinical activity of nivolumab was demonstrated in a variety of tumor types, including melanoma, RCC, and NSCLC. Clinical activity was noted across a range of doses (0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, and 10 mg/kg). In CA209003, as of the clinical cut-off date of 18-Mar-2013, a total of 304 subjects with melanoma, RCC, and NSCLC have been evaluated for clinical activity. A response of either CR or PR, as determined by investigator assessed tumor evaluations based on RECIST 1.1, has been reported at all dose levels. No responses (CR or PR) have been reported in subjects with colorectal carcinoma (MSI status was not determined in these subjects) or castrate-resistant prostate cancer.

In NSCLC, the most active doses were 3 and 10 mg/kg. An ORR of 19% to 26% was reported with a 24-week progression-free survival rate (PFSR) of 25% to 45%. Only a single response (1/33) was reported at 1 mg/kg. Durable responses were observed in both squamous and non-squamous subtypes. Historically, ORR of 5% to 10% and median PFS (mPFS) of 2 to 3 months has been reported with docetaxel treatment in previously-treated NSCLC subjects.

A complete response (CR) or partial response (PR) was reported in 33% (95%CI: 22%-41%) of the 107 response-evaluable subjects with melanoma treated with nivolumab monotherapy Q2W at doses ranging from 0.1 to 10 mg/kg in MDX1106-03. The responses were durable with a PFSR at 24 weeks of 44%.

Of the 34 response evaluable RCC subjects in MDX1106-03, responses were reported in both the 1 mg/kg (5 of 18 subjects, 27.8%) and 10 mg/kg (5 of 16 subjects, 31.3%) treatment groups. Estimated PFSR at 24 weeks was 50% in the 1 mg/kg and 67% in the 10 mg/kg nivolumab treatment groups.

Nivolumab Combined with Ipilimumab

As noted above, nivolumab monotherapy has not demonstrated responses in cases of CRC where MSI status has not been determined. Given the 4% prevalence of MSI-H in the population with metastatic disease, it is likely that the near entirety of these subjects would be non MSI-H. Thus, nivolumab monotherapy will not be assessed further in the non-MSI population in this trial. In other solid tumors, the combination of nivolumab and ipilimumab has shown response rates and depth of response exceeding the rates seen with monotherapy with either agent. This trial will first assess the safety of this combination in non MSI-H subjects before proceeding with an assessment of efficacy and safety in MSI-H subjects. Assessing activity in non-MSI-H disease in the initial safety cohort is beyond the scope of this non-comparative trial, although any anti-tumor activity in the dose escalation safety arm will be described. Details of the activity of the combination in other solid tumors follow.

As of the 15-Feb-2013 clinical cut-off in CA209004, of the 52 subjects evaluable for response, 21 subjects (40%) had an objective response by modified World Health Organization (mWHO) criteria. In an additional 2 subjects (4%) there was an unconfirmed objective response. In Cohort 1 (0.1 mg/kg nivolumab + 3 mg/kg ipilimumab), 3 out of 14 evaluable subjects had an objective response by mWHO (21%); 1 CR and 2 PRs with an additional PR by immune-related mWHO criteria (irPR). 55 In Cohort 2 (1 mg/kg nivolumab + 3 mg/kg ipilimumab), 9 out of 17 evaluable subjects had an objective response by mWHO (53%; 3 CRs (18%), 6 PRs (35%) with two additional subjects experiencing immune-related SD (irSD). In Cohort 2a (3 mg/kg nivolumab + 1 mg/kg ipilimumab), 6 out of 15 response evaluable subjects had an objective response rate by mWHO (40%; 1 CR (7%), 5 PRs (33%) with 2 additional uPRs (13%) and 2 irSDs and 1 irPR). In Cohort 3 (3 mg/kg nivolumab + 3 mg/kg ipilimumab), 3 out of 6 evaluable subjects had an objective response by mWHO (50%; 3 PRs (50%) with 1 additional irPR and 1 irSD. Preliminary analysis revealed 16 of the 52 evaluable subjects (31%) had > 80% reduction in the size of target tumor lesions by the week 12 evaluation. This is compared to < 2% for 3 mg/kg ipilimumab monotherapy based on CA184020 (N=540) and < 3% for nivolumab monotherapy based on

CA209003 (N=94, 0.1-10 mg/kg). The concurrent administration of nivolumab and ipilimumab was safe and resulted in rapid and deep tumor regressions. The combination of nivolumab with ipilimumab is currently also being investigated in NSCLC, metastatic clear cell renal cell carcinoma, and in advanced melanoma.

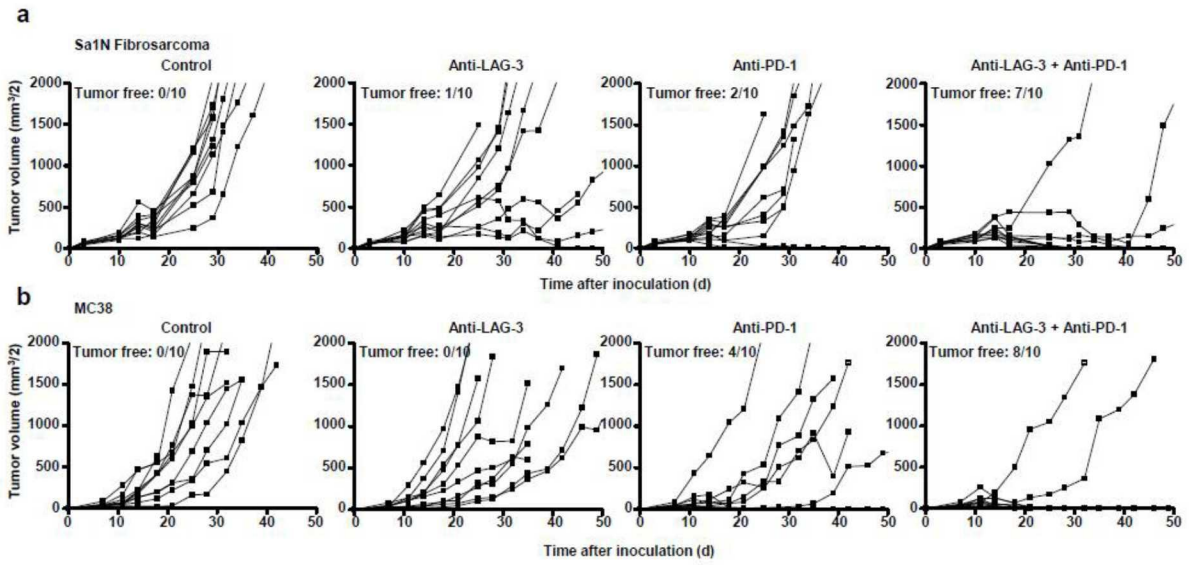
1.4.3 Nivolumab Combined with BMS-986016 (Cohort C5)

1.4.3.1 Nonclinical Pharmacology Studies utilizing Murine Anti-PD-1 and Anti-LAG-3 Antibodies

The importance of LAG-3 as an immunotherapy target was validated in murine in vivo models using 2 surrogate antibodies specific for mouse LAG-3. These studies evaluated tumor growth inhibition in syngeneic tumor models (Sa1N fibrosarcoma and MC38 colon adenocarcinoma) and monitored acceleration of autoimmunity in the non-obese diabetic (NOD) model. Anti-LAG-3 antibody administration resulted in both overall tumor growth inhibition and an increase in the number of tumor-free (TF) mice in those treatment groups (Figure 1.4.3.1-1).

Anti-LAG-3 antibody administered in combination with anti-PD-1 antibody provided enhanced antitumor activity above the activity of either agent alone. For example, in multiple Sa1N tumor models, anti-LAG-3 antibody resulted in 20%-30% TF mice compared to control and anti-PD-1 antibody-treated mice (0%-10% TF mice), while the combination of anti-LAG-3 and anti-PD-1 antibodies resulted in 60%-90% TF mice. In the MC38 model, anti-LAG-3 antibody showed modest tumor growth inhibition alone but when administered in combination with anti-PD-1 antibody, resulted in enhanced antitumor activity above that observed for anti-PD-1 antibody alone (80% vs. 40% TF mice, respectively).

Figure 1.4.3.1-1: Antitumor Activity of Anti-LAG-3 and Anti-PD-1 Antibodies in Murine Models



1.4.3.2 Clinical Pharmacology BMS-986016

The current Phase 1 clinical program is evaluating BMS-986016 in advanced solid tumors (special focus in NSCLC, RCC, and malignant melanoma) in Study CA224-020 and relapsed refractory hematological malignancies (Hodgkin and non-Hodgkin lymphomas) in Study CA224-022. As of 29-Jun-2016, 89 subjects have been treated with BMS-986016 in these 2 ongoing studies assessing PK, clinical activity, and safety. An interim determination of BMS-986016 multiple dose PK was carried out using all available serum concentrations data from Studies CA224 020 and CA224 022. In general, the Cmax and area under the concentration versus time curve over the dosing interval (AUC[TAU]) values over the first dosing interval increased approximately equal to the increment in the BMS 986016 dose. The PK of BMS-986016 and nivolumab was not altered when given in combination. BMS-986016 concentration time data were reasonably described by population PK model with linear, 2 compartment, zero-order IV infusion model with first order elimination. The model estimated mean T-HALF was 19 days, and the typical CLT was 13.7 mL/h. The population PK model will be used to understand the source of variability in BMS-986016 PK and effect of intrinsic and extrinsic factors.

Currently available data suggest that BMS-986016 monotherapy exhibits a low level of immunogenicity, with 6 out of 42 subjects having at least 1 post-baseline positive anti-drug antibody (ADA) samples. There are limited data available in combination cohort to make inference on immunogenicity rate.

1.4.3.3 Clinical Safety Combination Therapy (Nivolumab plus BMS-986016)

Based on preliminary data as of 20-Feb-2017, treatment with BMS 986016 in combination with nivolumab has been administered to 29 subjects in study CA224-020 at these dose levels:

- 20 mg BMS-986016 plus 80 mg nivolumab: 7 subjects
- 20 mg BMS-986016 plus 240 mg nivolumab: 9 subjects
- 80 mg BMS-986016 plus 240 mg nivolumab: 129 subjects
- 160 mg BMS-986016 plus 240 mg nivolumab: 6 subjects
- 240 mg BMS-986016 plus 240 mg nivolumab: 8 subjects

No MTD reached at the tested doses up to 160 mg BMS-986016 and 240 mg nivolumab (flat dose, Q2W). Evaluation of 240 mg BMS-986016 and 240 mg nivolumab combination dose is ongoing. There was no relationship between the incidence, severity, or causality of AEs and combination therapy. Most AEs were of low grade (Grade 1 to 2) with 7 drug-related SAEs across all combination cohorts, as follows: Grade 3-4 malignant neoplasm progression (n = 1), Grade 3-4 meningitis aseptic (n = 2), Grade 3-4 lipase increase (n = 1), Grade 3-4 mucosal inflammation (n = 1), Grade 3-4 pneumonia (n =1), Grade 3-4 Troponin I increase (n = 1), and Grade 4 ventricular fibrillation (n = 1). AEs were generally self-limited or reversible with appropriate therapy, except for the Grade 4 myocarditis event which progressed to Grade 5 after the clinical cut-off date. Grade 2 infusion-related reactions were reported in 2 subjects during infusion of nivolumab and were manageable following protocol guidelines. Fifteen deaths occurred in subjects treated with

combination therapy. All deaths were due to disease progression and were considered not related to study drug, except for the drug-related myocarditis death which occurred after the clinical cut-off date.

1.4.4 Daratumumab

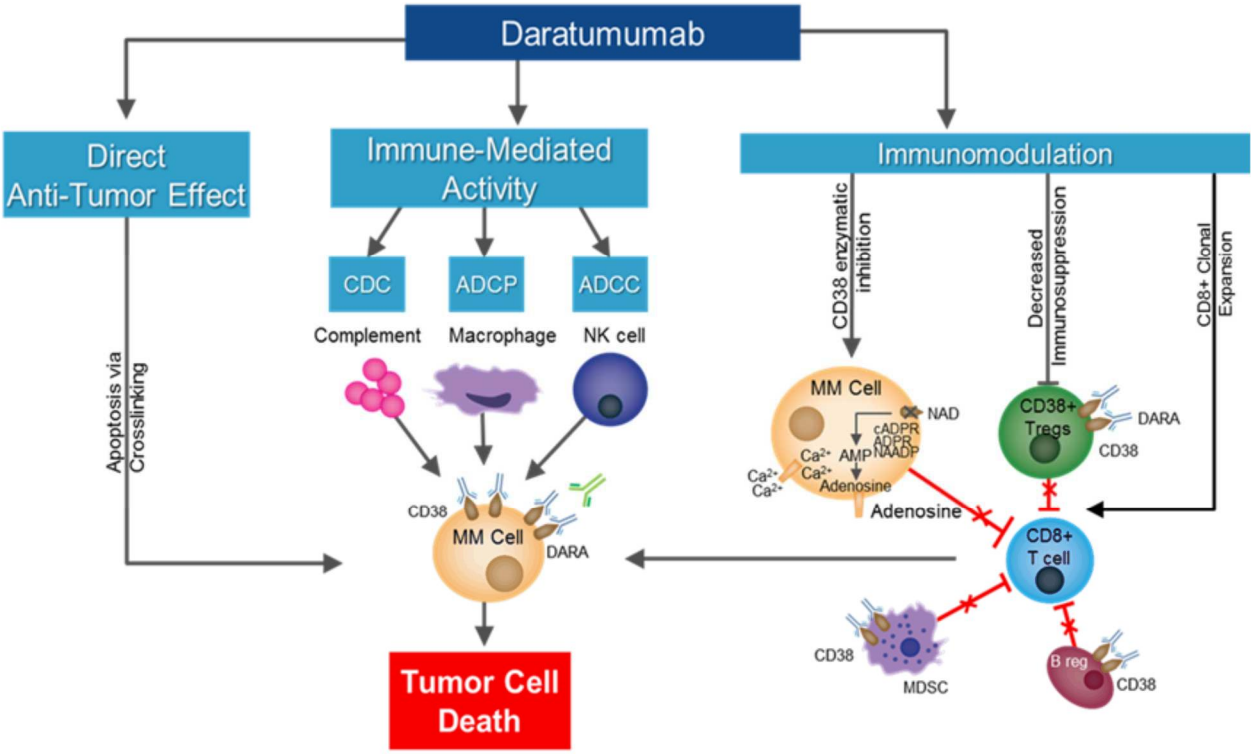
1.4.4.1 Mechanism of Action

Daratumumab is a targeted immunotherapy that binds to tumor cells that overexpress CD38, a transmembrane glycoprotein, in multiple myeloma plasma cells. Multiple mechanisms of action (MoA) have been observed for daratumumab, including complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC), induction of apoptosis by Fc gamma receptor mediated crosslinking of tumor-bound monoclonal antibodies, and antibody-dependent cellular phagocytosis (ADCP).

Translational biomarker studies of samples from patients treated in daratumumab Phase 1 and Phase 2 studies (Studies GEN501 and MMY2002, respectively) have revealed previously unknown immunomodulatory effects of daratumumab.[87] Detailed analysis by flow cytometry of changes in circulating immune cells demonstrated that daratumumab was able to induce large increases in CD8+ T numbers. Next generation TCR sequencing was utilized to evaluate changes in T cell clonality. Interestingly, in patients who responded to daratumumab, both the maximal individual increase in a T cell clone, as well as the sum of expanded T cell clones, were significantly increased suggesting that this T cell expansion may have a role in eliminating the myeloma cells. In order to assess the potential mechanism by which daratumumab could lead to these increases in T cell clones, additional analysis revealed that there was a rapid and sustained elimination of highly immunosuppressive subsets of $CD38^+$ Tregs, $CD38^+$ MDSCs, and $CD38^+$ Bregs in patients treated with daratumumab. Interestingly, the $CD38^+$ Tregs identified is a novel population of Tregs that are more immunosuppressive than $CD38^-$ Tregs. In addition, it has also been shown that daratumumab can modulate the enzymatic activity of CD38 and potentially lead to a reduction in immunosuppressive adenosine levels in the tumor microenvironment.[92]

Some of daratumumab's most differentiating attributes are the depth of response achieved in responders and the drug's multifaceted MoA. Based upon these new findings, it is hypothesized that daratumumab's deep and durable responses in patients with multiple myeloma are induced, in part, by the immunomodulatory activity that removes immune suppressive functions of CD38+ MDSC, CD38+ TReg, and CD38+ BReg cells and increases T cell clonality. A figure summarizing daratumumab's novel, converging MoAs is presented in Figure 1.4.4.1-1.

Figure 1.4.4.1-1: Daratumumab Mechanism of Action



ADCC= antibody dependent cellular cytotoxicity ADCP=antibody dependent cellular phagocytosis; CDC=complement-dependent cytotoxicity.

Note: Previously reported to kill tumor cells by immune-mediated mechanisms, such as ADCC, ADCP, and CDC, as well as by programmed cell death via cross linking of the antibody on the cell surface, it is now known that daratumumab also induces immunomodulatory effects via several different pathways that contribute to killing of CD38+ immune cells that modulate Tcell activity, namely MDSC, TReg, and BReg. This is a novel mechanism previously unreported that is hypothesized to drive development of multiple opportunities for daratumumab beyond CD38+ myeloma and other heme malignancies

1.4.4.2 Summary of Daratumumab Clinical Pharmacology

Daratumumab is a first-in-class immunoglobulin G1 kappa (IgG1κ) human monoclonal antibody (mAb) that specifically binds to the CD38 protein expressed on the surface of multiple myeloma tumor cells and other cell types at various levels. In vitro, daratumumab can induce tumor cell lysis through complement dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, and antibody-dependent cellular phagocytosis in malignancies expressing CD38.

The population pharmacokinetic (PK) analysis included patients with multiple myeloma who received daratumumab. Over the dose range from 1 to 24 mg/kg, AUC increases more than dose proportionally. Clearance decreases with increasing dose and repeated dosing, indicating target-mediated pharmacokinetics. Following the recommended dose and schedule, the Cmax at the end of weekly dosing is 2.9-fold higher than following the first infusion. Daratumumab steady state is achieved approximately 5 months into the every 4-week dosing period, and the Cmax at steady-state to Cmax after the first dose is 1.6. The mean (SD) linear clearance and mean (SD)

central volume of distribution are estimated to be 171.4 (95.3) mL/day and 4.7 (1.3) L, respectively. The mean (SD) estimated terminal half-life associated with linear clearance is approximately 18 (9) days. Population PK analyses indicated that the central volume of distribution and clearance of daratumumab increase with increasing body weight, supporting the body weight-based dosing regimen. Population PK analyses also show that age (31-84 years), gender, mild to severe renal impairment (15 to 89 mL/min), and mild hepatic impairment do not have clinically important effects on the pharmacokinetics of daratumumab.

Exposure-response analyses for efficacy and safety were conducted using data from trials GEN501 and MMY2002. The exposure-efficacy analysis shows that ORR increases with increasing daratumumab concentration, with a plateau achieved at daratumumab maximal pre-infusion concentrations (Cpre-infusion, max) ≥ 270 µg/mL. Furthermore, the median PFS appears shorter in patients with daratumumab Cpre-infusion,max < 270 µg/mL (1.9 month) and longer (6.6 months) in those with daratumumab concentrations > 270 µg/mL. However, this analysis was confounded by baseline risk factors such as disease severity. There was no exposure-safety relationship for infusion related reactions (IRR), thrombocytopenia, anemia, neutropenia and lymphopenia within the exposure range from 0.1 to 24 mg/kg studied in trials MMY2002 and GEN501.

1.4.4.3 Summary of Daratumumab Clinical Activity

Based on the preclinical activity of daratumumab, a Phase 1/2 study was initiated in MM patients with relapsed/refractory disease (GEN501 study).[79] In the first-in-human dose-escalation part of the study the MTD was not reached with dose levels up to 24 mg/kg. In the Phase 2 part of the study, patients with a median of 4 prior lines of therapy (majority refractory to lenalidomide and bortezomib) were treated with daratumumab at a dose of 8 mg/kg or 16 mg/kg. The ORR (at least PR) was 36% in the 16 mg/kg cohort and 10% in the 8 mg/kg group. Remarkably, in this extensively pretreated group of patients, 2 out of 42 patients treated with 16 mg/kg daratumumab achieved a first complete response. The median PFS in the 8 mg/kg and 16 mg/kg groups were 2.4 and 5.6 months, respectively. The 12-month survival was 77% for both groups. The most frequent adverse events were infusion-related reactions, which occurred in 71% of patients. The majority of these reactions included Grade 1 and 2 and were characterized by rhinitis, cough, headache, pyrexia, and dyspnea. Most infusion-related reactions occurred during the first daratumumab infusion, and only few patients (<10%) had infusion-related reactions with more than one infusion.

The SIRIUS (MMY2002) study confirmed the results from GEN501 study that demonstrated single agent activity of daratumumab with a favorable toxicity profile.[80] One hundred six patients, with a median of 5 prior lines of therapy (95% refractory to lenalidomide and bortezomib), received daratumumab monotherapy at a dose of 16 mg/kg. At least a PR was achieved in 29% of patients with stringent CR in 3%. The median duration of response was 7.4 months. The median PFS was 3.7 months and 1-year OS was 65%. Notably, subgroup analysis showed that in the group of patients who were refractory to lenalidomide, pomalidomide, bortezomib and carfilzomib, PR or better was achieved in 21% of these patients. Infusion-related reactions were observed in 43% of the patients and were predominantly Grade 1 and 2 and could be managed with interruption of

the infusion or extra corticosteroids and antihistamines. In conclusion, results from these studies show that daratumumab is well tolerated and that in the 16 mg/kg cohort at least a partial response can be achieved in 29-36% of the patients.[93,94,95] Virtually all patients with PR or CR, achieved 50% reduction in tumor load within 3 months after start of therapy.

Based on preclinical evidence showing potential benefit of combining daratumumab with lenalidomide,[96,97,98] another Phase 1/2 study is currently evaluating the combination of daratumumab plus lenalidomide and dexamethasone in relapsed/refractory MM (GEN503; NCT01615029). Preliminary safety data show a manageable toxicity profile and high efficacy of this three-drug regimen.[99,100]

Daratumumab has also been shown to be safe, tolerable and efficacious when combined with other immunomodulatory agents in two separate Phase 3 trials combining daratumumab with 1) lenalidomide and dexamethasone (POLLUX) and 2) pomalidomide and dexamethasone (CASTOR). In the POLLUX trial, lenalidomide-dexamethasone was combined with or without daratumumab in patients with relapsed/refractory myeloma with 1-3 previous lines of therapy (patients with lenalidomide-refractory disease were excluded).[101] In this study the daratumumab treated patients had a significantly higher CR rate and an unprecedented improvement in the PFS (HR: 0.37). There was no additional toxicity when daratumumab was added to lenalidomide-dexamethasone, except for infusion-related reactions, which occurred in approximately half of the patients mostly during the first infusion. Another Phase 3 trial compared bortezomib-dexamethasone with or without daratumumab.[102] Also in this study there was a significant improvement in CR rate, leading to a significant improvement of the PFS (HR: 0.39). Also, in the CASTOR study, daratumumab did not add toxicity to bortezomib-dexamethasone, except for infusion-related reactions occurring in approximately half of the patients, mostly during the first infusion of daratumumab.

1.5 Overall Risk/Benefit Assessment

Despite several therapies available for the treatment of mCRC, the incremental benefit of these treatments after treatment with a first-line regimen is small, as discussed in Section 1.1.1, and represents an area of unmet medical need. Furthermore, patients with MSI-H CRC do not appear to consistently have the same benefit from fluorouracil, the backbone of combination regimens for mCRC, as patients with non-MSI-H. Reliable testing methods exist to identify these subjects with MSI-H tumors who may not reliably respond to fluorouracil. Non-fluorouracil based treatment options include single agent cetuximab and regorafenib, both of which have demonstrated a survival advantage in the later line settings compared to BSC, but these benefits are less than 2 months and do not provide long term responses.

Patients with MSI-H CRC have distinct molecular and clinicopathologic phenotypes, including immune-related findings germane to the mechanism of action of nivolumab. Nivolumab monotherapy has demonstrated clinical activity across several tumor types, including advanced melanoma, NSCLC, and RCC. Nivolumab has demonstrated a manageable safety profile in patients > 1500 patients across all clinical trials. The most common AEs included fatigue, rash,

pruritus, diarrhea, and nausea. The AE profile for nivolumab monotherapy does not appear to be dose dependent and appears to be similar across a range of solid tumors studied.

Ipilimumab 3 mg/kg is approved for use in the US (advanced melanoma) and in the EU (for previously treated advanced melanoma) based on OS benefit in randomized trials. Furthermore, clinical activity with ipilimumab has been observed in patients with NSCLC, SCLC, and prostate carcinoma. The efficacy of ipilimumab in these tumor types is being investigated in ongoing Phase 3 trials. The currently approved dose for ipilimumab in melanoma patients is 3 mg/kg every 3 weeks for up to 4 doses. Ipilimumab has demonstrated a manageable safety profile and treatment guidelines for immune-related adverse events are established based on > 10,000 patients treated in clinical trials.

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). Studies investigating the efficacy and safety of nivolumab in combination with ipilimumab are ongoing in NSCLC and RCC.

The combination of nivolumab and ipilimumab has the potential for increased frequencies of adverse events 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 adverse events were laboratory in nature (ie, liver function tests [LFTs], lipase, amylase), were without clinical sequelae, 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 adverse event (toxic epidermal necrolysis, TEN) in the nivolumab + ipilimumab development program. Fatal TEN has previously been reported for ipilimumab monotherapy.

Evaluating both nivolumab monotherapy and the combination of nivolumab and ipilimumab in subjects with advanced or metastatic MSI-H CRC, who may not derive the same benefit from fluorouracil based regimens, will potentially generate efficacy signals as a basis for a further clinical development in this distinct tumor type.

Across multiple tumors, 3 mg/kg nivolumab monotherapy has demonstrated a tolerable AE profile in hundreds of subjects, and that profile 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 and is currently in Phase 3. The same regimen is currently being studied in RCC and

NSCLC. The following safety measures have been employed to ensure safety of the subjects in this current study:

- Two-stage design used which will stop an individual arm for lack of sufficient activity
- For the combination arm, an initial dose escalating safety evaluation phase will be performed to determine the optimal dose for advanced CRC.
- Intense toxicity monitoring will help to ensure the subjects' safety in Study CA209142, including frequent safety conference calls with investigators and representatives of the sponsor.
- A BMS safety management team (SMT) routinely reviews safety signals across the entire nivolumab program, including all ongoing combinations with ipilimumab.

MSI-H Cohort C3 (No prior Treatment in Metastatic Setting, Nivolumab + Ipilimumab):

Given the preliminary efficacy and tolerability of nivolumab + ipilimumab in a biomarker-selected population of dMMR/MSI-H mCRC patients, and the known toxicity of first-line chemotherapy for mCRC, the potential benefit of a first-line approach in dMMR/MSI-H mCRC appears to outweigh the potential risk.

MSI-H Cohort C5 (Nivolumab + BMS-986016):

The **combination of nivolumab plus BMS-986016** has the potential for increased benefit compared to monotherapy targeting the PD-1 pathway, ie, nivolumab monotherapy. In the nonclinical GLP toxicology study, lymphoplasmacytic infiltration in the choroid plexus (and spinal cord) was reported at the highest doses of anti-PD-1 antibody (3/6 animals) and the anti-LAG-3 + anti-PD-1 antibody combination (5/6). Importantly, these findings were not reported with anti-LAG-3 antibody alone at either 30 mg/kg or 100 mg/kg (highest dose).

These are nonspecific histopathology changes, without clinical manifestations in all but one of the animals treated with combination therapy, which have been observed in other studies with antibodies and small molecules in monkeys. However, an exaggerated immunostimulatory pharmacologic effect of the combination of BMS-986016 plus nivolumab cannot be disregarded. Also, given the short study period (6 weeks) and the long half-lives of BMS-986016 and nivolumab, a potential long-term effect has not been ruled out. Potential lymphoplasmacytic inflammation of the choroid plexus could manifest in human subjects as aseptic meningitis or encephalitis.

As of 29-Jun-2016, the observed drug-related AEs with potential for neurotoxic etiology have occurred in 10 subjects (10%) treated across all monotherapy and combination dose cohorts (up to and including the 80 mg BMS-986016/240 mg nivolumab cohort) in both the hematological malignancy and solid tumor early phase studies. Related AEs included headache (n=4), dysgeusia (n=3), peripheral neuropathy (n=2), blurred vision (n=1), and ataxia (n=1). The severity in all cases was Grade 1 except for a single Grade 2 headache and a single Grade 2 peripheral neuropathy. The Grade 1 ataxia resolved within 48 hours. None of the events have been associated with any

documented neurologic pathologic finding, nor did any of these events directly contribute to a dose interruption. Nonetheless, in this clinical study, monitoring measures include:

1) Exclusion of subjects with active neurological disease, confirmed history of encephalitis, meningitis, or uncontrolled seizures in the year prior to informed consent
2) Investigators and site personnel are trained on the use of treatment guidelines for neurological toxicity and immune-related AE management algorithms upon site initiation
3) Clinical monitoring of subjects for signs and symptoms of neurologic toxicities
4) The following protocol defined actions are triggered upon a ≥ Grade 2 neurological AE:
   a) Holding therapy
   b) Follow the neurological AE management algorithm
   c) Complete neurological examination performed by a neurologist

Treatment with BMS-986016 may be associated with a risk of aseptic meningitis or encephalitis. Increased safety precautions have been instituted in this study to mitigate this risk.

Therapy with BMS-986016 and nivolumab is investigational, and it is possible that a higher incidence of immune-related adverse events (irAEs) may occur with the combination of 2 antibodies targeting T cells. As of 29-Jun-2016, drug-related SAEs were reported in 4 of the 28 subjects treated with BMS-986016 in combination with nivolumab in Part B. These included Grade 3 mucosal inflammation (1 subject), Grade 3 dyspnea (1 subject), Grade 4 ventricular fibrillation (1 subject), and Grade 4 myocarditis (1 subject). Regarding non-serious AEs, treatment with BMS-986016 monotherapy, and in combination with nivolumab, in both early phase studies, low-grade, drug-related AEs consistent with immune-mediated AEs have been experienced. These events are indirect evidence of the ability of BMS-986016 to activate T-cells.

Low-grade, likely immune-related AEs experienced include 2 subjects experiencing Grade 2 hypothyroidism, 2 subjects experiencing Grade 1 alterations in TSH levels, 1 subject with Grade 1 thyroiditis, 1 subject with Grade 1 vitiligo (20 mg monotherapy), and 1 subject with Grade 2 pneumonitis (800 mg monotherapy).

As of 29-Jun-2016, drug-related SAEs were reported in 4 of the 28 subjects treated with BMS-986016 in combination with nivolumab in Part B of Study CA224-020. Two of these events were cardiovascular events: Grade 4 ventricular fibrillation and Grade 4 myocarditis. Additional safety measures for cardiovascular risks implemented for subjects receiving combination treatment with Cohort C5 have been added to the protocol:

1) Exclusion of subjects with history of myocarditis, regardless of etiology.
2) Exclusion Criteria under significant cardiac events: history of 2 or more myocardial infarctions (MIs) OR 2 or more coronary revascularization procedures.
3) Screening left ventricular ejection fraction (LVEF) assessment (if not performed in the last 6 months) with documented LVEF ≥ 50% by either transthoracic echocardiogram or multiple gated acquisition scan (transthoracic echocardiogram being the preferred test) for subjects.

4) Increased emphasis in clinical monitoring of subjects for signs and symptoms of cardiovascular toxicities during training meetings and safety teleconferences.
5) Addition of pre-dose ECG testing.
6) Addition of troponin laboratory testing

non-MSI-H Cohort C6 (Nivolumab + Daratumumab):

Daratumumab induces antimyeloma effects via multiple mechanisms of action. An additional mechanism of action has been proposed in which treatment with daratumumab eliminates a population of highly immunosuppressive CD38+ Tregs, T-cell MDSCs, and Bregs and thus stimulates T-cell effector functions.[82] This immunomodulatory effects of daratumumab, specifically its ability to promote T-cell expansion and activation, are expected to potentiate the effect of anti-PD-1 antibody. The combination of nivolumab plus daratumumab is expected to potentiate the effect of nivolumab by sensitizing the bone marrow T cells to PD-1 blockade, which would translate in augmented clinical benefit.

Daratumumab is approved as monotherapy for third-line treatment of MM patients who failed prior therapies.[79,80] Recent reported results demonstrated safety and efficacy when combined with other immunomodulatory therapies in second-line MM, including lenalidomide and dexamethasone.[97] Daratumumab's primary adverse events includes infusion reactions, which are reported to be uncommon with nivolumab (refer to nivolumab IB). However, infusion-related reactions to daratumumab occur in close to 50% of the patients, largely with the first infusion. According to the currently approved United States Prescribing Information (USPI),[103] daratumumab infusions should be interrupted for infusion reactions of any severity, and drug should be permanently discontinued in case of life-threatening infusion reactions. Pre-infusion and post-infusion medication should be administered to all patients, per the currently approved USPI.[103] Severe infusion-related reactions have been reported in less than 1% of subjects in clinical trials with nivolumab, with overall rates of infusion-related reactions of any grade ranging from 1% to 6%. The risk of infusion reactions is greater with the first and second infusions with daratumumab and decreases for subsequent doses. Therefore, to minimize the likelihood of infusion-related reactions to the nivolumab and daratumumab combinations, the first nivolumab dose is administered at Week 3 (ie, after the first two doses of daratumumab at Weeks 1 and 2). Further, on each dosing day when nivolumab is administered with daratumumab, the required pre-infusion medication for daratumumab is administered first, followed by the nivolumab infusion, and then by the daratumumab infusion.

Other AEs of any grade reported in a high frequency (>25%) of daratumumab-treated subjects include low-grade fatigue and nausea, which have been associated with nivolumab treatment. Only one severe AEs (Grade 3/4) of pneumonia has been reported with daratumumab (>5% frequency). Pneumonia is considered uncommon with nivolumab as reported in the USPI; however, severe cases have been reported. The hematological AEs that have been reported following treatment with daratumumab (anemia, thrombocytopenia, neutropenia, lymphopenia), which are common in subjects with hematological malignancies, are not expected to be observed

in subjects with solid tumors. In contrast to nivolumab, there have been no cases of immune-related AEs, including pneumonitis, reported in the label for daratumumab. When comparing the toxicity profile of daratumumab and nivolumab in hematologic malignancies, there is little overlap of AE profiles. Based on the above assessment, the potential benefit of combining nivolumab and daratumumab appears to outweigh the potential risk. The overall risk/benefit assessment supports the evaluation of these combinations in this setting.

It is possible that unforeseen or unanticipated AEs may occur. In order to minimize the overall risks to participating subjects, the protocol has inclusion-exclusion criteria appropriate to the population and specific follow-up safety assessments. Routine safety monitoring for all the AEs described above will be implemented in the protocol to ensure that we are monitoring the potential for overlapping toxicities. Toxicity monitoring will help to ensure the subjects' safety and will include frequent safety conference calls with investigators and routine reviews by a BMS SMT.

Adverse events and SAEs will continue to be reviewed expeditiously by the Medical Monitor, investigators, and the Pharmacovigilance group to monitor safety.

Treatment Duration and Re-Initiation Option in MSI-H/dMMR mCRC Cohorts

As detailed in Section 1.1.4.7, accumulating data suggest that 24 months of PD-1 checkpoint inhibitor treatment may be sufficient for long term benefit; therefore this duration was considered when modifying treatment duration for MSI-H/dMMR Cohorts of CA209-142 study. Given the fact that some subjects have been on treatment longer and MSI-H/dMMR might have a unique response pattern, a strict stopping rule at 2-years was not considered ideal for CA209-142. Subjects who achieved objective response within the second year of treatment will be required to continue to receive study therapy for additional 12 months before the option to discontinue treatment for maximum clinical benefit is allowed. (Section 3.1.4.1). These measures maintain a favorable overall risk-benefit assessment for Study CA209142 and justify the conduct of the trial and the incorporation of Revised Protocol 07.

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 subject 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 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 subjects 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, subject recruitment materials (eg, advertisements), and any other written information to be provided to subjects. The investigator or BMS should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to subjects and any updates.

The investigator 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 subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

In situations where consent cannot be given to subjects, their legally acceptable representatives are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the subject volunteers to participate.

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

Investigators must:

1) Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
2) Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
3) Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.
4) Obtain the IRB/IEC’s written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.
5) If informed consent is initially given by a subject’s legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject.
6) Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator,

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

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

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

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

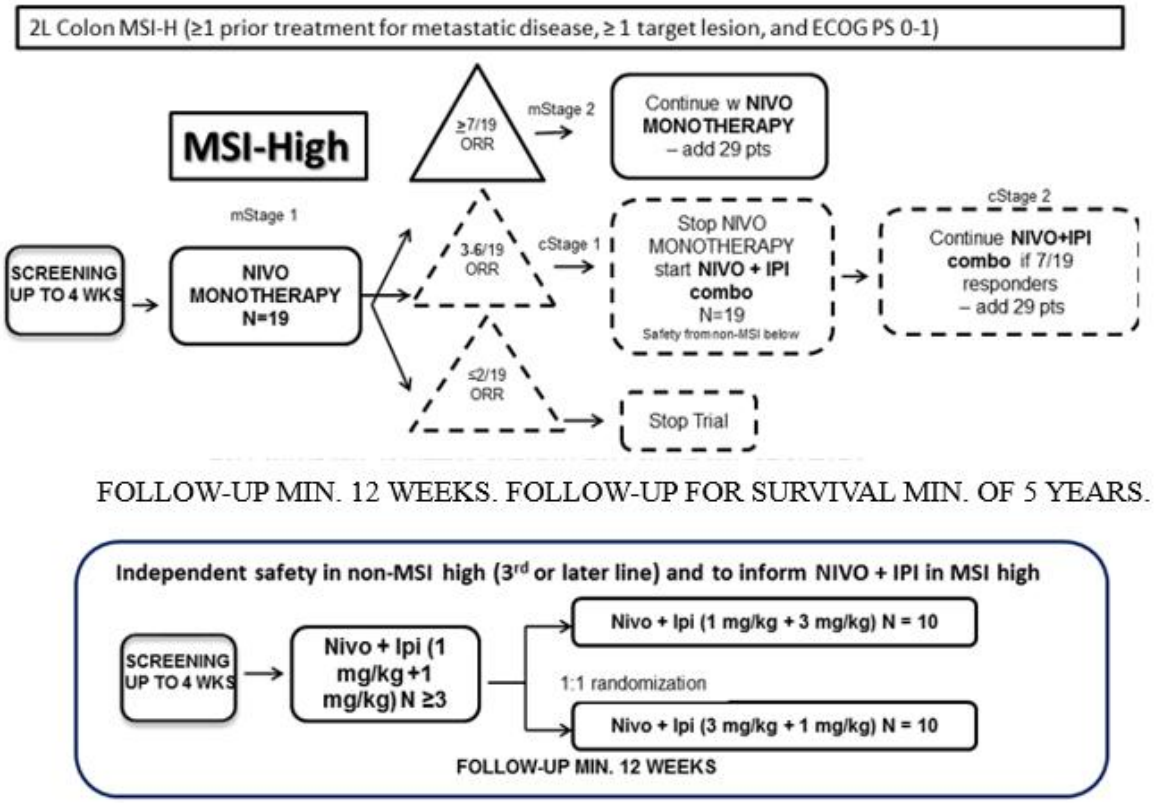
3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

CA209142 is a Phase 2 open-label, multi-center, trial of nivolumab monotherapy (Arm N) or in combination therapy (Cohort N + I) to estimate the response rate in MSI-H CRC and non-MSI-H CRC. CA209142 completed a safety cohort of subjects with non-MSI-H CRC to assess the safety and tolerability of nivolumab in combination with ipilimumab in subjects with non-MSI-H CRC in preparation for an analogous 2-stage assessment of the response rate for the combination in MSI-H CRC.

As described in Figure 3.1-1, subjects with recurrent or metastatic CRC received nivolumab or nivolumab with ipilimumab, depending on the response rate in the monotherapy MSI-H cohort and the tolerability of the nivolumab combined with ipilimumab combination in the non-MSI safety cohort.

Figure 3.1-1: Study Design Schematic (Arm N and Arm N +I) and Non-MSI-H Safety Cohort



mStage = monotherapy Stage; cStage = combination Stage; Arm N = Nivolumab monotherapy; Arm N+I = nivolumab in combination with ipilimumab; nMSI-H N+I = non-MSI-H nivolumab in combination with ipilimumab

For the monotherapy mStage 1, if 7 or more subjects with microsatellite metastatic CRC (MSI-H mCRC) have a confirmed PR or CR, mStage 2 will open to enroll an additional 29 subjects. A confirmed PR or CR is defined as a subsequent confirmatory scan performed ≥ 4 weeks after the first scan. If there are more than 2 but less than 7 responses in the first 19 subjects, accrual to the mStage1 arm will be stopped, and the combination cStage1 arm will be opened for accrual.

CA209142 will also contain a safety cohort of subjects with non-MSI-H mCRC to assess the safety and tolerability of nivolumab in combination with ipilimumab in subjects with non-MSI-H mCRC and provide the starting dose for cStage 1.

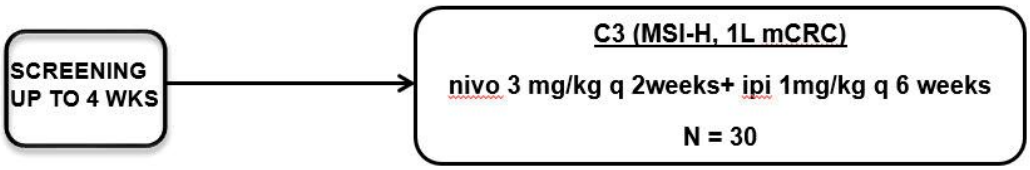
If 7 or more subjects in cStage 1 with MSI-H mCRC have a confirmed PR or CR, cStage 2 will open to enroll an additional 29 subjects. If 6 or fewer of the first 19 subjects with MSI-H mCRC have a confirmed PR or CR, cStage 1 will close, and the trial will end. Additionally, if 2 or fewer of the first 19 subjects in mStage 1 have a confirmed CR or PR, the trial will close. The determination of response rate will be based on investigator-assessed tumor response per RECIST

1.1 criteria. Subjects in mStage 1 or cStage 1 who remain on treatment should complete a 24-week follow up for an assessment of ORR.

For the monotherapy mStage 1/2 and the combination therapy cStage 1/2, the option to discontinue treatment at maximum clinical benefit as assessed by the Investigator and defined in Section 3.1.4.1 has been incorporated. Re-initiation of treatment upon progression after discontinuation at maximum clinical benefit is an option for eligible MSI-H subjects as described in Section 3.1.4.8.

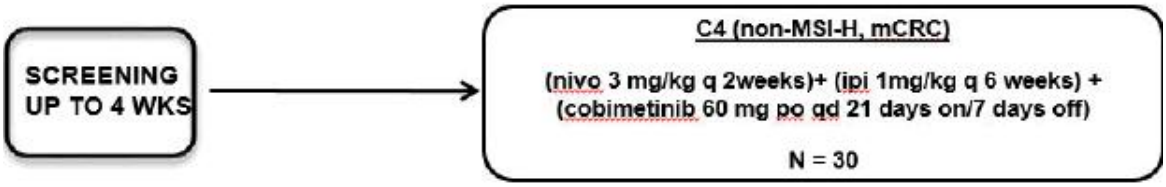
The CA209142 study also includes an additional C3 cohort as described below in Figure 3.1-2. The C3 cohort will enroll 30 MSI-H subjects who have not had prior therapy for their metastatic disease. For Cohort C3, the option to discontinue treatment at maximum clinical benefit as assessed by the Investigator and defined in Sections 3.1.4.1 has been incorporated. Re-initiation of treatment upon progression after discontinuation at maximum clinical benefit is an option for eligible MSI-H subjects as described in Section 3.1.4.8.

Figure 3.1-2: Study Schematic for Cohort 3



The CA209142 study includes an additional C4 cohort as described below in Figure 3.1-3. All information pertaining to the C4 cohort was added via a site-specific Amendment 06. This cohort is only open at 2 sites. This cohort will enroll 30 previously-treated non-MSI-H subjects with metastatic CRC.

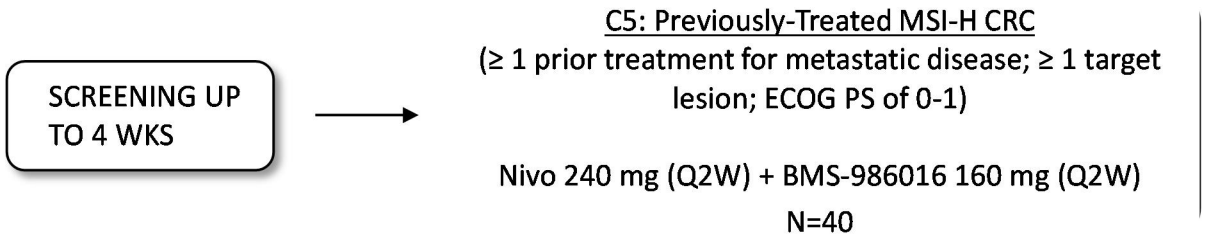
Figure 3.1-3: Study Schematic for Cohort 4



The CA209142 study includes a C5 cohort as described below in Figure 3.1-4. The C5 cohort will enroll 40 previously-treated MSI-H subjects who have not had prior anti-PD-1 therapy for their metastatic CRC disease. For Cohort C5, the option to discontinue treatment at maximum clinical benefit as assessed by the Investigator and defined in Sections 3.1.4.1 has been incorporated. Re-

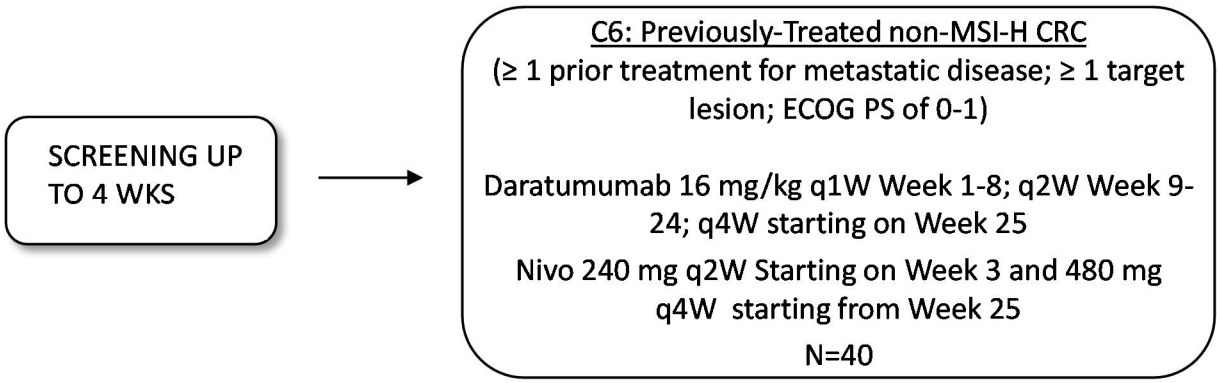
initiation of treatment upon progression after discontinuation at maximum clinical benefit is an option for eligible MSI-H subjects as described in Section 3.1.4.8.

Figure 3.1-4: Study Schematic for Cohort 5 (C5)



The CA209142 study includes a C6 cohort as described below in Figure 3.1-5. The C6 cohort will enroll 40 previously-treated non-MSI-H subjects with metastatic CRC.

Figure 3.1-5: Study Schematic for Cohort 6 (C6)



All subjects will undergo screening evaluations to determine eligibility within 28 days prior to the start of therapy. A baseline tumor imaging assessment will be performed prior to the start of therapy. Tumor tissue must be provided for biomarker analysis. Central lab must provide IVRS with confirmation of receipt of evaluable tumor tissue prior to study treatment. Subjects whose repeat testing does not confirm MSI-H status will be replaced but will be allowed to continue on study therapy. Subjects on C3 will be accepted with a valid local MSI result.

Treatment beyond initial investigator-assessed progression is permitted if the subject has an investigator-assessed clinical benefit and is tolerating study drug, see Section 4.3.8. The investigator-assessed tumor response based on RECIST 1.1 criteria will be used to guide the stage 1 decision and for the primary analysis of the ORR. In addition, an independent radiology review

committee (IRRC) will perform central review of the imaging per RECIST 1.1 criteria upon study completion. Details will be included in the IRRC charter.

3.1.1 Mismatch Repair/Microsatellite Instability Testing

MSI-H (Microsatellite Instability High) is most frequently determined by PCR. MSI-H in tumors refers to changes in two or more of the five National Cancer Institute-recommended panels of microsatellite markers in tumor tissue. The original (1997) Bethesda guidelines proposed a panel of five microsatellite markers for the uniform analysis of MSI in 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.[104] 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.

Mismatch repair deficiency (dMMR) 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.

dMMR/MSI-H can also be diagnosed by next-gen sequencing (NGS) through pathogenic mutations in the MMR genes or MSI.

Sites should query a subject's medical history for prior MSI testing detected by an accredited laboratory per local regulations to select subjects for the MSI-H or non-MSI-H cohorts. MSI-H or non-MSI-H status in potential subjects will be determined prior to screening as part of standard diagnostic testing by investigators. Please refer to Appendix 4 regarding MSI testing panel descriptions and classification of MSI status to ensure historic MSI status determination is aligned with the protocol prior to enrollment.

For both the mStage1/2 and cStage1/2 MSI-H and the dose finding non-MSI-H cohorts, a PCR test will be utilized for repeat testing. For all cohorts, additional tumor samples must be sent to BMS for future confirmatory studies of the *in vitro* diagnostic. A lab manual separate from the protocol will provide detailed information regarding MSI testing and sample requirements.

3.1.2 Non-MSI-H Subjects (Independent Safety Sub-Trial)

An independent safety sub-trial in non-MSI H subjects will inform the safe and tolerable dose level for cStage 1 in subjects with MSI-H mCRC. The combination of nivolumab and ipilimumab is already being evaluated in Phase 3 in advanced melanoma and has more recently been tested in NSCLC and RCC. This regimen is expected to also be tolerable in mCRC, but given the potential for gastrointestinal toxicities with ipilimumab and nivolumab (eg, colitis), a dose escalating safety phase will assess the safety and tolerability of nivolumab in combination with ipilimumab and evaluate different doses of each agent. Enrollment in the non-MSI-H N+I Safety Sub Trial will occur in parallel to mStage 1.

3.1.2.1 Dose Escalating Safety Evaluation for Nivolumab in Combination with Ipilimumab in non-MSI- H Subjects

Table 3.1.2.1-1 contains the dose levels for the non-MSI-H dose escalation safety cohort.

Table 3.1.2.1-1: Dose Cohort for Safety non-MSI-H N+I

Dose Cohort Level	Nivolumab (mg/kg)	Ipilimumab (mg/kg)
-1	0.3	1
1	1	1
2a	1	3
2b	3	1

The first dose cohort will be Dose Level 1, 1 mg/kg each of nivolumab and ipilimumab. If this combination is deemed tolerable, then subjects will be randomized (1:1) to one of two dose levels:

- Dose Level 2a (N1+I3): 1 mg/kg nivolumab + 3 mg/kg ipilimumab, or
- Dose Level 2b (N3 + I1): 3 mg/kg nivolumab + 1 mg/kg ipilimumab

The tolerable dose of the combination will be brought into an analogous 2-stage design if nivolumab monotherapy (mStage 1) does not have 7 or more responders out of the first 19 subjects.

If Level 1 is not tolerable, then Level -1 will be initiated. There will be no dose escalation beyond Levels 2a and 2b. Once the decision on the dose level for further investigation has been confirmed, that dosing level will be used in cStage 1 in subjects with MSI-H (Section 3.1.4.3).

Subjects need to be followed up for at least 6 weeks after start of study treatment before determination of the tolerability of a dose level. However, tolerability beyond 6 weeks may also be taken into consideration.

The criteria for tolerability for Dose Level 1 (and -1 if necessary) (Table 3.1.2.1-2) are based on drug-related adverse events leading to permanent discontinuation (listed in Section 4.3.6) and include:

- If none of the first 3 subjects in the dose level permanently discontinue treatment due to study drug-related adverse events within the first 6 weeks, then this dose cohort will be deemed as tolerable.
- If one or two of the first 3 subjects in the dose level permanently discontinue treatment within the first 6 weeks due to study drug related adverse events, this cohort will be expanded to 6 subjects.
- If one of 6 subjects in the dose level permanently discontinues treatment due to study drug related adverse events within the first 6 weeks, then the dose level will be deemed as tolerable.
- If two of 6 subjects in the dose level permanently discontinue treatment within the first 6 weeks due to study treatment related adverse events, this dose level may be expanded to 9 subjects.

If an expansion is not possible because of the severity of the adverse events leading to permanent discontinuation, then this dose cohort will be deemed not tolerable.

- If no more than two of 9 subjects in the dose level permanently discontinue treatment due to study treatment related adverse events within the first 6 weeks, then the dose level will be deemed as tolerable.
- If at least three of the first 9 subjects in Dose Level 1 permanently discontinue treatment within the first 6 weeks due to study treatment related adverse events, a Dose Level -1 Cohort may proceed.

For the decision to enroll a Dose Level -1, the clinical severity of the adverse events leading to permanent discontinuation in Dose Cohort 1 will be taken into consideration.

Table 3.1.2.1-2: Dose Level Decisions (Dose Level 1 and Dose Level -1) for Arm non-MSI-H N+I

Number of subjects treated and followed up for at least 6 weeks after start of study treatment	Number of subjects with permanent discontinuation due to treatment related adverse events	Next Step
3	0	Dose tolerable
3	1-2	Expand to 6 subjects
6	≤ 1	Dose tolerable
6	2	Expand to 9 subjects
9	≤ 2	Dose tolerable
9	≥ 3	Dose not tolerable[a]

[a] discussion with investigators to review risk/benefit taking into account reversibility of AEs and depth of response

Table 3.1.2.1-3 contains the dosing schedule for Arm N+I weeks 1-12.

Table 3.1.2.1-3: Dosing Schedule for Arm nMSI-H N+I (Week 1-12) - Nivolumab + Ipilimumab Combination

Every 3 Week Dosing				
Study Part	**Day 1 Dose 1/Week 1**	**Day 1 Dose 2/Week 4**	**Day 1 Dose 3/Week 7**	**Day 1 Dose 4/Week 10**
Dose Escalation Phase Dose Level -1	0.3 mg/kg Nivolumab 1 mg/kg Ipilimumab	0.3 mg/kg Nivolumab 1 mg/kg Ipilimumab	0.3 mg/kg Nivolumab 1 mg/kg Ipilimumab	0.3 mg/kg Nivolumab 1 mg/kg Ipilimumab
Dose Escalation Phase Dose Level 1	1 mg/kg Nivolumab 1 mg/kg Ipilimumab	1 mg/kg Nivolumab 1 mg/kg Ipilimumab	1 mg/kg Nivolumab 1 mg/kg Ipilimumab	1 mg/kg Nivolumab 1 mg/kg Ipilimumab

Table 3.1.2.1-3: Dosing Schedule for Arm nMSI-H N+I (Week 1-12) - Nivolumab + Ipilimumab Combination				
Every 3 Week Dosing				
Study Part	**Day 1 Dose 1/Week 1**	**Day 1 Dose 2/Week 4**	**Day 1 Dose 3/Week 7**	**Day 1 Dose 4/Week 10**
Dose Escalation Phase Dose Level 2a	1 mg/kg Nivolumab 3 mg/kg Ipilimumab	1 mg/kg Nivolumab 3 mg/kg Ipilimumab	1 mg/kg Nivolumab 3 mg/kg Ipilimumab	1 mg/kg Nivolumab 3 mg/kg Ipilimumab
Dose Escalation Phase Dose Level 2b	3 mg/kg Nivolumab 1 mg/kg Ipilimumab	3 mg/kg Nivolumab 1 mg/kg Ipilimumab	3 mg/kg Nivolumab 1 mg/kg Ipilimumab	3 mg/kg Nivolumab 1 mg/kg Ipilimumab

Table 3.1.2.1-4 contains the dosing schedule for Arm N+I weeks 13 and following.

Table 3.1.2.1-4: Dosing Schedule for Arm nMSI-H N+I (Week 13 and following) Nivolumab + Ipilimumab Combination Escalation Cohort		
Every 2 Week Dosing		
Day 1 Week 13	**Day 1** Week 15	**Day 1, Week 17, 19, 21** and every other week thereafter
3 mg/kg Nivolumab	3 mg/kg Nivolumab	3 mg/kg Nivolumab

Approximately 10 subjects with recurrent or metastatic nMSI-H CRC will be randomized (1:1) to Dose Level 2a (N1+I3) and Dose Level 2b (N3+ I1). Tolerability and safety of a treatment arm will be determined after all subjects per arm have completed four doses of the combination or have discontinued dosing prior to completing four doses. However, tolerability beyond four doses of the combination during the nivolumab monotherapy time period may also be taken into consideration. All subjects will continue to be followed for safety, progression, and overall survival after discontinuation of study medication. The tolerability criteria used to advance the dose level to the MSI-H cStage 1 will based on drug-related adverse events leading to permanent discontinuation (listed in Section 4.3.6) and include the following:

- If no more than one-third of the subjects in either Dose Level 2a or 2b permanently discontinue study medication prior to completing four doses due to treatment-related adverse events then this dose cohort will be deemed as tolerable.
- If more than one-third of subjects in either Dose Level 2a or 2b permanently discontinue study medication prior to completing four doses due to treatment-related adverse events, then the safety and tolerability of that treatment arm will be reviewed prior to randomizing any additional subjects. A decision will be made by the sponsor whether to continue enrollment or advance either treatment arm into the MSI-H Cohort, ie, cStage 1.

If both Dose Level 2a and 2b are deemed tolerable, the sponsor will review the adverse events and efficacy results to determine which dose level will advance to cStage 1. If both Dose Level 2a and 2b are not deemed tolerable, Dose Level 1 will be advanced to cStage 1.

Subjects enrolled in the non-MSI high safety cohort who discontinue from treatment prior to 6 weeks of exposure to study drug due to reasons not related to study drug toxicity will be replaced, if necessary.

3.1.2.2 Evaluation of Risk/Benefit for Doses that Do Not Meet Tolerable Criteria

In the event of ≥ 3 of the first 9 subjects requiring permanent discontinuation in Dose Level -1, a discussion with investigators may be held to review the risk/benefit of this regimen. The rationale for this evaluation is that the most frequent severe drug-related AEs for the combination in melanoma have been asymptomatic, reversible laboratory events (ie, LFTs and lipase), and there is preliminary evidence of deep and durable responses in the N+I arm in advanced melanoma (CA209004). Therefore, a discussion of the risk/benefit of the regimen will be triggered if the following criteria are met:

- A majority of subjects who discontinue due to treatment-related AEs have deep tumor response (ie, > 80% reduction)
- All treatment-related AEs leading to discontinuation are non-fatal, reversible and without severe sequela (ie, GI perforation)
- A majority of the treatment related AEs are laboratory in nature, asymptomatic, and monitorable via routine blood draws

If a decision is made to continue with a regimen because of a favorable risk/benefit profile (ie, non-fatal AEs in subjects with near CRs that are durable) and despite meeting the 'not tolerable' criteria above, then IRBs must be notified, ICFs must be updated, and discussion of the risk/benefit must be documented with all future subjects who enroll on this regimen.

3.1.3 Screening

- Begins by establishing the subject's initial eligibility and signing of the informed consent form (ICF).
- Subject is enrolled using the Interactive Voice Response System (IVRS) must be provided for biomarker analyses.
- Tumor tissue obtained in the metastatic setting or from an unresectable site of disease
  - Sufficient tumor tissue (as determined by local pathologist) obtained before start of study treatment in the metastatic setting or from an unresectable site (block or minimum of 30 slides, obtained from core biopsy, punch biopsy, excisional biopsy or surgical specimen) will be submitted to the central laboratory.
  - The central lab must provide IVRS with confirmation of receipt of evaluable tumor tissue prior to initiating study treatment.
  - For subjects where a biopsy is not feasible, archival tumor material must be made available. Subjects should have not received systemic therapy subsequent to archived biopsy.

  - 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 quantity. Accordingly, all subjects must also have archive tumor tissue obtained prior to the last systemic therapy received in the metastatic setting or from an unresectable site of disease.

- For all cohorts, medical record documentation of MSI testing results will be available prior to screening. Detailed instructions of the obtaining, processing, labeling, handling, storage, and shipment of these specimens will be provided in a separate Laboratory Manual at the time of study initiation.
- Determine KRAS and BRAF Mutation status. This test is expected to be already performed for this population.
- Baseline disease or tumor imaging assessments should be performed within 28 days of Treatment Day 1 (according to Table 5.1-1)
- Subject is assessed for study eligibility within the required timeframe found in Table 5.1-1.
- The screening phase either ends with confirmation of full eligibility and treatment assignment for the subject, or with the confirmation that the subject is a screen failure.
- See subsections in Section 3.3.1 for cohort-specific screening requirements.

3.1.4 Treatment

3.1.4.1 Study Treatment Duration (MSI-H Cohorts Only)

In MSI-H Cohorts only [mStage 1/2, cStage 1/2, C3 (1L), C5 (BMS-986016 /anti-LAG3] study treatment will be given until one of the following conditions is met, whichever occurs first:

1) Disease progression, except for subjects eligible for treatment beyond progression (See Section 4.3.8)
2) Unacceptable toxicity
3) Withdrawal of consent
4) Maximum clinical benefit (optional) - Subjects who attain **all** of the following criteria will have the option to discontinue treatment:
   a) Maximum clinical benefit per Investigator
   b) Minimum 12 months of treatment (in the absence of unacceptable toxicity) after date of first response (PR or CR) if the patient achieved response
   c) Minimum 24 months between first dose of study treatment and discontinuation for maximum clinical benefit
   d) No progression since week 12 of study treatment.

   Restaging imaging must be evaluated before decision to discontinue at maximum clinical benefit. If the subject's BOR is SD, it is encouraged to ensure approximately 24 months of treatment before the decision to discontinue at maximum clinical benefit in order to capture any late responses.

   Please see Section 3.1.4.8 and Figure 3.1.4.8-1: for treatment options upon progression for subjects who discontinue at maximum clinical benefit per above description. All criteria

listed above must have been met and the subject must have continued required safety and efficacy follow up procedures to be eligible for re-initiation consideration.

Re-initiation of treatment is an option for eligible MSI-H subjects who progress within 1 year (≤ 52 weeks) of discontinuation for maximum clinical benefit. Subjects who discontinuation for maximum clinical benefit and progress after 52 weeks of follow-up will not have the option to re-initiate treatment.

5) The end of study

3.1.4.2 MSI-H Nivolumab Monotherapy (Arm N): mStage 1 and 2

- Administration of nivolumab should begin within 3 days of treatment assignment.
- Women of child bearing potential (WOCBP) must have a negative pregnancy test to be done within 24 hours prior to first dose, and then every 4 weeks (± 1 week) regardless of dosing schedule.
- On trial laboratory and vital sign assessments (after D1W1) should be drawn within 72 hours prior to dosing according to the schedule in Table 5.1-2. Specific laboratories will be performed more frequently during the first dose administration (according to Table 5.1-2).
- Adverse event assessments should be documented at each clinic visit.

Biomarker, PK, and immunogenicity samples will be obtained according to the schedules in Table 5.5.1-2 and Table 5.6.8-1.

- Study drug dosing may be delayed for toxicity up to 6 weeks from the last dose. See Section 4.3.3.
- Patient-reported outcome(s) (PRO) instruments (EORTC QLQ-C30 & EQ-5D Questionnaires) will be completed for subjects, except for those enrolled in the non-MSI-H Safety Cohort, following drug vial assignment but before first dose and every 6 weeks thereafter per Table 5.1-2.
- Nivolumab is administered as an IV infusion at a dose of 480 mg Q4W (replacing the dose of 3 mg/kg every 2 weeks) until discontinuation of study therapy and for reasons described in Section 3.1.4.1, Study Treatment Discontinuation. in subjects receiving nivolumab beyond progression, discontinuation due to toxicity, withdrawal of consent, or the study ends.
- This phase ends when the subject is discontinued from study therapy for reasons specified in Section 3.5 and Section 4.3.6. Subjects who discontinue treatment at Maximum Clinical Benefit as specified in Section 3.1.4.1 may re-initiate treatment (see Sections 3.1.4.8 and 4.3.1) if all eligibility criteria are met (Section 4.3.9). All subjects will proceed to follow-up as described in Section 3.1.9 and in Table 5.1-7 regardless of the reason for discontinuation from the original treatment phase of the study. Study schedule of assessments for re-initiation screening, re-initiation treatment, and follow-up after re-initiation are presented in Section 5.1.

3.1.4.3 MSI-H Nivolumab + Ipilimumab (Arm N+I): cStage 1 and 2

- Administration of nivolumab in combination with ipilimumab should begin within 3 days from treatment assignment

- Women of child bearing potential (WOCBP) must have a negative pregnancy test within 24 hours prior to first dose, and then every 4 weeks (1 week) regardless of dosing schedule.
- Adverse event assessments will be documented at each visit throughout the study.
- On trial laboratory and vital sign assessments (after D1W1) should be drawn within 72 hours prior to dosing according to the schedule in Table 5.1-3. Specific laboratories will be performed more frequently during the treatment administration (according to Table 5.1-3).

Biomarker, PK and immunogenicity samples will be obtained according to the schedules in Table 5.5.1-1 and Table 5.6.8-2.

- Study drug dosing may be delayed for toxicity up to 6 weeks from the last dose. See Section 4.3.3.
- Patient-reported outcome(s) (PRO) instruments (EORTC QLQ-C30 & EQ-5D Questionnaires) will be completed for all subjects, except for those enrolled in the non-MSI-H Safety Cohort, following drug vial assignment but before first dose, and every 6 weeks thereafter per Table 5.1-3.
- For Weeks 1-12, the non-MSI-H safety cohort will provide the dosing level for the every three week dosing of nivolumab in combination with ipilimumab:
- For Weeks 13 and following (beyond Dose 4 of nivolumab in combination with ipilimumab), nivolumab is administered as an IV infusion at a dose of 480 mg Q4W (replacing the dose of 3 mg/kg every 2 weeks).
- Administration of nivolumab in combination with ipilimumab (Dose 1 through Dose 4 of combination) or nivolumab alone (beyond Dose 4/Week 12 of combination) continues until discontinuation of study therapy for reasons described in Section 3.1.4.1, “Study Treatment Duration”.
- This phase ends when the subject is discontinued from study therapy for reasons specified in Section 3.5 and Section 4.3.6. Subjects who discontinue treatment at Maximum Clinical Benefit as specified in Section 3.1.4.1 may re-initiate treatment (see Sections 3.1.4.8 and 4.3.1) if all eligibility criteria are met (Section 4.3.9.). All subjects will proceed to follow-up as described in Section 3.1.9 and in Table 5.1-7 regardless of the reason for discontinuation from the original treatment phase of the study. Study schedule of assessments for re-initiation screening, re-initiation treatment, and follow-up after re-initiation are presented in Section 5.1.

3.1.4.4 Non-MSI-H Safety Cohort (Nivolumab + Ipilimumab)

- Administration of nivolumab in combination with ipilimumab should begin within 3 days of treatment assignment.
- Women of child bearing potential (WOCBP) must have a negative pregnancy test within 24 hours prior to first dose, and then every 4 weeks (±1 week) regardless of dosing schedule.
- Dose Escalation Phase:
  - **Dose Level -1,** Nivolumab 0.3 mg/kg IV combined with ipilimumab 1 mg/kg IV Q3W for 4 doses, then nivolumab 3 mg/kg IV Q2W
  - **Dose Level 1**, Nivolumab 1 mg/kg IV combined with ipilimumab 1 mg/kg IV Q3W for 4 doses, then nivolumab 3 mg/kg IV Q2W.

- **Dose Level 2:** Randomization (1:1) to the following arms
  - **Dose Level 2a:** Nivolumab 1 mg/kg IV combined with ipilimumab 3 mg/kg IV Q3W for 4 doses, then nivolumab 3 mg/kg IV Q2W.
  - **Dose Level 2b:** Nivolumab 3 mg/kg IV combined with ipilimumab 1 mg/kg IV Q3W for 4 doses, then nivolumab 3 mg/kg IV Q2W.

Staged Enrollment Phase: Dose Level determined in Dose Escalation Phase. See Table 3.1.2.1-1, Table 3.1.2.1-2, Table 3.1.2.1-3, and Table 3.1.2.1-4.

- Adverse event assessments will be documented at each visit throughout the study.
- On-study laboratory assessments (after D1W1) should be drawn within 72 hours prior to dosing according to the schedule in Table 5.1-3.

Biomarker, PK, and immunogenicity samples will be obtained according to the schedules in Table 5.5.1-1 and Table 5.6.8-2.

- Study drug dosing may be delayed for toxicity for up to 6 weeks from the last dose. See Section 4.3.3.
- For Weeks 13 and following (beyond Dose 4 of nivolumab in combination with ipilimumab), nivolumab is administered as an IV infusion at a dose of 3 mg/kg every 2 weeks.
- Administration of nivolumab in combination with ipilimumab (Dose 1 through Dose 4 of combination) or nivolumab alone (beyond Dose 4/Week 12 of combination) continues until disease progression or until discontinuation of study therapy in subjects receiving study therapy beyond progression, discontinuation due to toxicity, withdrawal of consent, or the study ends.
- This phase ends when the subject is discontinued from study therapy. Please refer to Section 3.5 and Section 4.3.6 for reasons for discontinuation.

3.1.4.5 *MSI-H C3 Cohort (No Prior Treatment in Metastatic Setting, Nivolumab + Ipilimumab)*

- Administration of nivolumab in combination with ipilimumab should begin within 3 days of treatment assignment.
- Women of child bearing potential (WOCBP) must have a negative pregnancy test within 24 hours prior to first dose, and then every 4 weeks (±1 week) regardless of dosing schedule.
- Adverse event assessments will be documented at each visit throughout the study.
- On-study laboratory assessments (after D1W1) should be drawn within 72 hours prior to dosing according to the schedule in Table 5.1-4.
- Biomarker, PK and immunogenicity samples will be obtained according to the schedules in Table 5.5.1-3 and Table 5.6.8-3.
- Study drug dosing may be delayed for toxicity for up to 6 weeks from the last dose. See Section 4.3.3.

- Administration of study drug continues until discontinuation of study therapy for reasons described in Section 3.1.4.1, “Study Treatment Duration”.
- Patient-reported outcome(s) (PRO) instruments (EORTC QLQ-C30 & EQ-5D Questionnaires) will be completed following drug vial assignment but before first dose, and every 6 weeks thereafter per Section 5.7.
- This phase ends when the subject is discontinued from study therapy for reasons specified in Section 3.5 and Section 4.3.6. Subjects who discontinue treatment at Maximum Clinical Benefit as specified in Section 3.1.4.1 may re-initiate treatment (see Sections 3.1.4.8 and 4.3.1) if all eligibility criteria are met (Section 4.3.9.). All subjects will proceed to follow-up as described in Section 3.1.9 and in Table 5.1-7 regardless of the reason for discontinuation from the original treatment phase of the study. Study schedule of assessments for re-initiation screening, re-initiation treatment, and follow-up after re-initiation are presented in Section 5.1.

3.1.4.6 MSI-H C5 Cohort (2L in Metastatic Setting, Nivolumab + BMS-986016)

- Administration of nivolumab in combination with BMS-986016 should begin within 3 days of treatment assignment.
- Women of child bearing potential (WOCBP) must have a negative pregnancy test within 24 hours prior to first dose, and then every 4 weeks (±1 week) regardless of dosing schedule.
- Adverse event assessments will be documented at each visit throughout the study.
- Neurological exams by a neurologist should be performed in subjects who experience a study drug related ≥ Grade 2 neurological AE.
- On-study laboratory assessments, including cardiac troponin levels, (after D1W1) should be drawn within 72 hours prior to dosing according to the schedule in Table 5.1-5.
- 12-lead ECG to be performed within 72 hours prior to dosing
- Biomarker, PK, and immunogenicity samples will be obtained according to the schedules in Table 5.5.1-4 and Table 5.6.8-3.
- Study drug dosing may be delayed for toxicity for up to 6 weeks from the last dose. See Section 4.3.3.
- Administration of study drug continues until discontinuation of study therapy for reasons described in Section 3.1.4.1, “Study Treatment Duration”..
- Patient-reported outcome(s) (PRO) instruments (EORTC QLQ-C30 & EQ-5D Questionnaires) will be completed following drug vial assignment but before first dose, and every 6 weeks thereafter per Table 5.1-5.
- This phase ends when the subject is discontinued from study therapy for reasons specified in Section 3.5 and Section 4.3.6. Subjects who discontinue treatment at Maximum Clinical Benefit as specified in Section 3.1.4.1 may re-initiate treatment (see Sections 3.1.4.8 and 4.3.1) if all eligibility criteria are met (Section 4.3.9.). All subjects will proceed to follow-up as described in Section 3.1.9 and in Table 5.1-7 regardless of the reason for discontinuation from the original treatment phase of the study. Study schedule of assessments for re-initiation screening, re-initiation treatment, and follow-up after re-initiation are presented in Section 5.1.

3.1.4.7 non-MSI-H C6 Cohort (Nivolumab + Daratumumab)

- Administration of study drug should begin within 3 days of treatment assignment.
- Women of child bearing potential (WOCBP) must have a negative pregnancy test within 24 hours prior to first dose, and then every 4 weeks (±1 week) regardless of dosing schedule.
- Adverse event assessments will be documented at each visit throughout the study.
- On-study laboratory assessments (after D1W1) should be drawn within 72 hours prior to dosing according to the schedule in Table 5.1-6.
- Herpes Zoster virus antiviral prophylaxis should be initiated within 1 week after starting daratumumab and continue during the Treatment Phase per institutional guidelines, and for 3 months following treatment discontinuation.
- Biomarker, PK, and immunogenicity samples will be obtained according to the schedules in Table 5.5.1-5 and Table 5.6.8-3.
- Study drug dosing may be delayed for toxicity for up to 6 weeks from the last dose. See Section 4.3.3.
- Administration of study drug continues until disease progression or until discontinuation of study therapy in subjects receiving study therapy beyond progression, discontinuation due to toxicity, withdrawal of consent, or the study ends.
- Patient-reported outcome(s) (PRO) instruments (EORTC QLQ-C30 & EQ-5D Questionnaires) will be completed following drug vial assignment but before first dose, and every 6 weeks through Week 24 and then at each dose, starting with Week 25 according to Table 5.1-6.
- This phase ends when the subject is discontinued from study therapy. Please refer to Section 3.5 and Section 4.3.6 for reasons for discontinuation.

3.1.4.8 Treatment Options Upon Progression after Treatment Discontinuation At Maximum Clinical Benefit

Subjects who have discontinued study treatment after achieving maximum clinical benefit as specified in Section 3.1.4.1 must continue imaging every 12 weeks, and the investigator must ensure close monitoring of symptoms and complete safety follow up as indicated for AEs.

- **If progression occurs ≤ 52 weeks after last dose of study treatment,** subjects **have the option** to re-initiate treatment with nivolumab monotherapy, or the combination of nivolumab with ipilimumab or with BMS-986016 (anti-LAG3) based on the initial cohort assignment, following new baseline assessments for eligibility.

  The inclusion/exclusion criteria for re-initiation are described in Section 4.3.9. Re-initiation treatment schedules are described in Section 4.3.1 and Table 4.3.1-1. Time and events schedule of study assessments during re-initiation screening, during re-initiation treatment and during follow-up after re-initiation are included in Section 5.1

  Treatment duration after re-initiation, inclusive of treatment beyond progression, will be for a maximum of 24 months.

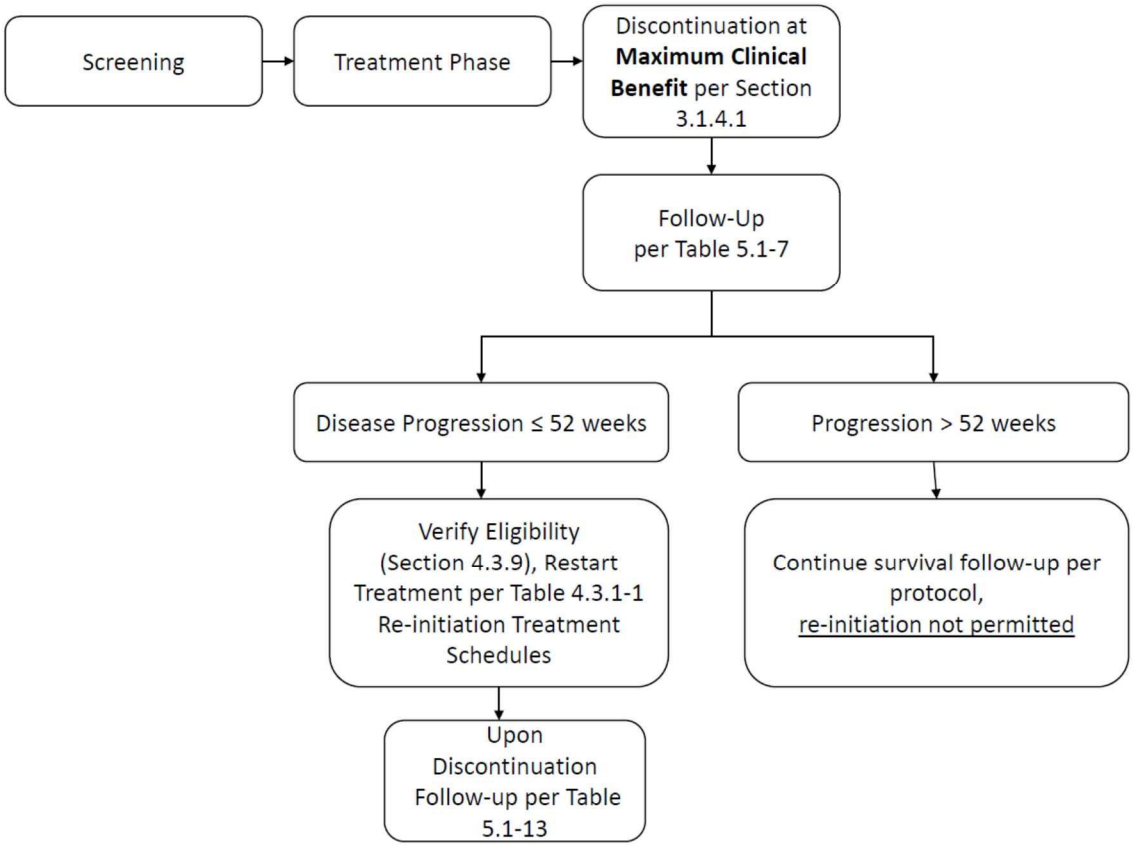
- **If progression occurs > 52 weeks after last dose of study treatment,** continue survival follow-up per Table 5.1-7.

Re-initiation of treatment is not permitted after 52 weeks of discontinuation at maximum clinical benefit.

Subjects who discontinue re-initiated treatment for PD are eligible for treatment beyond progression (See Section 4.3.8).

Treatment options for subjects in MSI-H cohorts who discontinue treatment at maximum clinical benefit are presented below:

Figure 3.1.4.8-1: Treatment Options at Progression for MSI-H subjects who Discontinue Treatment at Maximum Clinical Benefit



3.1.5 Review of Safety

The subjects' safety will be monitored on an ongoing basis as described fully in Section 6. Decisions for the safety evaluation phase of Arm N+I and for continuing from Stage 1 to Stage 2 in both treatment arms will be made in conjunction with the investigators. In addition, a BMS SMT routinely reviews safety signals across the entire nivolumab program including combination studies with ipilimumab.

3.1.6 Treatment beyond progression

Treatment beyond investigator-assessed RECIST 1.1-defined progression will be permitted if the subject experiences investigator-assessed clinical benefit and the subject is tolerating the study treatment. All decisions to continue treatment beyond initial progression must be discussed with the BMS Medical Monitor. Subjects who re-initiate treatment are eligible for treatment beyond progression. See Section 4.3.8 for additional details.

3.1.7 Intrasubject Dose Reductions

Intrasubject dose reduction is not permitted for any reason. Dose delays for the management of study treatment-related adverse events are described in Section 4.3.3.

3.1.8 Mandatory Availability of Tumor Material

Tumor tissue must be submitted to the Central Laboratory prior to treatment for retrospective biomarker analyses. Submission of tumor tissue prior to start of re-initiation is optional, but strongly encouraged.

3.1.9 Follow up

3.1.9.1 Follow -up for all Cohorts After Initial Study Treatment

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

Subjects who started a systemic cancer treatment outside of this study will not continue with tumor imaging assessments.

Subjects who discontinue treatment for reasons other than tumor progression will continue to have tumor imaging assessments beginning 6 weeks (± 1week) after first dose and continuing every 6 weeks (± 1 week) for the first 24 weeks from first dose, and every 12 weeks (± 1 week) thereafter until disease progression (investigator-assessed RECIST 1.1-defined progression).

In order to help reduce unnecessary participant burden and help optimize participant safety by reducing the possible radiation exposure risk of a secondary malignancy, investigators should reduce scan frequency for participants having disease control 3 years after the first dose per Table 5.1-14b. The participant's tumor assessment schedule should be modified to every 24 weeks, unless clinically indicated, to continue tumor assessments every 12 weeks.

- Subjects will be followed for drug-related toxicities until these toxicities resolve, return to baseline, or are deemed irreversible. All adverse events will be documented for a minimum of 100 days after last dose.
- After completion of the first two follow-up visits, subjects enrolled in the MSI-H cohort (Cohorts N and N+I) and Cohorts C3, C4, C5, and C6 will continue to survival follow-up per Table 5.1-7. Please see Section 3.1.10 for end of the study definition and duration of follow-up for survival.
- Refer to Table 5.1-7 for additional follow-up assessments.

3.1.9.2 Follow-up for Re-initiated Subjects in MSI-H Cohorts

Follow-up for re-initiated subjects begins when the decision to discontinue a subject from re-initiated study therapy is made (no further treatment with study therapy). Refer to Table 5.1-13 for the schedule of assessments after the discontinuation of re-initiated treatment.

3.1.10 End of Study Definition

The start of the trial is defined as FPFV. The study will conclude when a minimum of 5 years of follow-up from first treatment for the last participant is reached or survival follow-up is concluded for all subjects, whichever occurs first. Study completion is defined as the final date on which data for the primary endpoint was or is expected to be collected, if this is not the same.

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

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

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

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

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

3.2 Post Study Access to Therapy

At the conclusion of the study, subjects who continue to demonstrate clinical benefit will be eligible to receive study drug. Study drug 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 study drug if any of the following occur: a) the marketing application is rejected by responsible health authority; b) the study is terminated due to safety concerns; c) the subject can obtain medication from a government sponsored or private health program; or d) therapeutic alternatives become available in the local market.

3.3 Study Population

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

3.3.1 Inclusion Criteria

1) Signed Written Informed Consent

a) Subjects 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 subject care.

b) Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests, tumor biopsies, and other requirements of the study.

2) Target Population

a) Histologically confirmed CRC

b) Metastatic or recurrent CRC

c) Microsatellite instability expression detected by an accredited laboratory per local regulations, see Section 3.1.1 and Appendix 4

i) Subjects with MSI-H tumors will enroll in the MSI-H Cohort (Cohort N and Cohort N + I) (mStage and cStage groups), the C3 Cohort, and the C5 Cohort.

ii) Subjects with phenotypes that are non-MSI-H will enroll in the non-MSI-H Safety Cohort and the C6 Cohort.

d) Prior treatment:

i) For subjects with recurrent or metastatic CRC in the MSI-H Cohorts:

(1) Progression during, after, or have been intolerant to ≥ 1 line treatment(s) for their metastatic disease, which must include at least

(i) A fluoropyrimidine, and

(ii) Oxaliplatin or irinotecan,

1. Subjects who received 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.

OR

(2) Subject actively refuses chemotherapy for the treatment of metastatic (Stage IV) or locally advanced disease considered as standard treatment for this disease stage, despite being informed by the investigator about the treatment options. The subject's refusal must be thoroughly documented. The investigator will discuss each individual subject refusing chemotherapy with the sponsor's medical monitor to confirm eligibility.

ii) For subjects with non-MSI-H CRC for the non-MSI-H Safety Cohort:

(1) Progression during, after, or been intolerant following the last administration of approved standard therapies, which must include at minimum a fluoropyrimidine and oxaliplatin or irinotecan, as well as at least one of the following agents, if approved in standard national guidelines, bevacizumab, cetuximab or panitumumab (if KRAS wild type), and regorafenib.

OR

(2) Subject actively refuses chemotherapy (including drugs or biologics) for the treatment of metastatic (Stage IV) or locally advanced disease considered as standard treatment for this disease stage, despite being informed by the investigator about the treatment options. The subject's refusal must be thoroughly documented. The investigator will discuss each individual subject refusing chemotherapy with the sponsor's medical monitor to confirm eligibility.

iii) For subjects with metastatic or recurrent CRC in the MSI-H C3 Cohort, subjects must have not had treatment for their metastatic disease.

iv) For subjects with metastatic or recurrent CRC in the C6 Cohort: Progression during, after, or been intolerant following the last administration of approved standard therapies, which must include at minimum a fluoropyrimidine, and oxaliplatin or irinotecan

e) Subjects must have measurable disease per RECIST 1.1. Subjects 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.

f) Subject willing to comply to provide tumor tissue (archival or fresh biopsy specimen), including possible pre-treatment biopsy, for PD-L1 expression analysis and other biomarker correlative studies (See Section 3.1.3 for additional details regarding the requirements for tumor tissue).

g) ECOG Performance Status of 0-1. See Appendix 2 for ECOG Performance Status scale.

h) Prior palliative radiotherapy must have been completed at least 2 weeks prior to study drug administration.

i) Screening laboratory values must meet the following criteria and should be obtained within 14 days prior to first dose:

i) WBC ≥ 2000/µL

ii) Neutrophils ≥ 1500/µL

iii) Platelets ≥ 100 x10^3/µL

iv) Hemoglobin > 9.0 g/dL

v) Serum creatinine ≤ 1.5 x ULN or creatinine clearance (CrCl) ≥ 40 mL/min (using the Cockcroft-Gault formula):

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

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

vi) AST/ALT ≤ 3 x ULN

(1) For subjects in Cohort 6: AST/ALT ≤2.5 x ULN

vii) Total Bilirubin ≤ 1.5 x ULN (except subjects with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dL).

viii) Cardiac Troponin T (cTnT) or I (cTnI) ≤ 2 × institutional ULN. Subjects with cTnT or cTnI levels between > 1 to 2 × ULN will be permitted if repeat levels within 24 hours are ≤ 1 ULN (**Cohort C5 only**)

(1) If cTnT or cTnI levels are >1 ULN at 24 hours, the subject may undergo a cardiac evaluation and be considered for treatment, following a discussion with the BMS Medical Monitor or designee.

j) Re-enrollment: This study permits the re-enrollment of a subject that has discontinued the study as a pre-treatment failure (ie, subject has not been treated / has not been treated). If re-enrolled, the subject must be re-consented.

k) LVEF assessment with documented LVEF ≥ 50% by either TTE or MUGA (TTE preferred test) within 6 months from first study drug administration (**Cohort C5 only**)

3) Age and Reproductive Status

a) Men and women, ages ≥ 18 years of age

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

c) Women must not be breastfeeding

d) WOCBP must agree to follow instructions for method(s) of contraception from the time of enrollment for the duration of treatment with study drug(s) plus time required for the investigational drug to undergo approximately five half-lives plus 30 days (duration of ovulatory cycle) for a total of 5 months post treatment completion.

e) Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug(s) plus time required for the investigational drug to undergo approximately five half-lives plus 90 days (duration of sperm turnover) for a total of 7 months post-treatment completion.

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

g) During the study and for 3 months after receiving the last dose of daratumumab, a woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction.

Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% per year when used consistently and correctly.

At a minimum, subjects must agree to use one highly effective method of contraception See Appendix 5 for recommended methods of contraception.

3.3.2 Exclusion Criteria

1) Target Disease Exceptions

a) Active brain metastases or leptomeningeal metastases. Subjects with brain metastases are eligible if these have been treated and there is no magnetic resonance imaging (MRI except where contraindicated in which CT scan is acceptable) evidence of progression for at least 8 weeks after treatment is complete and within 28 days prior to first dose of study drug administration. Cases should be discussed with the medical monitor. There must also be no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration.

2) Medical History and Concurrent Diseases

a) 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 subject to receive protocol therapy, or interfere with the interpretation of study results.

b) Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast.

c) Subjects with active, known or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

d) Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.

e) 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. Prior treatment with daratumumab or other anti-CD-38 therapies.

f) All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have resolved to Grade 1 (NCI CTCAE version 4) or baseline before administration of study drug. Subjects with toxicities attributed to prior anti-cancer therapy which are not expected to resolve and result in long lasting sequelae, such as neuropathy after platinum based therapy, are permitted to enroll.

g) Treatment with any chemotherapy, curative intent radiation therapy, biologics for cancer, or investigational therapy within 28 days of first administration of study treatment (subjects 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 CTCAE version 4). Prior focal palliative radiotherapy must have been completed at least 2 weeks before study drug administration.

h) Active neurological disease or confirmed history of encephalitis, meningitis, or uncontrolled seizures in the year prior to informed consent for **Cohort C5 only**

i) Uncontrolled or significant cardiovascular disease including, but not limited to, any of the following (**Cohort C5 only)**:

i) Myocardial infarction (MI) or stroke/transient ischemic attack (TIA) within the 6 months prior to consent

ii) Uncontrolled angina within the 3 months prior to consent

iii) Any history of clinically significant arrhythmias (such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes)

iv) QTc prolongation > 480 msec

v) History of other clinically significant cardiovascular disease (ie, cardiomyopathy, congestive heart failure with New York Heart Association [NYHA] functional classification III-IV, pericarditis, significant pericardial effusion, significant coronary stent occlusion, deep venous thrombosis, etc)

vi) Cardiovascular disease-related requirement for daily supplemental oxygen

vii) History of two or more MIs OR two or more coronary revascularization procedures

viii) Subjects with history of myocarditis, regardless of etiology

j) For **Cohort C6** only

i) Known history of stage 3 or 4 chronic obstructive pulmonary disease (COPD).

ii) Known moderate or severe persistent asthma within the past 2 years, or uncontrolled asthma of any classification. Note that subjects who currently have controlled intermittent asthma or controlled mild persistent asthma are allowed to participate in the study.

iii) Screening 12-lead ECG showing a baseline QT interval as corrected (QTc) > 480 msec

iv) Vaccination with live attenuated vaccines within 4 weeks of first study agent administration

3) Physical and Laboratory Test Findings

a) Positive test for hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus (ribonucleic acid or HCV antibody) indicating acute or chronic infection

b) Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).

4) Allergies and Adverse Drug Reaction

a) History of allergy to study drug components.

b) History of severe hypersensitivity reaction to any monoclonal antibody.

5) Sex and Reproductive Status

a) WOCBP who are pregnant, breastfeeding

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

6) Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated

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

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

3.3.3 Women of Childbearing Potential

A woman of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause 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, women under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40mIU/mL to confirm menopause.*

*Women 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. The duration of the washout period below are suggested guidelines and the investigators should use their judgment in checking serum FSH levels. If the serum FSH level is > 40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal:

- 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.

3.4 Concomitant Treatments

3.4.1 Prohibited and/or Restricted Treatments

The following medications are prohibited during the study:

- Immunosuppressive agents (except to treat a drug-related adverse event)
- Systemic corticosteroids > 10 mg daily prednisone equivalent (except as stated in Section 3.4.3 or to treat a drug-related adverse event).
- Live/attenuated vaccines (eg, varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella [MMR])

- Any concurrent antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, radiation therapy except for palliative radiation therapy described in Section 3.4.3 or standard or investigational agents for treatment of cancer).
- Coronavirus disease 2019 (COVID-19) vaccines that are NOT live are permitted during the study and after the last dose of investigation product. 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
  study drug is unknown.
  - The following are NOT live vaccines: inactivated vaccines (eg, heat-killed and formalin-killed vaccines), subunit vaccines (eg, influenza and pneumococcal vaccines), toxoid vaccines, nucleic acid vaccines that do not encode potentially infectious virus (eg, Pfizer/BioNTech and Moderna COVID-19 vaccines) and replication-incompetent recombinant vector vaccines (eg, AstraZeneca/University of Oxford COVID-19 vaccine).
  - Please contact the Clinical Trial Physician/Medical Monitor with any questions related to COVID-19 vaccines.

Supportive care for disease-related symptoms may be offered to all subjects on the trial.

3.4.2 Other Restrictions and Precautions

3.4.2.1 Surgical Resection Following Initial Response

Investigators may choose to resect solitary lesions in subjects with residual disease and render the subject free of macroscopic disease. Subjects 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. Subjects with a confirmed PR who go on to have surgical resection of remaining disease will be considered a PR. Subjects with SD who go on to have surgical resection of remaining disease will be considered a SD. Subjects may continue treatment after surgery. Tumor tissue of any resected solitary lesion should be submitted to BMS (see Section 5.6.8). 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.

3.4.2.2 Blood Typing (C6 Cohort Only)

Blood Type, Rh, and IAT (Indirect Antiglobulin Test) should be done before the first dose of daratumumab. Subject RBC phenotyping (standard or extended) is an alternative option to the IAT test, if locally required. Either method must be completed prior to first daratumumab infusion.

Daratumumab interferes with the IAT, which is a routine pre-transfusion test performed to identify a patient's antibodies to minor antigens so that suitable donor blood can be given for transfusion. Daratumumab does not interfere with ABO/RhD typing. CD38 is expressed at very low levels on erythrocytes. Daratumumab binds to the CD38 on erythrocytes, which results in a positive IAT (Indirect Coombs Test). This positive result masks the detection of antibodies to minor antigens

and may prevent or delay blood banks from issuing donor blood for transfusion. This effect occurs during daratumumab treatment and for up to 6 months after treatment ends. Subjects will receive a patient identification wallet card for the study that includes the blood profile (ABO, Rh, and IAT or phenotyping) determined before the first infusion of daratumumab along with information on the IAT interference for healthcare providers/blood banks. Subjects are to carry this card throughout the treatment period and for at least 6 months after treatment ends. Blood banks can eliminate the daratumumab interference with IAT by treating reagent RBCs with dithiothreitol (DTT).[105]

Possible methods for blood banks to provide safe RBCs for transfusion to subjects receiving daratumumab include:

1) Providing ABO/RhD compatible, phenotypically (standard or extended phenotyping) or genotypically matched units
2) Providing ABO/RhD compatible, K-negative units after ruling out or identifying alloantibodies using DTT-treated reagent RBCs

Uncrossmatched, ABO/RhD compatible RBC units should be administered if transfusion is needed emergently as per local blood bank practice.

Despite daratumumab binding to CD38 on erythrocytes, no indication of clinically significant hemolysis has been observed in daratumumab studies.

3.4.2.3 Herpes Zoster Virus Antiviral Prophylaxis (C6 Cohort Only)

Prophylaxis for Herpes Zoster Virus reactivation is recommended for patients receiving daratumumab in this study. In the randomized controlled combination therapy studies of patients with multiple myeloma with daratumumab, herpes zoster was reported in 2%-5% of subjects.[103]

Oral Prophylaxis for herpes zoster reactivation is recommended during the Treatment Phase. Initiate antiviral prophylaxis within 1 week after starting daratumumab. Continue antiviral prophylaxis during the Treatment Phase as per institutional guidelines and for 3 months following treatment discontinuation.

3.4.3 Permitted Therapy

Subjects are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Adrenal replacement steroid doses including 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.

The potential for overlapping toxicities with radiotherapy and nivolumab alone or in combination with either ipilimumab, BMS-986016, or daratumumab currently is not known. Therefore, palliative radiotherapy is not recommended while receiving study drugs. If palliative radiotherapy is required, then study drugs should be withheld for at least 1 week before, during, and 1 week after radiation. Subjects should be closely monitored for any potential toxicity during and after

receiving radiotherapy, and AEs considered related to radiotherapy should resolve to Grade ≤ 1 prior to resuming study drugs. Only non-target lesions included in the planned radiation field or CNS lesions may receive palliative radiotherapy. Details of palliative radiotherapy should be documented in the source records and electronic case report form (eCRF). Details in the source records should include: dates of treatment, anatomical site, dose administered and fractionation schedule, and adverse events. Subjects receiving limited field palliative radiation therapy will be considered to have unequivocal progression of disease in the non-target lesion. Symptoms requiring palliative radiotherapy should be evaluated for objective evidence of disease progression. Administration of additional study drugs to subjects who received limited field palliative radiation should follow guidelines specified in Section 4.3.8 Treatment beyond Disease Progression.

3.5 Discontinuation of Subjects from Treatment

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

- Subject's request to stop study treatment
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Any drug-related adverse event requiring discontinuation according to the management algorithms in the Appendix of the nivolumab IB.
- Additional protocol specified reasons for discontinuation (see Sections3.1.4.1 and 4.3.6)

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 subjects 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 subject withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study treatment is discontinued prior to the subject's completion of the study, the reason for the discontinuation must be documented in the subject's medical records and entered on the appropriate case report form (CRF) page.

3.6 Post Treatment Study Follow up

In this study, objective response rate is the primary endpoint of the study. Tumor responses initiated by immunotherapy with nivolumab or nivolumab combined with ipilimumab, BMS-986016, and daratumumab may evolve after treatment discontinuation. Therefore, post treatment study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study treatment must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with Section 5 until death or the conclusion of the study.

3.6.1 Withdrawal of Consent

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

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

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

- If, after all attempts, the participant remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the participant's medical records.

4 TREATMENTS

Study drugs include both Non-investigational (NIMP) and Investigational Medicinal Products (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, and
- 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

4.1 Study Treatments

Table 4.1-1: Product Description: Treatment Period

Product Description / Class and Dosage Form	Potency/Route of Administration	IP/Non-IMP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (Per Label)
Nivolumab (BMS-936558-01) Solution for Injection[a]	100 mg (10 mg/ml) and 40 mg (10 mg/mL)	IP	Open label	Vial or Various packaging configurations	Refer to the label on container and/or pharmacy manual
Ipilimumab (BMS-734016) Solution for Injection	200 mg (5 mg/mL)	IP	Open label	Vial or Various packaging configurations	Refer to the label on container and/or pharmacy manual
Anti-LAG-3 (BMS-986016-01[b]) Solution for Injection	100 mg (10 mg/mL) or 80 mg	IP	Open label	Vial or Various packaging configurations	Refer to the label on container and/or pharmacy manual
Daratumumab Solution for Injection	100 mg (20 mg/mL) and/or 400 mg (20 mg/mL)	IP	Open label	Vial or Various packaging configurations	Refer to label on container or package insert/summary of product characteristics

[a] Nivolumab is labeled as BMS-936558-01 Solution for Injection

[b] Designated as BMS-986016 in the protocol

4.1.1 Investigational Product

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

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 subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

In this protocol, investigational products are: nivolumab and ipilimumab.

The investigational products are nivolumab combined with BMS-986016 for Cohort C5.

The investigational products are nivolumab combined with daratumumab for Cohort C6.

4.1.2 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.

In this protocol, non-investigational product(s) is/are: Not applicable for this study.

4.1.3 Handling 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.

Investigational product documentation 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 non-investigational product, if marketed product is utilized, it should be stored in accordance with the package insert, summary of product characteristics (SmPC), or similar.

Please refer to the current version of the Investigator Brochure and/or Pharmacy Manual for complete storage, handling, dispensing, and infusion information for nivolumab, ipilimumab, BMS-986016, and daratumumab.

4.1.3.1 Nivolumab

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

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.

4.1.3.2 Ipilimumab

Please refer to the current version of the Investigator Brochure and/or Pharmacy Manual for complete storage, handling, dispensing, and infusion information for ipilimumab.

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 dextrose.

4.1.3.3 Nivolumab and Ipilimumab Combination

When both nivolumab and ipilimumab 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 ipilimumab infusion. The second infusion will always be ipilimumab and will start no sooner than 30 minutes after completion of the nivolumab infusion.

4.1.3.4 Nivolumab and BMS-986016 Combination

In Cohort C5, where both nivolumab and BMS-986016 are administered, nivolumab will be administered first, 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 (nivolumab and BMS-986016) 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 BMS-986016 infusion. The second infusion will be BMS-986016 and will start after the infusion line has been flushed, filters changed, and patient has been observed to ensure no infusion reaction has occurred. BMS-986016 infusion will start within 60 minutes after completion of the nivolumab infusion. Further details regarding preparation and administration will be provided separately in the pharmacy manual.

4.1.3.5 Nivolumab and Daratumumab Combination

In Cohort C6, daratumumab injection for IV infusion is considered IMP for this study. Daratumumab is an immunoglobulin G1 kappa human monoclonal antibody against CD38 antigen, produced in a mammalian cell line (Chinese Hamster Ovary [CHO]) using recombinant DNA technology. The molecular weight of daratumumab is approximately 148 kDa. Daratumumab is supplied as a colorless to pale yellow preservative-free solution for intravenous infusion in single-dose vials. Starting on Week 3, when both nivolumab and daratumumab are administered, nivolumab should be administered first followed by daratumumab by at least 30 minutes after completion of nivolumab infusion.

Pre-infusion medications should be administered before starting daratumumab infusions. On days when nivolumab and daratumumab are being administered, daratumumab pre-infusion medications can be administered prior to the nivolumab infusion. The post-infusion medications should be administered after daratumumab infusions.

Therefore, the sequence of administration on days when nivolumab and daratumumab are administered should be as follows:

- Daratumumab pre-medications
- Nivolumab
- Daratumumab
- Daratumumab post-infusion medications.

Daratumumab Preparation

Please refer to the current version of the Investigator Brochure and/or Pharmacy Manual for complete preparation information for daratumumab.

Daratumumab Administration

Because of this high risk of infusion-related reactions daratumumab infusions will be administered per the Investigator's Brochure by a healthcare professional, with immediate access to emergency equipment and appropriate medical support to manage infusion reactions if they occur, and all subjects will receive pre-infusion and post-infusion medication per the descriptions in Section 4.1.4.

Before administration the drug product should be stored and prepared as per the instructions in pharmacy manual. Daratumumab (dose) will be administered as an IV infusion. Each subject's dose will be calculated based on the subject's weight at Cycle 1 Day 1 rounded to the nearest kilogram. The dose of daratumumab to be administered to a subject will be calculated by multiplying the subject's weight (kg) by 16 mg/kg. The dose of daratumumab will remain constant throughout the study, unless the subject's weight changes more than 10% from Cycle 1 Day 1. All infusions will be planned as outpatient visits. Subjects will receive pre-infusion medications and post-infusion medications as detailed in Section 4.1.4.

The infusion start and stop time will be recorded in the CRF. If the infusion is stopped mid-session for any reason, the stop/start time must be recorded together with an explanation.

The dilution volumes, initial infusion rates, and increment for the first, second, and subsequent doses are provided in Table 4.1.3.5-1. The first infusion, with a volume of 1,000 mL, takes approximately 8 hours; the second and subsequent infusions, with volumes of 500 mL, takes approximately 4 hours. The maximum infusion rate for all infusions is 200 mL/hour. The sponsor may modify the infusion rates or the pre-infusion medications prospectively based upon the information collected to date from this and other studies. Additional details for administration times and rates, as well as pre-infusion medications, will be provided in the pharmacy manual.

Table 4.1.3.5-1: Daratumumab Infusion Rates

	Dilution Volume	Initial Infusion Rate (first hour)	Increments of Infusion Rate	Maximum Infusion Rate
First infusion	1000 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Second infusion[a]	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Subsequent infusions[b]	500 mL	100 mL/hour	50 mL/hour every hour	200 mL/hour

[a] Modified rates should only be used if the first infusion of daratumumab was well tolerated as defined by an absence of > Grade 1 infusion-related reactions during the first 3 hours.

[b] Modified rates should only be used if the first 2 infusions of daratumumab were well tolerated as defined by an absence of > Grade 1 infusion-related reactions during a final infusion rate of ≥ 100 mL/hr.

4.1.4 Guidelines for Prevention and Management of Infusion Reactions (Daratumumab and Nivolumab + Daratumumab Combination)

4.1.4.1 Pre-infusion Medication for Daratumumab

Pre-infusion medication to be administered to all subjects approximately 1 hour prior to every daratumumab infusion:

- IV corticosteroid. Methylprednisolone 100 mg, or equivalent dose administered intravenously. Following the second infusion, the dose of methylprednisolone may be reduced (oral or IV methylprednisolone 60 mg) PLUS
- Oral antipyretics (acetaminophen 650 to 1000 mg), PLUS
- Oral or IV antihistamine (diphenhydramine 25 to 50 mg or Leukotriene Inhibitor (optional) on Cycle 1 Day 1: montelukast 10 mg PO, or equivalent). Avoid IV use of promethazine

4.1.4.2 Post-Infusion Medication for Daratumumab

Post-infusion medication to be administered to all subjects to reduce the risk of delayed infusion reactions:

- Oral corticosteroid (20 mg methylprednisolone or equivalent dose of a corticosteroid in accordance with local standards) on the first and second day after all infusions
- At the investigator discretion, for subjects with a history of obstructive pulmonary disorder, short and long-acting bronchodilators and inhaled corticosteroids can be administered. Following the first 4 infusions, if subjects experience no major infusion reactions, these additional inhaled post-infusion medications may be discontinued.

Subjects should be carefully monitored for infusion reactions during daratumumab administration. If an acute infusion reaction is noted, subjects should be managed according to the Investigator's

Brochure. All subjects should have blood pressure monitored before and after all infusions. For the first two infusions, blood pressure should also be monitored during the infusion.

There will be no dose escalations or reductions of daratumumab allowed. Doses of daratumumab may be interrupted, delayed, or discontinued depending on how well the subject tolerates the treatment.

For subjects with a higher risk of respiratory complications (eg, subjects with mild asthma or subjects with COPD who have an FEV1 <80% at screening or developed FEV1 <80% during the study without any medical history), the following post-infusion medications should be considered:

- Antihistamine (diphenhydramine or equivalent)
- Leukotriene inhibitor (montelukast or equivalent)
- Short-acting β2 adrenergic receptor agonist such as salbutamol aerosol
- Control medications for lung disease (eg, inhaled corticosteroids ± long-acting β2 adrenergic receptor agonists for subjects with asthma; long-acting bronchodilators such as tiotropium or salmeterol ± inhaled corticosteroids for subjects with COPD)

In addition, these at-risk subjects may be hospitalized for monitoring for up to 2 nights after an infusion. If subjects are hospitalized, then their spirometry test (FEV1) should be performed before discharge. If these subjects are not hospitalized, then a follow-up telephone call should be made to monitor their condition within 48 hours after all infusions. If no infusion-related reaction has occurred, the follow-up telephone call 48 hours after the infusion is not required. If the subject has not experienced a significant medical event but is hospitalized overnight only for observation, then the hospitalization should not be reported as a serious adverse event. Investigators may prescribe bronchodilators, H1-antihistamines, and corticosteroids that are deemed necessary to provide adequate supportive care in the event a bronchospasm occurs after subjects are released from the hospital/clinic. If an at-risk subject experiences no major infusion-related reactions, then these post-infusion medications may be waived after 4 doses at the investigator's discretion.

4.2 Method of Assigning Subject Identification

The subject number will be assigned through an interactive voice response system (IVRS) once the subject has signed the informed consent form and is registered. Every subject that signs the informed consent form must be assigned a subject number in IVRS. Specific instructions for using IVRS will be provided to the investigational site in a separate document.

The investigator or designee will register the subject for enrollment by following the enrollment procedures established by BMS. The following information is required for enrollment:

- Date that informed consent was obtained
- Date of birth
- Gender at birth
- Pre-treatment status (For C3 Cohort. Subjects must have not received prior therapy for mCRC)
- MSI Status

Once enrolled in IVRS, enrolled subjects that have met all eligibility criteria will be ready for treatment assignment and drug vial assignment through the IVRS.

For Cohorts C3, C5, and C6, tissue submitted for subjects will be assessed for quality with an H&E stain, and only those subjects who have met tissue quality thresholds can be assigned study drug.

The following information is required for drug vial assignment:

- Subject number
- Date of birth
- MSI status
- Subjects meeting all eligibility criteria will be assigned to the appropriate cohort through the IVRS
- Specific instructions (including an enrollment worksheet) for central enrollment and treatment assignment procedure will be provided to the site

Re-initiation

Subjects treated in cohorts mStage 1/2 (C1; Arm N), cStage 1/2 (C2; Arm N +I), C3 or C5 will be eligible for re-initiation within the IVRS if Revised Protocol 07 has been approved at their site and if all criteria for re-initiation have been met. Subjects' original cohort assignment will determine their re-initiation treatment regime as specified in Section 4.3.1 and their treatment assignment will be as in Table 4.3.1-1; note that subjects initially treated in cStage or mStage cohorts or Cohort 3 will have a different dosing schedule than during the initial phase of treatment.

The following information is required for drug vial assignment for Re-initiation:

Subject number

Date of birth

Previously Assignment into C1,C2, C3 or C5

Subjects meeting all eligibility criteria will be reinitiated through the IVRS.

4.3 Selection and Timing of Dose for Each Subject

The dosing regimen and schedule for Arm N and Arm N+I are detailed in Table 4.3-1 (Arm N), Table 4.3-2 (Arm N+I, Week 1-12), Table 4.3-3 (Arm N+I, Week 13 and following). Table 4.3-4 describes the dosing regimen for the C3 Cohort. Table 4.3-5 describes the dosing regimen for the C5 Cohort. Table 4.3-6 describes the dosing regimen for the C6 Cohort.

Table 4.3-1: Dosing Schedule for Arm N - Nivolumab Monotherapy

Every 4-Week Dosing
480 mg Nivolumab

Note: See for Section 3.1.4.1 for treatment duration

Table 4.3-2: Dosing Schedule for cStage 1/2 Arm N+I (Week 1-12) - Nivolumab + Ipilimumab Combination

Every 3 Week Dosing				
Study Part	**Day 1 Dose 1/Week 1**	**Day 1 Dose 2/Week 4**	**Day 1 Dose 3/Week 7**	**Day 1 Dose 4/Week 10**
Dose Escalation Phase Dose Level -1	0.3 mg/kg Nivolumab 1 mg/kg Ipilimumab	0.3 mg/kg Nivolumab 1 mg/kg Ipilimumab	0.3 mg/kg Nivolumab 1 mg/kg Ipilimumab	0.3 mg/kg Nivolumab 1 mg/kg Ipilimumab
Dose Escalation Phase Dose Level 1	1 mg/kg Nivolumab 1 mg/kg Ipilimumab	1 mg/kg Nivolumab 1 mg/kg Ipilimumab	1 mg/kg Nivolumab 1 mg/kg Ipilimumab	1 mg/kg Nivolumab 1 mg/kg Ipilimumab
Dose Escalation Phase Dose Level 2a	1 mg/kg Nivolumab 3 mg/kg Ipilimumab	1 mg/kg Nivolumab 3 mg/kg Ipilimumab	1 mg/kg Nivolumab 3 mg/kg Ipilimumab	1 mg/kg Nivolumab 3 mg/kg Ipilimumab
Dose Escalation Phase Dose Level 2b	3 mg/kg Nivolumab 1 mg/kg Ipilimumab	3 mg/kg Nivolumab 1 mg/kg Ipilimumab	3 mg/kg Nivolumab 1 mg/kg Ipilimumab	3 mg/kg Nivolumab 1 mg/kg Ipilimumab
Efficacy (cStage)[a]	(3 mg/kg Nivolumab + 1 mg/kg Ipilimumab) Q3W x4			

[a] The staged phase uses maximum tolerable dose identified in escalation phase.

Table 4.3-3: Dosing Schedule for cStage 1/2 Arm N+I (Week 13 and following) - Nivolumab + Ipilimumab Combination

Every 4 Week Dosing
480 mg Nivolumab

Note: See for Section 3.1.4.1 for treatment duration

Table 4.3-4: Dosing Schedule for C3 Cohort: Nivolumab + Ipilimumab Combination

Every 2 or 6 Week Dosing		
Day 1 Week 1	**Day 1, Week 3, 5, 7, 9 and every other week thereafter**	**Day 1 Week 7, 13, 19 and every 6 weeks thereafter***
3 mg/kg Nivolumab	3 mg/kg nivolumab over 30 minutes	

Table 4.3-4: Dosing Schedule for C3 Cohort: Nivolumab + Ipilimumab Combination

Every 2 or 6 Week Dosing		
Day 1 Week 1	**Day 1, Week 3, 5, 7, 9 and every other week thereafter**	**Day 1 Week 7, 13, 19 and every 6 weeks thereafter***
1 mg/kg Ipilimumab		1 mg/kg ipilimumab over 30 minutes

Note: See for Section 3.1.4.1 for treatment duration

Nivolumab and Ipilimumab combination:

When both nivolumab and ipilimumab 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 ipilimumab infusion. The second infusion will always be ipilimumab and will start no sooner than 30 minutes after completion of the nivolumab infusion.

Dosing calculation based on weight:

The dosing calculations should be based on the body weight. If the subject's weight on the day of dosing differs by > 10% from the weight used to calculate the dose, the dose must be recalculated. The weight used to calculate the dose should always be the most recently recorded weight. All doses should be rounded to the nearest milligram. There will be no dose modifications allowed.

Body weight is determined as detailed in the Flow Chart/Time and Events Schedule of this protocol.

Dosing modifications:

There will be no dose modifications allowed for the management of toxicities of individual subjects.

For Q2W nivolumab dosing cycles, subjects may be dosed no less than 12 days between doses. For Q3W nivolumab dosing cycles, subjects may be dosed no less than 19 days between doses. For Q4W nivolumab dosing cycles, participants may be dosed no less than 25 days from the previous dose. For Q6W ipilimumab dosing cycles, participants may be dosed no less than 5 weeks from the previous dose. If dosing is delayed, both nivolumab and ipilimumab must be delayed together. If dosing is resumed after a delay, both nivolumab and ipilimumab must be resumed on the same day.

Table 4.3-5: Dosing Schedule for C5 Cohort: Nivolumab + BMS-986016 Combination	
Day 1 Week 1	**Day 1, Week 3, 5, 7, 9** and every other week thereafter*
240 mg nivolumab flat dose	240 mg nivolumab flat dose IV over 30 minutes
160 mg BMS-986016	160 mg BMS986016 IV over 60 minutes

Note: See for Section 3.1.4.1 for treatment duration

Table 4.3-6: Dosing Schedule for C6 Cohort: Nivolumab + Daratumumab Combination

Drug	Dose	Frequency of administration	Route of administration	Duration
Nivolumab	240 mg flat dose	every 2 weeks starting on Week3	30 minute Intravenous (IV) infusion	Until progression, toxicity, or discontinuation from study
Nivolumab	480 mg flat dose	every 4 weeks starting on Week 25	30 minute Intravenous (IV) infusion	Until progression, toxicity, or discontinuation from study
Daratumumab	16 mg/kg	Every week (Weeks 1-8) Every 2 weeks (Weeks 9-24) Every 4 weeks (Starting on Week 25 and thereafter)	(IV) infusion Please refer to the daratumumab investigators brochure or pharmacy manual for infusion details.	Until progression, toxicity, or discontinuation from study

4.3.1 Re-initiation Dose Schedules

Subjects in the cohorts listed in Table 4.3.1-1 who met eligibility criteria for re-initiation of treatment (Section 3.1.4.8) will receive treatment as presented below:

Table 4.3.1-1: Treatment Schedules for Re-Initiation

Cohort	Treatment upon Re-initiation
mStage 1/2	Nivolumab 480 mg Q4W
cStage 1/2	Nivo 240 mg + Ipi 1 mg/kg Q3W for 4 doses, followed by Nivolumab 480 mg (Q4W)
C3 (1L)	Nivo 360mg Q3W + Ipi 1mg/kg Q6W
C5 (BMS-986016 /anti-LAG3)	Nivo 240mg Q2W + BMS-986016 (LAG3) 160mg Q2W

Note: “Re-initiation” relates to maximum clinical benefit participants.

Treatment duration after re-initiation, inclusive of treatment beyond progression will be a maximum of 24 months.

4.3.2 Antiemetic Premedications

Antiemetic medications should not be routinely administered prior to dosing of drugs. See Section 4.3.7 for subsequent premedication recommendations following a study drug-related infusion reaction.

4.3.3 Dose Delay Criteria

Dose delay criteria apply for all drug-related adverse events (regardless of whether or not the event is attributed to nivolumab, ipilimumab, BMS-986016, daratumumab, or combinations). All study drugs must be delayed until treatment can resume (see Section 4.3.5). Treatment delays up to 6 weeks from the last dose are allowable. 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.

Nivolumab and ipilimumab administration should be delayed for the following:

- Any Grade ≥ 2 non-skin, drug-related adverse event, with the following exceptions:
  - Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay
- Any Grade 3 skin, drug-related adverse event
- Any Grade 3 drug-related laboratory abnormality, with the following exceptions for asymptomatic amylase or lipase, AST, ALT, or total bilirubin:
  - Grade 3 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis do not require a dose delay.
  - If a subject has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity
  - If a subject has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity

Nivolumab and BMS-986016 (C5 Cohort treatment) administration should be delayed for the following:

- Select drug-related AEs and drug-related laboratory abnormalities:
  - ≥ Grade 3 skin
  - ≥ Grade 1 pneumonitis
  - ≥ Single grade increase shift in abnormality in AST, ALT, and total bilirubin
  - ≥ Grade 2 creatinine
  - ≥ Grade 2 diarrhea or colitis

  - ≥ Grade 2 neurological AE
  - Grade 4 amylase and/or lipase abnormalities regardless of symptoms or clinical manifestations
  - ≥ 1x ULN troponin, hold dose and repeat troponin after 24 hours. All troponin elevations require a dose delay to allow for prompt cardiac evaluation. Following this evaluation, determination of further treatment will be based on the discretion of the PI.
- Any AE, laboratory abnormality, or concurrent illness that, in the judgment of the Investigator, warrants delaying the dose of study drug
- Grade 2 Myocarditis

Nivolumab and daratumumab (C6 Cohort treatment) administration should be delayed for the following:

- Grade 4 hematologic toxicity, except for Grade 4 lymphopenia
- Grade 3 or higher thrombocytopenia with bleeding
- Febrile neutropenia
- Neutropenia with infection, of any grade
- Grade 3 or higher non-hematologic toxicities with the following exceptions:
  - Grade 3 nausea that responds to antiemetic treatment within 7 days
  - Grade 3 vomiting that responds to antiemetic treatment within 7 days
  - Grade 3 diarrhea that responds to antidiarrheal treatment within 7 days
  - Grade 3 fatigue that was present at baseline or that lasts for < 7 days after the last administration of daratumumab
  - Grade 3 asthenia that was present at baseline or that lasts for < 7 days after the last administration of daratumumab

In Weeks 1 to 8, daratumumab doses that fall outside of the pre-specified window of -1 to +3 days must be skipped.

In Weeks 9 to 24, daratumumab dosing may be delayed for up to 1 week. If unable to administer within 1 week, then the dose should be skipped, and resumption of the daratumumab continues per the protocol defined schedule.

From Week 25 and beyond, the first dose (Week 25) can be delayed 21 days. Doses that fall outside the allowed window should be skipped.

During periods when daratumumab doses are skipped, daratumumab PK and immunogenicity samples should not be drawn.

Table 4.3.3-1: Daratumumab Dose Delay Guidance			
Week	**Frequency**	**Dose Held**	**Dosing Re-start**
1-8	Weekly (q1wk)	> 3 days	next planned weekly dosing date
9-24	Biweekly (q2wks)	> 7 days	next planned biweekly dosing date
25+	Every 4 weeks (q4wks)	> 21 days	next planned every 4 weeks dosing date

Subjects experiencing a Grade 4 infusion reaction or their third Grade 3 infusion reaction related to daratumumab must permanently discontinue daratumumab. See Section 4.3.7 for additional details on the treatment of infusion reactions.

Any adverse event deemed to be related to daratumumab that requires a dose hold of more than 3 consecutive planned doses will result in permanent discontinuation of daratumumab. If a dose delay occurs, then pharmacokinetic and pharmacodynamic assessments should be performed on the actual day of study drug administration, not on the original scheduled administration day

Subjects whose dose are missing ≥ 3 consecutive planned doses of daratumumab for reasons other than toxicity should be withdrawn from study drug, unless, upon consultation with the sponsor and the review of safety and efficacy, continuation is agreed upon. Subjects who are withdrawn from daratumumab may continue to receive nivolumab.

- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Because of the potential for immunotherapy-related AEs requiring early recognition and prompt intervention, management algorithms have been developed for suspected pulmonary toxicity, GI toxicity, hepatotoxicity, endocrinopathy, skin toxicity, neurological toxicity, and nephrotoxicity.

In order to standardize the management of adverse events for all subjects, treatment management algorithms recommended for utilization in this study are included in Appendix 1. Adverse event treatment management algorithms included in the nivolumab IB or ipilimumab IB might be considered for individual cases.

4.3.3.1 Management Algorithms for Immuno-Oncology Agents

Immuno-oncology (I-O) agents are associated with adverse events that can differ in severity and duration than adverse events caused by other therapeutic classes. Nivolumab, ipilimumab, BMS-986016, and daratumumab are considered immuno-oncology agents in this protocol. Early recognition and management of adverse events 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 adverse events:

- Gastrointestinal
- Renal
- Pulmonary

- Hepatic
- Endocrinopathies
- Skin
- Neurological
- Myocarditis

While the ipilimumab investigator brochure contains safety management algorithms for similar adverse events, the recommendations are to follow the nivolumab algorithms for immuno-oncology agents (I-O) in order to standardize the safety management. Therefore, the algorithms recommended for utilization in this protocol are included in Appendix 1.

For subjects expected to require more than 4 weeks of corticosteroids or other immunosuppressants to manage an adverse event, consider recommendations provided in Appendix 1.

4.3.4 Dose Modifications

There will be no dose reductions for nivolumab, ipilimumab, BMS-986016 or daratumumab.

4.3.5 Criteria to Resume Treatment

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

- Subjects may resume treatment in the presence of Grade 2 fatigue
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- Subjects with baseline Grade 1 AST/ALT or total bilirubin 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. Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (Section 4.3.6) should have treatment permanently discontinued
- Drug-related pulmonary toxicity, diarrhea, or colitis, must have resolved to baseline before treatment is resumed
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment
- Subjects in the C5 Cohort may resume treatment with BMS-986016 when troponin levels return to normal

In the case of prior SARS-CoV-2 infection, symptoms should have resolved in order to resume study treatment and there should be no sequelae that would place the participant at a higher risk of receiving study intervention.

If the criteria to resume treatment are met, the subject should restart treatment at the next scheduled time point per protocol. However, if the treatment is delayed past the scheduled time point per protocol, the scheduled study treatment administration will be delayed, but not skipped, until

dosing resumes. In particular, this is to ensure that subjects in Arm N+I will receive 4 administrations of combined nivolumab and ipilimumab treatment if toxicity allows.

If dose delay is necessary for subjects in Arm N+I during Week 1-12 and for subjects in Cohort C3, both nivolumab and ipilimumab must be delayed until treatment can resume. However, if a nivolumab-related infusion reaction prevents subsequent infusion of ipilimumab on the same day, the dose of ipilimumab should be replaced as soon as possible. In such instances, at least 19 days must elapse between the replacement dose of ipilimumab and the administration of the next dose of nivolumab combined with ipilimumab.

If treatment is delayed > 6 weeks from the last dose, the subject must be permanently discontinued from study therapy, except as specified in Section 4.3.6.

Subjects may resume treatment with daratumumab in Cohort 6, upon recovery from toxicity to Grade 2 or baseline, with the exception that Grade 2 laryngeal edema or Grade 2 bronchospasm must be fully recovered. If the daratumumab administration does not commence within the pre-specified window of the scheduled administration date, then the dose will be considered a missed dose. Administration may resume at the next planned dosing date**.**

4.3.6 Discontinuation Criteria

Treatment with nivolumab, ipilimumab, and/or BMS-986016 should be permanently discontinued for 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 adverse event lasting > 7 days, with the following exceptions for drug-related laboratory abnormalities, endocrinopathies, uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reactions, and infusion reactions:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, myocarditis, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
  - For Grade 3 endocrinopathy adverse events such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidosis, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (steroids, thyroid hormones) or glucose controlling agents, respectively, do not require treatment discontinuation
  - 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
    - Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
      - AST or ALT > 8 x ULN

  - Total bilirubin > 5 x ULN
  - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN
- Any Grade 4 drug-related adverse event or laboratory abnormality (including but not limited to creatinine, AST, ALT, or Total Bilirubin), except for the following events which do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia or leukopenia
  - Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis.
  - 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
- Any dosing interruption lasting > 6 weeks from the last dose with the following exceptions:
  - Dosing interruptions to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks from the last dose, the BMS medical monitor/designee must be consulted. Tumor imaging assessments should continue as per protocol even if dosing is interrupted.
  - Dosing interruptions > 6 weeks from the last dose that occur for non-drug-related reasons may be allowed if approved by the BMS medical monitor/designee. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks from the last dose, the monitor/designee must be consulted. Tumor imaging assessments should continue as per protocol even if dosing is interrupted.

Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab, ipilimumab, and/or BMS-986016 dosing.

Daratumumab treatment should be permanently discontinued for the following reasons:

- Grade 4 infusion reactions related to daratumumab.
- For Grade 3 infusion reactions related to daratumumab: Once reaction symptoms resolve, consider restarting the infusion at no more than half the rate at which the reaction occurred. If the patient does not experience additional symptoms, resume infusion rate escalation at increments and intervals as outlined in Table 4.1.3.5-1. Repeat the procedure above in the event of recurrence of Grade 3 symptoms. Permanently discontinue daratumumab upon the third occurrence of a Grade 3 or greater infusion reaction.

Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject, **regardless of cohort**, with continued study drug dosing should discontinue the study drugs.

The consideration to re-initiate study therapy in selected cases at any time point after discontinuation could be made on a case-by-case basis after considering the overall benefit/risk profile and in consultation between the Investigator and the study Sponsor. The selected subjects will need to meet eligibility criteria. The original dose and schedule and protocol rules would apply accordingly (Section 4.3.6).

The assessment for discontinuation of study drug should be made separately considering each study drug component in the nivolumab and ipilimumab, and nivolumab and daratumumab (Cohort C6) combinations. If discontinuation criteria are attributed with only one drug used in this trial, once the subject meets criteria to resume therapy, the subject may continue dosing with nivolumab if nivolumab was not attributed to criteria for discontinuation.

In the nivolumab and BMS-986016 combination (Cohort C5), if discontinuation criteria are met, both drugs (nivolumab and BMS-986016) will be discontinued regardless of the assessment of attribution to a particular study drug.

If a subject meets criteria for discontinuation and the investigator is unable to determine whether the event is related to both or one study drug, the subject should discontinue all study drugs and be taken off the treatment phase of the study.

4.3.7 Treatment of Study Drug Related Infusion Reactions

Since nivolumab, ipilimumab, and BMS-986016 contain only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, 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 subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional nivolumab 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 study drug infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor subject until resolution of symptoms. Corticosteroid 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 subject closely. If symptoms recur then no further study drug will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF). The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional study drug administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

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

Immediately discontinue infusion of study drug. Begin an IV infusion of normal saline, and treat the subject as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 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. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Study drug will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms. In the 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).

Management of daratumumab infusion-related reactions

Subjects should be carefully observed during daratumumab infusions. Trained study staff at the clinic should be prepared to intervene in case of any infusion reactions, and resources necessary for resuscitation must be available. Attention to staffing should be considered when multiple subjects will be dosed at the same time.

For infusion reactions of any grade/severity, immediately interrupt the daratumumab infusion and manage symptoms. Management of infusion reactions may further require reduction in the rate of infusion, or treatment discontinuation of daratumumab.

Grade 1-2 (mild to moderate): Once reaction symptoms resolve, resume the infusion at no more than half the rate at which the reaction occurred. If the patient does not experience any further reaction symptoms, infusion rate escalation may resume at increments and intervals as appropriate as outlined in Table 4.1.3.5-1.

Grade 3 (severe): Once reaction symptoms resolve, consider restarting the infusion at no more than half the rate at which the reaction occurred. If the subject does not experience additional symptoms, resume infusion rate escalation at increments and intervals as outlined in Table 4.1.3.5-1. Repeat the procedure above in the event of recurrence of Grade 3 symptoms. Permanently discontinue daratumumab upon the third occurrence of a Grade 3 or greater infusion-related reaction.

Grade 4 (life threatening): Permanently discontinue daratumumab treatment.

4.3.8 Treatment Beyond Disease Progression

Accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of PD.[106] The assessment of clinical benefit should take into account whether the subject is clinically deteriorating and unlikely to receive further benefit from continued treatment.

Subjects will be permitted to continue treatment for up to 24 months beyond initial RECIST 1.1 defined PD assessed by the investigator.

Subjects who progress following re-initiation of treatment have the option to be treated beyond progression for a cumulative maximum of 24 months from re-initiation dose.

All decisions to continue treatment beyond initial progression must be discussed with the BMS Medical Monitor and documented in the study records.

All subjects treated beyond progression must meet the criteria below:

1) Investigator-assessed clinical benefit, and do not have rapid disease progression
2) Tolerance of study drug
3) Stable performance status
4) Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases)
5) Subject provides written informed consent prior to receiving any additional nivolumab treatment, or nivolumab in combination with ipilimumab treatment, using an ICF describing any reasonably foreseeable risks or discomforts, or other alternative treatment options.

Treatment beyond progression may be administered during or after localized interventions (surgery/radiation therapy).

For subjects with time point response of progression being treated beyond progression, scans should be repeated every 12 weeks or earlier, as clinically indicated, to assess further disease progression.

Subjects will be re-consented with an ICF describing any reasonably foreseeable risks or discomforts. For subjects who have re-initiated treatment per Revised Protocol 07, treatment beyond progression will be according to the dose schedule during the re-initiation period.

Subjects should discontinue study therapy upon further evidence of further progression, defined as an additional 10% or greater increase with a minimum 5 mm absolute increase in tumor burden volume from time of initial progression (including all target lesions and new measurable lesions). Study treatment should be discontinued permanently upon documentation of further progression.

New lesions are considered measurable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes, which must have a short axis of at least 15 mm). Any new lesion considered non-measurable at the time of initial progression may become measurable and therefore included in the tumor burden measurement if the longest diameter increases to at least 10 mm (except for pathological lymph nodes, which must have an increase in short axis to 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.

For statistical analyses that include the investigator-assessed progression date, subjects who continue treatment beyond initial investigator-assessed, RECIST 1.1-defined progression will be considered to have investigator-assessed progressive disease at the time of the initial progression event.

4.3.9 Treatment Re-initiation Inclusion Criteria: MSI-H Cohorts

Subjects in MSI-H cohorts who discontinue study treatment at Maximal Clinical Benefit, (Section 3.1.4.1) are permitted to re-initiate treatment (see Section 3.1.4.8 and Table 4.3.1-1), if disease progression defined by RECIST criteria occurs within 1 year (≤ 52 weeks) and the following criteria are met:

1) Investigator assessed clinical benefit and no rapid disease progression
2) Tolerance of study drug
3) Stable performance status
4) Adequate blood, liver, kidney and cardiac function per Inclusion criteria 2i (Section 3.3.1)
5) Adequate re-initiation screening requirements per Table 5.1-8
6) Treatment Re-initiation will not delay an imminent intervention to prevent serious complications of disease progression (eg. CNS metastases)
7) Subjects have signed and dated an IRB/IEC approved written informed consent form for re-initiation in accordance with regulatory and institutional guidelines.

4.4 Blinding/Unblinding

Not applicable.

4.5 Treatment Compliance

Treatment compliance will be monitored by drug accountability as well as the subject's medical record and eCRF.

4.6 Destruction and Return of Study Drug

4.6.1 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 and 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 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.

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.

4.6.2 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 BMS 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.

4.7 Retained Samples for Bioavailability / Bioequivalence

Not applicable for this study.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: Screening Procedural Outline (CA209142)

Procedure	Screening Visit	Notes
Eligibility Assessments		
Informed Consent	X	Original IC in screening for protocol participation; Study allows for re-enrollment of a subject that has discontinued the study as a pre-treatment failure. If re-enrolled, the subject must be re-consented and assigned a new subject number from IVRS.
Inclusion/Exclusion Criteria	X	All inclusion/exclusion criteria should be assessed at screening and confirmed prior to first dose.
Medical History	X	
Tumor Tissue Sample (biopsy)	X	Sufficient tumor tissue (as determined by local pathologist) obtained before start of study treatment in the metastatic setting or from an unresectable site (block or minimum of 30 slides, obtained from core biopsy, punch biopsy, excisional biopsy or surgical specimen). For subjects where a biopsy is not feasible, archival tumor material must be available. See Section 3.1.3. For Cohorts C3-C6, tumor tissue submitted will be assessed for quality with a H&E stain and only those subjects who have met tissue quality thresholds can be assigned study drug.
MSI Status	X	Sites must submit and document prior MSI testing and results. Tissue must be available for all subjects for repeat MSI testing. Confirm availability of pathology report containing MSI testing results. Report must contain MSI results and should also contain specific results per markers tested for MSI. For C6 Cohort: Subjects with phenotypes that are non-MSI-H may enroll and may be treated. Locally-obtained MSI testing results are not required prior to study treatment assignment. A MSI status must ultimately be determined if a subject is assigned study treatment.
Determine KRAS Mutation Status	X	
Determine BRAF Mutation Status	X	
Prior Medications	X	

Table 5.1-1: Screening Procedural Outline (CA209142)		
Procedure	**Screening Visit**	**Notes**
Record History of Lynch Syndrome (if tested or if not tested; record result if tested)	X	
ECOG Performance Status	X	Within 14 days prior to first dose. See Appendix 2 for ECOG Performance Status scale.
Safety Assessments		
Physical Examination	X	
Vital Signs	X	Including BP, HR, and temperature. Obtain vital signs at the screening visit and within 72 hours prior to first dose.
Physical Measurements	X	Height and Weight. Within 14 days prior to first dose
Assessment of Signs and Symptoms	X	Within 14 days prior to first dose
Echocardiogram Performed for the C5 Cohort Only	X	LVEF assessment with documented LVEF ≥ 50% by either TTE or MUGA (TTE preferred test) within 6 months from first study drug administration Performed for the C5 Cohort Only
ECG	X	Within 14 days prior to first dose. For C5 and C6 Cohorts: Subjects with screening 12-lead ECG showing a QT interval as corrected (QTc) >480 msec are excluded.
Concomitant Medication Collection	X	Within 14 days prior to first dose

Table 5.1-1: Screening Procedural Outline (CA209142)		
Procedure	**Screening Visit**	**Notes**
Laboratory Tests	X	CBC w/differential and platelet count, Chemistry panel including: LDH, AST, ALT, ALP, T.Bili, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, Glucose, amylase, lipase, TSH, Free T4, Free T3, Hepatitis B surface antigen (HBV sAg), and hepatitis C antibody (HCV Ab) or Hepatitis C RNA (HCV RNA), within 14 days prior to first dose. Safety laboratory tests do not need to be repeated if they were performed within 14 days of first dose. Performed for the C5 Cohort Only: Cardiac Troponin Levels: T (cTnt) or I (cTnI) Performed for C6 Cohort Only: Blood Type, Rh, and IAT should be done before the first dose of daratumumab. Subject RBC phenotyping (standard or extended) is an alternative option to the IAT test, if locally required. Either method must be completed prior to first daratumumab infusion.
Pregnancy Test (WOCBP only)	X	Serum or urine to be done at screening visit and repeated within 24 of first dose of study therapy
Efficacy Assessment		
Baseline Tumor Imaging Assessment	X	CT or MRI chest, abdomen, pelvis and all known or suspected sites of disease within 28 days prior to first dose of study therapy.
IVRS		
Register Subject in IVRS	X	A call must be made to the IVRS to register subject after signing informed consent.

Table 5.1-2: Short-Term Procedural Outline (Nivolumab Monotherapy, CA209142): MSI-H (Arm N, mStage 1/2)		
Procedure	**During Treatment Day 1 every 4 weeks See Section 3.1.4.1 for treatment duration**	**Notes Visit Window : ± 2 Days**
Safety Assessments		
Targeted Physical Examination	X	Targeted examination must include at a minimum the following body systems: • Cardiovascular • Gastrointestinal • Pulmonary • Neurological exam for subjects with brain metastases
Vital Signs	X	Including BP, HR, and temperature. Obtain vital signs within 72 hours prior to first dose.
Physical Measurements (including performance status)	X	Weight and ECOG performance status. See Appendix 2 for ECOG Performance Status scale.
Review of Concomitant Medication	X	
Adverse Events Assessment	X	
Laboratory Tests	X	On-study local CBC, chemistry, and thyroid laboratory assessments (after first dose) should be done within 72 hours prior to each dose and include: CBC w/differential and platelet count, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, TSH with reflexive Free T4, Free T3.
Pregnancy Test (WOCBP only)	X	Serum or urine pregnancy test to be done within 24 hours prior to first dose, and then every 4 weeks (± 1 week) regardless of dosing schedule

Table 5.1-2: Short-Term Procedural Outline (Nivolumab Monotherapy, CA209142): MSI-H (Arm N, mStage 1/2)		
Procedure	**During Treatment Day 1 every 4 weeks See Section 3.1.4.1 for treatment duration**	**Notes Visit Window : ± 2 Days**
Efficacy Assessments		
Tumor Imaging Assessment	See separate Table 5.1-14	
Outcomes Research Assessment		
EORTC QLQ-C30 & EQ-5D Questionnaires	Assessed following drug vial assignment but before first dose and every 6 weeks when coinciding with clinic visits. Assessed at follow-up visit 1 & 2. Assessments should be completed at the start of the study visit prior to any study-related procedures or speaking with the physician. For all subjects, except for those enrolled in the non-MSI-H Safety Cohort	
Pharmacokinetic Assessments		
Nivolumab PK blood sample	See separate Table 5.5.1-2	
Immunogenicity Assessments		
Nivolumab Immunogenicity blood sample collection	See separate Table 5.5.1-2	
Exploratory Biomarker Testing		
Soluble Biomarkers (Serum)	See separate Table 5.6.8-1	
Peripheral Blood Mononuclear Cells (PBMCs) Immuno-phenotyping	See separate Table 5.6.8-1	
Ex vivo Functional assay (PBMCs)	See separate Table 5.6.8-1	
Tumor tissue sample (biopsy)	See separate Table 5.6.8-1	
Whole blood gene expression	See separate Table 5.6.8-1	
Stool sample	See separate Table 5.6.8-1	
Plasma Sample	See separate Table 5.6.8-1	
SNP (whole blood)	See separate Table 5.6.8-1	

Table 5.1-2: Short-Term Procedural Outline (Nivolumab Monotherapy, CA209142): MSI-H (Arm N, mStage 1/2)		
Procedure	**During Treatment** **Day 1 every 4 weeks** **See Section 3.1.4.1 for treatment duration**	**Notes** **Visit Window : ± 2 Days**
MSI Status Determination		
Submit Redacted Pathology Report to BMS Containing Local MSI Results	**To be submitted at Week 1 Day 1. Report must contain MSI results and should also contain specific results per markers tested for MSI.**	
Clinical Drug Supplies		
IVRS Drug Vial Assignment	X	Vials may be assigned up to 2 days prior to first dose date.
Dispense Study Drug	X	Within 3 days from vial allocation, the subject must receive the first dose of study medication. Subjects may be dosed no less than 25 days between doses. The dosing calculations should be based on the body weight. All doses should be rounded to the nearest milligram.

Table 5.1-3: Short-term Procedural Outline (Nivolumab Ipilimumab Combination, CA209142): MSI-H (Arm N +I, cStage 1/2) and non-MSI-H (Independent Safety Study)

Procedure	During Treatment Day 1 (Dose 1/week 1, Dose 2/week 4, Dose 3/week 7, Dose 4/week 10)	During Treatment Day 1 (week 13 and every 4 weeks thereafter)	Notes Visit Window : ± 2 Days
	For MSH-H (Arm N+I) only, see Section 3.1.4.1 for treatment duration.		
Safety Assessments			
Targeted Physical Examination	X	X	Targeted examination must include at a minimum the following body systems: Cardiovascular Gastrointestinal Pulmonary Neurological exam for subjects with brain metastases
Vital Signs	X	X	Including BP, HR, and temperature. Obtain vital signs within 72 hours prior to first dose
Physical Measurements (including performance status)	X	X	Weight and ECOG performance status. See Appendix 2 for ECOG Performance Status scale.
Review of Concomitant Medication	X	X	
Adverse Events Assessment	X	X	
Laboratory Tests	X	X	On-study local laboratory assessments (after first dose) should be done within 72 hours prior to each dose and include: CBC w/differential and platelet count, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, TSH with reflexive Free T4, Free T3.

Table 5.1-3: Short-term Procedural Outline (Nivolumab Ipilimumab Combination, CA209142): MSI-H (Arm N +I, cStage 1/2) and non-MSI-H (Independent Safety Study)

Procedure	During Treatment Day 1 (Dose 1/week 1, Dose 2/week 4, Dose 3/week 7, Dose 4/week 10)	During Treatment Day 1 (week 13 and every 4 weeks thereafter)	Notes Visit Window : ± 2 Days
	For MSH-H (Arm N+I) only, see Section 3.1.4.1 for treatment duration.		
Pregnancy Test (WOCBP only)	X	X	Serum or urine pregnancy test to be done within 24 hours prior to first dose, and then every 4 weeks (± 1 week) regardless of dosing schedule
Efficacy Assessments			
Tumor Imaging Assessment	See separate Table 5.1-14		
Outcomes Research Assessment			
EORTC QLQ-C30 & EQ-5D Questionnaires	Assessed following drug vial assignment but before first dose and every 6 weeks when coinciding with clinic visits. Assessed at follow-up visit 1 & 2. Assessments should be completed at the start of the study visit prior to any study-related procedures or speaking with the physician. For all subjects, except for those enrolled in the non-MSI-H Safety Cohort		
Pharmacokinetic Assessments			
Nivolumab PK blood sample	See separate Table 5.5.1-1		
Ipilimumab PK blood sample	See separate Table 5.5.1-1		
Immunogenicity Assessments			
Nivolumab Immunogenicity blood sample collection	See separate Table 5.5.1-1		
Ipilimumab Immunogenicity blood sample collection	See separate Table 5.5.1-1		
Exploratory Biomarker Testing			
Soluble Biomarkers (Serum)	See separate Table 5.6.8-2		

Table 5.1-3: Short-term Procedural Outline (Nivolumab Ipilimumab Combination, CA209142): MSI-H (Arm N +I, cStage 1/2) and non-MSI-H (Independent Safety Study)

Procedure	During Treatment Day 1 (Dose 1/week 1, Dose 2/week 4, Dose 3/week 7, Dose 4/week 10)	During Treatment Day 1 (week 13 and every 4 weeks thereafter)	Notes Visit Window : ± 2 Days
	For MSH-H (Arm N+I) only, see Section 3.1.4.1 for treatment duration.		
Peripheral Blood Mononuclear Cells (PBMCs) Immuno-phenotyping	See separate Table 5.6.8-2		
Ex vivo Functional assay (PBMCs)	See separate Table 5.6.8-2		
Tumor tissue sample (biopsy)	See separate Table 5.6.8-2		
Whole blood gene expression	See separate Table 5.6.8-2		
Stool sample	See separate Table 5.6.8-2		
Plasma Sample	See separate Table 5.6.8-2		
SNP (whole blood)	See separate Table 5.6.8-2		
MSI Status Determination			
Submit Redacted Pathology Report to BMS Containing Local MSI Results	**To be submitted at Week 1 Day 1. Report must contain MSI results and should also contain specific results per markers tested for MSI.**		

Table 5.1-3: Short-term Procedural Outline (Nivolumab Ipilimumab Combination, CA209142): MSI-H (Arm N +I, cStage 1/2) and non-MSI-H (Independent Safety Study)

Procedure	During Treatment Day 1 (Dose 1/week 1, Dose 2/week 4, Dose 3/week 7, Dose 4/week 10)	During Treatment Day 1 (week 13 and every 4 weeks thereafter)	Notes Visit Window : ± 2 Days
	For MSH-H (Arm N+I) only, see Section 3.1.4.1 for treatment duration.		
Clinical Drug Supplies			
IVRS Drug Vial Assignment	X*	X**	Vials may be assigned up to 2 days prior to first dose date. * Nivolumab Ipilimumab Combination ** Nivolumab Monotherapy
Dispense Study Drug	X*	X**	Within 3 days from vial allocation, the subject must receive the first dose of study medication. Subjects may be dosed no less than 19 days between doses during administration of nivolumab/ipilimumab in combination and no less than 25 days between doses once nivolumab only is administered (ie, as of Week 13). The dosing calculations should be based on the body weight. * Nivolumab Ipilimumab Combination ** Nivolumab Monotherapy

Table 5.1-4: Short-term Procedural Outline for C3 Cohort [Nivolumab 3 mg/kg Q2W + Ipilimumab 1 mg/kg Q6W] No Prior Treatments in Metastatic Setting: MSI-H		
Procedure	**To Be Performed at Each Dosing Visit, Unless Otherwise Specified in Notes or Separate Table**	**Notes** **Visit Window : ± 2 Days** **See Section 3.1.4.1 for treatment duration**
Safety Assessments		
Targeted Physical Examination	X	Targeted examination must include at a minimum the following body systems: Cardiovascular Gastrointestinal Pulmonary Neurological exam for subjects with brain metastases
Vital Signs	X	Including BP, HR, temperature. Obtain vital signs within 72 hours prior to first dose.
Physical Measurements (including performance status)	X	Weight and ECOG performance status. See Appendix 2 for ECOG Performance Status scale.
Review of Concomitant Medication	X	
Adverse Events Assessment	X	
Laboratory Tests	X	On-study local laboratory assessments (after first dose) should be done within 72 hours prior to each dose through Week 23 and every alternate dose thereafter and include: CBC w/differential and platelet count, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, TSH with reflexive Free T4, Free T3.
Pregnancy Test (WOCBP only)	X	Serum or urine pregnancy test to be done within 24 hours prior to first dose, and then every 4 weeks (± 1 week) regardless of dosing schedule

Table 5.1-4: Short-term Procedural Outline for C3 Cohort [Nivolumab 3 mg/kg Q2W + Ipilimumab 1 mg/kg Q6W] No Prior Treatments in Metastatic Setting: MSI-H		
Procedure	**To Be Performed at Each Dosing Visit, Unless Otherwise Specified in Notes or Separate Table**	**Notes** **Visit Window : ± 2 Days** **See Section 3.1.4.1 for treatment duration**
Efficacy Assessments		
Tumor Imaging Assessment	See separate Table 5.1-14	
Outcomes Research Assessment		
EORTC QLQ-C30 & EQ-5D Questionnaires	Assessed following drug vial assignment but before first dose and every 6 weeks thereafter. Assessed at follow-up visit 1 & 2. Assessments should be completed at the start of the study visit prior to any study-related procedures or speaking with the physician.	
Pharmacokinetic Assessments		
Nivolumab PK blood sample	See separate Table 5.5.1-3	
Ipilimumab PK blood sample	See separate Table 5.5.1-3	
Immunogenicity Assessments		
Nivolumab Immunogenicity blood sample collection	See separate Table 5.5.1-3	
Ipilimumab Immunogenicity blood sample collection	See separate Table 5.5.1-3	
Exploratory Biomarker Testing		
Soluble Biomarkers (Serum)	See separate Table 5.6.8-3	
Peripheral Blood Mononuclear Cells (PBMCs) Immuno-phenotyping	See separate Table 5.6.8-3	
Ex vivo Functional assay (PBMCs)	See separate Table 5.6.8-3	
Tumor tissue sample (biopsy)	See separate Table 5.6.8-3	
Whole blood gene expression	See separate Table 5.6.8-3	

Table 5.1-4:	**Short-term Procedural Outline for C3 Cohort [Nivolumab 3 mg/kg Q2W + Ipilimumab 1 mg/kg Q6W] No Prior Treatments in Metastatic Setting: MSI-H**	
Procedure	**To Be Performed at Each Dosing Visit, Unless Otherwise Specified in Notes or Separate Table**	**Notes** **Visit Window : ± 2 Days** **See Section 3.1.4.1 for treatment duration**
Stool sample	See separate Table 5.6.8-3	
Plasma Sample	See separate Table 5.6.8-3	
SNP (whole blood)	See separate Table 5.6.8-3	
MSI Status Determination		
Submit Redacted Pathology Report to BMS Containing Local MSI Results	**To be submitted at Week 1 Day 1. Report must contain MSI results and should also contain specific results per markers tested for MSI.**	
Clinical Drug Supplies		
IVRS Drug Vial Assignment	X	Vials may be assigned up to 2 days prior to first dose date.
Dispense Study Drug	X	Within 3 days from treatment assignment, the subject must receive the first dose of study medication. Subjects may be dosed no less than 12 days between nivolumab doses, and no less than 5 weeks between ipilimumab doses. The dosing calculations should be based on the body weight. All doses should be rounded to the nearest milligram.

Table 5.1-5: Short-term Procedural Outline for C5 Cohort [Nivolumab + Anti-Lag-3 (BMS-986016)]: MSI-H

Procedure	To Be Performed at Each Dosing Visit, Unless Otherwise Specified in Notes or Separate Table	Notes Visit Window : ± 2 Days See Section 3.1.4.1 for treatment duration
Safety Assessments		
Targeted Physical Examination	X	Targeted examination must include at a minimum the following body systems: Cardiovascular Gastrointestinal Pulmonary Neurological exam for subjects with brain metastases
Neurological Exam	X	Obtain neurological exam (performed by a neurologist) in subjects who experience a study drug related ≥ Grade 2 neurological AE.
Vital Signs	X	Including BP, HR, temperature. Obtain vital signs within 72 hours prior to first dose
Physical Measurements (including performance status)	X	Weight and ECOG performance status. See Appendix 2 for ECOG Performance Status scale.
12-lead electrocardiogram (ECG)	X	12-lead ECG to be performed within 72 hours prior to dosing
Review of Concomitant Medication	X	
Adverse Events Assessment	X	

Table 5.1-5: Short-term Procedural Outline for C5 Cohort [Nivolumab + Anti-Lag-3 (BMS-986016)]: MSI-H

Procedure	To Be Performed at Each Dosing Visit, Unless Otherwise Specified in Notes or Separate Table	Notes Visit Window : ± 2 Days See Section 3.1.4.1 for treatment duration
Laboratory Tests	X	On-study local laboratory assessments (after first dose) should be done within 72 hours prior to each dose through Week 23 and every alternate dose thereafter and include: CBC w/differential and platelet count, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, TSH with reflexive Free T4, Free T3. Performed for the C5 Cohort Only: Cardiac Troponin Levels: T (cTnt) or I (cTnI). Labs are performed locally, and may be collected within 72 hours prior to dosing. Results must be reviewed by the Investigator or appropriate designee prior to dose administration.
Pregnancy Test (WOCBP only)	X	Serum or urine pregnancy test to be done within 24 hours prior to first dose, and then every 4 weeks (± 1 week) regardless of dosing schedule
Efficacy Assessments		
Tumor Imaging Assessment	See separate Table 5.1-14	
Outcomes Research Assessment		
EORTC QLQ-C30 & EQ-5D Questionnaire	Assessed following drug vial assignment but before first dose and every 6 weeks thereafter. Assessed at follow-up visit 1 & 2. Assessments should be completed at the start of the study visit prior to any study-related procedures or speaking with the physician.	
Pharmacokinetic Assessments		
Nivolumab PK blood sample	See separate Table 5.5.1-4	
BMS-986016 PK blood sample	See separate Table 5.5.1-4	

Table 5.1-5: Short-term Procedural Outline for C5 Cohort [Nivolumab + Anti-Lag-3 (BMS-986016)]: MSI-H

Procedure	To Be Performed at Each Dosing Visit, Unless Otherwise Specified in Notes or Separate Table	Notes Visit Window : ± 2 Days See Section 3.1.4.1 for treatment duration
Immunogenicity Assessments		
Nivolumab Immunogenicity blood sample collection	See separate Table 5.5.1-4	
Ipilimumab Immunogenicity blood sample collection	See separate Table 5.5.1-4	
Exploratory Biomarker Testing		
Soluble Biomarkers (Serum)	See separate Table 5.6.8-3	
Peripheral Blood Mononuclear Cells (PBMCs) Immuno-phenotyping	See separate Table 5.6.8-3	
Ex vivo Functional assay (PBMCs)	See separate Table 5.6.8-3	
Tumor tissue sample (biopsy)	See separate Table 5.6.8-3	
Whole blood gene expression	See separate Table 5.6.8-3	
Stool sample	See separate Table 5.6.8-3	
Plasma Sample	See separate Table 5.6.8-3	
SNP (whole blood)	See separate Table 5.6.8-3	
MSI Status Determination		
Submit Redacted Pathology Report to BMS Containing Local MSI Results	**To be submitted at Week 1 Day 1. Report must contain MSI results and should also contain specific results per markers tested for MSI.**	

Table 5.1-5: Short-term Procedural Outline for C5 Cohort [Nivolumab + Anti-Lag-3 (BMS-986016)]: MSI-H

Procedure	To Be Performed at Each Dosing Visit, Unless Otherwise Specified in Notes or Separate Table	Notes Visit Window : ± 2 Days See Section 3.1.4.1 for treatment duration
Clinical Drug Supplies		
IVRS Drug Vial Assignment	X	Vials may be assigned up to 2 days prior to first dose date.
Dispense Study Drug	X	Within 3 days from treatment assignment, the subject must receive the first dose of study medications.

Table 5.1-6: Short-term Procedural Outline for C6 Cohort [Nivolumab + Daratumumab] non-MSI-H

Procedure	To Be Performed at Each Dosing Visit, Unless Otherwise Specified in Notes or Separate Table	Notes Visit Window : ± 2 Days
Safety Assessments		
Targeted Physical Examination	X	Targeted examination must include at a minimum the following body systems: Cardiovascular Gastrointestinal Pulmonary Neurological exam for subjects with brain metastases
Vital Signs	X	Including BP, HR, and temperature. Obtain vital signs within 72 hours prior to first dose. Should be monitored extensively on Cycle 1 Day 1 before, during, and after the first infusion of daratumumab. For all other infusions, vital signs should be measured before the start of the infusion and at the end of the daratumumab infusion. If a subject experiences any significant medical event, assess if overnight hospitalization is necessary. If the subject does not experience a significant medical event and is hospitalized overnight only for observation, do not consider as a serious adverse event.
Physical Measurements (including performance status)	X	Weight and ECOG performance status. See Appendix 2 for ECOG Performance Status scale.
Review of Concomitant Medication	X	
Adverse Events Assessment	X	
Laboratory Tests	X	On-study local laboratory assessments (after first dose) should be done within 72 hours prior to each dose: CBC w/differential and platelet count, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, TSH with reflexive Free T4, Free T3.

Table 5.1-6: Short-term Procedural Outline for C6 Cohort [Nivolumab + Daratumumab] non-MSI-H

Procedure	To Be Performed at Each Dosing Visit, Unless Otherwise Specified in Notes or Separate Table	Notes Visit Window : ± 2 Days
Pregnancy Test (WOCBP only)	X	Serum or urine pregnancy test to be done within 24 hours prior to first dose, and then every 4 weeks (± 1 week) regardless of dosing schedule
Efficacy Assessments		
Tumor Imaging Assessment	Tumor imaging assessments should occur every 6 weeks from the date of first dose (±1 week) for the first 24 weeks, then every 12 weeks (± 1 wk) thereafter until disease progression or treatment is discontinued (whichever occurs later). CT or MRI of chest, abdomen, pelvis and all known sites of disease. Use same imaging method as was used at screening/baseline. Subjects with a history of brain metastasis may have surveillance MRI approximately every 12 weeks from the date of first dose, or sooner if clinically indicated All PR or CR evaluations must be confirmed by a second scan performed ≥ 4 weeks later.	
Outcomes Research Assessment		
EORTC QLQ-C30 & EQ-5D Questionnaires	Assessments should be completed at the start of the study visit prior to any study-related procedures or speaking with the physician. Assessed following drug vial assignment but before first dose and every 6 weeks through Week 24. Starting Week 25, assessments will be completed at each dose visit. Assessed at follow-up visit 1 & 2.	
Pharmacokinetic Assessments		
Nivolumab PK blood sample	See separate Table 5.5.1-5	
Daratumumab PK blood sample	See separate Table 5.5.1-6	
Immunogenicity Assessments		
Nivolumab Immunogenicity blood sample collection	See separate Table 5.5.1-5	
Daratumumab Immunogenicity blood sample collection	See separate Table 5.5.1-6	
Exploratory Biomarker Testing		
Soluble Biomarkers (Serum)	See separate Table 5.6.8-3	

Table 5.1-6: Short-term Procedural Outline for C6 Cohort [Nivolumab + Daratumumab] non-MSI-H

Procedure	To Be Performed at Each Dosing Visit, Unless Otherwise Specified in Notes or Separate Table	Notes Visit Window : ± 2 Days
Peripheral Blood Mononuclear Cells (PBMCs) Immuno-phenotyping	See separate Table 5.6.8-3	
Ex vivo Functional assay (PBMCs)	See separate Table 5.6.8-3	
Tumor tissue sample (biopsy)	See separate Table 5.6.8-3	
Whole blood gene expression	See separate Table 5.6.8-3	
Stool sample	See separate Table 5.6.8-3	
Plasma Sample	See separate Table 5.6.8-3	
SNP (whole blood)	See separate Table 5.6.8-3	
MSI Status Determination		
Submit Redacted Pathology Report to BMS Containing Local MSI Results	**Please submit report if local MSI testing was performed. Report must contain MSI results and should also contain specific results per markers tested for MSI.**	
Herpes Zoster Virus Antiviral Prophylaxis	See Section 3.4.2.3 Initiate antiviral prophylaxis within 1 week after starting daratumumab. Continue antiviral prophylaxis during the Treatment Phase as per institutional guidelines, and for 3 months following treatment discontinuation.	
Clinical Drug Supplies		
IVRS Drug Vial Assignment	X	Vials may be assigned up to 2 days prior to first dose date.
Dispense Study Drug	X	Within 3 days from treatment assignment, the subject must receive the first dose of study medication. See Table 4.3.3-1 for daratumumab dosing window guidance Subjects may be dosed no less than 12 days between nivolumab doses through Week 24 (240 mg). Subjects may be dosed no less than 21 days between nivolumab doses beyond Week 25 (480 mg)

Table 5.1-6: Short-term Procedural Outline for C6 Cohort [Nivolumab + Daratumumab] non-MSI-H

Procedure	To Be Performed at Each Dosing Visit, Unless Otherwise Specified in Notes or Separate Table	Notes Visit Window : ± 2 Days
		The dosing calculations should be based on the body weight. All doses should be rounded to the nearest milligram.

Table 5.1-7: Follow-Up Period (All treatment groups, CA209142)			
Procedure	**Follow Up, Visits 1 and 2[a]**	**Survival Follow-Up Visits[b]**	**Notes**
Safety Assessments			
Targeted Physical Examination	X		To assess for potential late emergent study drug related issues Targeted examination must include at a minimum the following body systems: • Cardiovascular • Gastrointestinal • Pulmonary • Neurological exam for subjects with brain metastases
Adverse Events Assessment	X		In Survival Follow-Up period only to include toxicities from study therapy
ECG	X		Only at FU1
Review of Concomitant Medication	X	X	Subsequent Cancer Therapy
Laboratory Tests	X		CBC w/ differential and platelet count, LFTs, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, Glucose, amylase, lipase, TSH (+ reflex Free T4 and Free T3) To be done at FU1. To be repeated at FU2 if study related toxicity persists.
Troponin	X	X*	Performed for the C5 Cohort Only. All results should be checked as soon as possible. *Troponin testing as clinically indicated, at the discretion of the treating physician during survival follow-up.
Pregnancy Test (WOCBP only)	X		Serum or urine
Efficacy Assessments			
Tumor Imaging Assessment	See note	See note	Refer to Figure 3.1.4.8-1. See separate Table 5.1-14

Table 5.1-7: Follow-Up Period (All treatment groups, CA209142)			
Procedure	**Follow Up, Visits 1 and 2[a]**	**Survival Follow-Up Visits[b]**	**Notes**
Outcomes Research Assessment			
EORTC QLQ-C30 & EQ-5D Questionnaires	X	X*	For all subjects except subjects in independent non-MSI safety cohort. *Only EQ-5D Questionnaire is required at Survival Follow-Up Visits
Herpes Zoster Virus Antiviral Prophylaxis	X		See Section 3.4.2.3 Initiate antiviral prophylaxis within 1 week after starting daratumumab. Continue antiviral prophylaxis during the Treatment Phase as per institutional guidelines, **and for 3 months following treatment discontinuation.**
Subject Status			
Survival Status		X	Every 3 months after F-U 2; may be accomplished by visit, phone contact or email, to assess subsequent anti-cancer therapy for a minimum of 5 years, in all cohorts except the non-MSI-H Safety Cohort. (Please see Section 3.1.10 for end of the study definition.)

[a] Subjects must be followed for at least 100 days after last dose of study therapy. Follow-up visit #1 (FU1) occurs approximately 35 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 80 days (± 7 days) after FU1.

[b] Survival visits = every 3 months from FU2. Survival visits will be conducted for all cohorts except the non-MSI-H Safety Cohort.

Table 5.1-8: Re-Initiation Screening Procedural Outline (CA209142)

Procedure	Screening Visit	Notes
Eligibility Assessments		
Informed Consent	X	Separate ICF required at time of re-initiation
Medical History	X	Investigator must verify subject is eligible for re-initiation per Section 4.3.9
Tumor Tissue Sample (biopsy)	X	Optional
ECOG Performance Status	X	Within 14 days prior to first dose. See Appendix 2 for ECOG Performance Status scale.
Safety Assessments		
Physical Examination	X	
Vital Signs	X	Including BP, HR, and temperature. Obtain vital signs at the screening visit and within 72 hours prior to first dose.
Physical Measurements	X	Height and Weight. Within 14 days prior to first dose
Assessment of Signs and Symptoms	X	Within 14 days prior to first dose
Echocardiogram Performed for the C5 Cohort Only	X	LVEF assessment with documented LVEF ≥ 50% by either TTE or MUGA (TTE preferred test) within 6 months from first study drug administration of re-initiation Performed for the C5 Cohort Only
ECG	X	Within 14 days prior to first dose. For C5 Cohort: Subjects with screening 12-lead ECG showing a QT interval as corrected (QTc) >480 msec are excluded.
Concomitant Medication Collection	X	Within 14 days prior to first dose

Table 5.1-8: Re-Initiation Screening Procedural Outline (CA209142)

Procedure	Screening Visit	Notes
Laboratory Tests	X	CBC w/differential and platelet count, Chemistry panel including: LDH, AST, ALT, ALP, T.Bili, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, Glucose, amylase, lipase, TSH, Free T4, Free T3, Hepatitis B surface antigen (HBV sAg), and hepatitis C antibody (HCV Ab) or Hepatitis C RNA (HCV RNA), within 14 days prior to first dose. Safety laboratory tests do not need to be repeated if they were performed within 14 days of first dose. Performed for the C5 Cohort Only: Cardiac Troponin Levels: T (cTnt) or I (cTnI)
Pregnancy Test (WOCBP only)	X	Serum or urine to be done at screening visit and repeated within 24 of first dose of study therapy
Efficacy Assessment		
Re-initiation Baseline Tumor Imaging Assessment	X	CT or MRI chest, abdomen, pelvis and all known or suspected sites of disease within 28 days prior to first dose of re-initiation treatment.

Table 5.1-9: Re-initiation Procedural Outline (Nivolumab Monotherapy, CA209142): MSI-H (Arm N, mStage 1/2)

Procedure	Nivolumab 480 mg Q4W See Section 4.3.1 for Re-initiation Treatment Schedule and Duration To Be Performed at Each Dosing Visit	Notes Visit Window : ± 2 Days
Safety Assessments		
Targeted Physical Examination	X	Targeted examination must include at a minimum the following body systems: Cardiovascular Gastrointestinal Pulmonary Neurological exam for subjects with brain metastases
Vital Signs	X	Including BP, HR, and temperature. Obtain vital signs within 72 hours prior to first dose.
Physical Measurements (including performance status)	X	Weight and ECOG performance status. See Appendix 2 for ECOG Performance Status scale.
Review of Concomitant Medication	X	
Adverse Events Assessment	X	
Laboratory Tests	X	On-study local CBC, chemistry, and thyroid laboratory assessments (after first dose) should be done within 72 hours prior to each dose every 4 weeks and include: CBC w/differential and platelet count, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, TSH with reflexive Free T4, Free T3.
Pregnancy Test (WOCBP only)	X	Serum or urine pregnancy test to be done within 24 hours prior to first dose, and then every 4 weeks (± 1 week) regardless of dosing schedule

Table 5.1-9: Re-initiation Procedural Outline (Nivolumab Monotherapy, CA209142): MSI-H (Arm N, mStage 1/2)

Procedure	Nivolumab 480 mg Q4W See Section 4.3.1 for Re-initiation Treatment Schedule and Duration To Be Performed at Each Dosing Visit	Notes Visit Window : ± 2 Days
Efficacy Assessments		
Tumor Imaging Assessment	See separate Table 5.1-14	
Exploratory Biomarker Testing		
Soluble Biomarkers (Serum)	See separate Table 5.6.8-4	
Peripheral Blood Mononuclear Cells (PBMCs) Immuno-phenotyping	See separate Table 5.6.8-4	
Ex vivo Functional assay (PBMCs)	See separate Table 5.6.8-4	
Tumor tissue sample (biopsy) (optional)	See separate Table 5.6.8-4	
Whole blood gene expression	See separate Table 5.6.8-4	
Plasma Sample	See separate Table 5.6.8-4	
SNP (whole blood)	See separate Table 5.6.8-4	
Clinical Drug Supplies		
IVRS Drug Vial Assignment	X	Vials may be assigned up to 2 days prior to first dose date.
Dispense Study Drug	X	Within 3 days from vial allocation, the subject must receive the first dose of study medication. Following first nivolumab dose, subsequent nivolumab dosing will be based on the actual date of administration of the previous dosing. Subjects may be dosed within a ± 3-day window of scheduled dose due to scheduling conflict. Subjects may be dosed no less than 25 days from the previous dose.

Table 5.1-10: Re-initiation Procedural Outline (Nivolumab Ipilimumab Combination, CA209142): MSI-H (Arm N+I, cStage 1/2)

Procedure	See Section 4.3.1 for Re-initiation Treatment Schedule and Duration To Be Performed at Each Dosing Visit	Notes Visit Window : ± 2 Days
Safety Assessments		
Targeted Physical Examination	X	Targeted examination must include at a minimum the following body systems: Cardiovascular Gastrointestinal Pulmonary Neurological exam for subjects with brain metastases
Vital Signs	X	Including BP, HR, and temperature. Obtain vital signs within 72 hours prior to first dose
Physical Measurements (including performance status)	X	Weight and ECOG performance status. See Appendix 2 for ECOG Performance Status scale.
Review of Concomitant Medication	X	
Adverse Events Assessment	X	
Laboratory Tests	X	On-study local laboratory assessments (after first dose) should be done within 72 hours prior to each dose every 4 weeks and include: CBC w/differential and platelet count, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, TSH with reflexive Free T4, Free T3.
Pregnancy Test (WOCBP only)	X	Serum or urine pregnancy test to be done within 24 hours prior to first dose, and then every 4 weeks (± 1 week) regardless of dosing schedule
Efficacy Assessments		
Tumor Imaging Assessment	See separate Table 5.1-14	

Table 5.1-10: Re-initiation Procedural Outline (Nivolumab Ipilimumab Combination, CA209142): MSI-H (Arm N+I, cStage 1/2)

Procedure	See Section 4.3.1 for Re-initiation Treatment Schedule and Duration To Be Performed at Each Dosing Visit	Notes Visit Window : ± 2 Days
Exploratory Biomarker Testing		
Soluble Biomarkers (Serum)	See separate Table 5.6.8-5	
Peripheral Blood Mononuclear Cells (PBMCs) Immuno-phenotyping	See separate Table 5.6.8-5	
Ex vivo Functional assay (PBMCs)	See separate Table 5.6.8-5	
Tumor tissue sample (biopsy) (optional)	See separate Table 5.6.8-5	
Whole blood gene expression	See separate Table 5.6.8-5	
Plasma Sample	See separate Table 5.6.8-5	
SNP (whole blood)	See separate Table 5.6.8-5	
Clinical Drug Supplies		
IVRS Drug Vial Assignment	X	Vials may be assigned up to 2 days prior to first dose date.
Dispense Study Drug	X	Within 3 days from vial allocation, the subject must receive the first dose of study medication. Following first nivolumab dose, subsequent nivolumab dosing will be based on the actual date of administration of the previous dosing. Subjects may be dosed within a ± 3-day window of scheduled dose due to scheduling conflict. Subjects may be dosed no less than 19 days between doses for the first 4 doses of nivolumab and ipilimumab. For the remaining doses, subjects may be dosed no less than 25 days between doses of nivolumab.

Table 5.1-11: Re-initiation Schedule for C3 Cohort [Nivolumab 360 mg Q3W + Ipilimumab 1 mg/kg Q6W] No Prior Treatments in Metastatic Setting		
Procedure	**To Be Performed at Each Dosing Visit, Unless Otherwise Specified in Notes or Separate Table**	**Notes** **Visit Window : ± 2 Days** **See Section 4.3.1 for Re-initiation Treatment Schedule and Duration**
Safety Assessments		
Targeted Physical Examination	X	Targeted examination must include at a minimum the following body systems: Cardiovascular Gastrointestinal Pulmonary Neurological exam for subjects with brain metastases
Vital Signs	X	Including BP, HR, temperature. Obtain vital signs within 72 hours prior to first dose.
Physical Measurements (including performance status)	X	Weight and ECOG performance status. See Appendix 2 for ECOG Performance Status scale.
Review of Concomitant Medication	X	
Adverse Events Assessment	X	
Laboratory Tests	X	On-study local laboratory assessments (after first dose) should be done within 72 hours prior to each dose through Week 23 and every dose thereafter and include: CBC w/differential and platelet count, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, TSH with reflexive Free T4, Free T3.
Pregnancy Test (WOCBP only)	X	Serum or urine pregnancy test to be done within 24 hours prior to first dose, and then every 4 weeks (± 1 week) regardless of dosing schedule

Table 5.1-11:	**Re-initiation Schedule for C3 Cohort [Nivolumab 360 mg Q3W + Ipilimumab 1 mg/kg Q6W] No Prior Treatments in Metastatic Setting**	
Procedure	**To Be Performed at Each Dosing Visit, Unless Otherwise Specified in Notes or Separate Table**	**Notes** **Visit Window : ± 2 Days** **See Section 4.3.1 for Re-initiation Treatment Schedule and Duration**
Efficacy Assessments		
Tumor Imaging Assessment	See separate Table 5.1-14	
Exploratory Biomarker Testing		
Soluble Biomarkers (Serum)	See separate Table 5.6.8-5	
Peripheral Blood Mononuclear Cells (PBMCs) Immuno-phenotyping	See separate Table 5.6.8-5	
Ex vivo Functional assay (PBMCs)	See separate Table 5.6.8-5	
Tumor tissue sample (biopsy) (optional)	See separate Table 5.6.8-5	
Whole blood gene expression	See separate Table 5.6.8-5	
Plasma Sample	See separate Table 5.6.8-5	
SNP (whole blood)	See separate Table 5.6.8-5	
Clinical Drug Supplies		
IVRS Drug Vial Assignment	X	Vials may be assigned up to 2 days prior to first dose date.
Dispense Study Drug	X	Within 3 days from treatment assignment, the subject must receive the first dose of study medication. Subjects may be dosed no less than 19 days between nivolumab doses, and no less than 5 weeks between ipilimumab doses.

Table 5.1-12: Re-initiation for C5 Cohort (Nivolumab: MSI-H Nivolumab 240 mg Q2W + BMS-986016 [LAG3] 160 mg Q2W)

Procedure	To Be Performed at Each Dosing Visit, Unless Otherwise Specified in Notes or Separate Table	Notes Visit Window : ± 2 Days See Section 4.3.1 for Re-initiation Treatment Schedule and Duration
Safety Assessments		
Targeted Physical Examination	X	Targeted examination must include at a minimum the following body systems: Cardiovascular Gastrointestinal Pulmonary Neurological exam for subjects with brain metastases
Neurological Exam	X	Obtain neurological exam (performed by a neurologist) in subjects who experience a study drug related ≥ Grade 2 neurological AE.
Vital Signs	X	Including BP, HR, temperature. Obtain vital signs within 72 hours prior to first dose
Physical Measurements (including performance status)	X	Weight and ECOG performance status. See Appendix 2 for ECOG Performance Status scale.
12-lead electrocardiogram (ECG)	X	12-lead ECG to be performed within 72 hours prior to dosing
Review of Concomitant Medication	X	
Adverse Events Assessment	X	

Table 5.1-12: Re-initiation for C5 Cohort (Nivolumab: MSI-H Nivolumab 240 mg Q2W + BMS-986016 [LAG3] 160 mg Q2W)

Procedure	To Be Performed at Each Dosing Visit, Unless Otherwise Specified in Notes or Separate Table	Notes Visit Window : ± 2 Days See Section 4.3.1 for Re-initiation Treatment Schedule and Duration
Laboratory Tests	X	On-study local laboratory assessments (after first dose) should be done within 72 hours prior to each dose through Week 23 and every alternate dose thereafter and include: CBC w/differential and platelet count, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, TSH with reflexive Free T4, Free T3. Performed for the C5 Cohort Only: Cardiac Troponin Levels: T (cTnt) or I (cTnI). Labs are performed locally, and may be collected within 72 hours prior to dosing. Results must be reviewed by the Investigator or appropriate designee prior to dose administration.
Pregnancy Test (WOCBP only)	X	Serum or urine pregnancy test to be done within 24 hours prior to first dose, and then every 4 weeks (± 1 week) regardless of dosing schedule
Efficacy Assessments		
Tumor Imaging Assessment	See separate Table 5.1-14	
Exploratory Biomarker Testing		
Soluble Biomarkers (Serum)	See separate Table 5.6.8-6	
Peripheral Blood Mononuclear Cells (PBMCs) Immuno-phenotyping	See separate Table 5.6.8-6	
Ex vivo Functional assay (PBMCs)	See separate Table 5.6.8-6	
Tumor tissue sample (biopsy) (optional)	See separate Table 5.6.8-6	
Whole blood gene expression	See separate Table 5.6.8-6	

Table 5.1-12: Re-initiation for C5 Cohort (Nivolumab: MSI-H Nivolumab 240 mg Q2W + BMS-986016 [LAG3] 160 mg Q2W)

Procedure	To Be Performed at Each Dosing Visit, Unless Otherwise Specified in Notes or Separate Table	Notes Visit Window : ± 2 Days See Section 4.3.1 for Re-initiation Treatment Schedule and Duration
Plasma Sample	See separate Table 5.6.8-6	
SNP (whole blood)	See separate Table 5.6.8-6	
Clinical Drug Supplies		
IVRS Drug Vial Assignment	X	Vials may be assigned up to 2 days prior to first dose date.
Dispense Study Drug	X	Within 3 days from treatment assignment, the subject must receive the first dose of study medication.

Table 5.1-13: Follow-Up (Discontinuation of Re-initiated Treatment, CA209142)			
Procedure	**Re-initiation (R) Follow Up, Visits 1(R) and 2(R)[a]**	**Survival Follow-Up Visits[b]**	**Notes**
Safety Assessments			
Targeted Physical Examination	X		To assess for potential late emergent study drug related issues Targeted examination must include at a minimum the following body systems: • Cardiovascular • Gastrointestinal • Pulmonary • Neurological exam for subjects with brain metastases
Adverse Events Assessment	X		In Survival Follow-Up period only to include toxicities from study therapy
ECG	X		Only at FU1(R)
Review of Concomitant Medication	X	X	Subsequent Cancer Therapy
Laboratory Tests	X		CBC w/ differential and platelet count, LFTs, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, Glucose, amylase, lipase, TSH (+ reflex Free T4 and Free T3) To be done at FU1(R). To be repeated at FU2(R) if study related toxicity persists.
Troponin	X	X*	Performed for the C5 Cohort Only. All results should be checked as soon as possible. *Troponin testing as clinically indicated, at the discretion of the treating physician during survival follow-up.
Pregnancy Test (WOCBP only)	X		Serum or urine
Efficacy Assessments			
Tumor Imaging Assessment	See note	See note	See separate Table 5.1-14

Table 5.1-13: Follow-Up (Discontinuation of Re-initiated Treatment, CA209142)			
Procedure	**Re-initiation (R) Follow Up, Visits 1(R) and 2(R)[a]**	**Survival Follow-Up Visits[b]**	**Notes**
Subject Status			
Survival Status		X	Every 3 months after F-U 2 (R); may be accomplished by visit, phone contact or email, to assess subsequent anti-cancer therapy for a minimum of 5 years, in all cohorts. (Please see Section 3.1.10 for end of the study definition.)

[a] Subjects must be followed for at least 100 days after last dose of study therapy. Follow-up visit #1 after re-initiation (FU1 R) occurs approximately 35 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 after re-initiation visit #2 (FU2 R) occurs approximately 80 days (± 7 days) after FU1 (R).

[b] Survival visits = every 3 months from FU2 (R). Survival visits will be conducted for all MSI-H subjects who have re-initiated treatment.

Table 5.1-14a: Standard Tumor Imaging Assessment
Tumor imaging assessments will occur every 6 weeks from the date of first dose (± 1 week) for the first 24 weeks, then every 12 weeks (± 1 week) thereafter until disease progression or treatment is discontinued (whichever occurs later).

Table 5.1-14b: Reduced Tumor Imaging Assessment	
All Subjects (Except Re-initiation Subjects)	**Re-initiation Subjects**
Scans every 12 weeks (± 1 week) for 3 years after first dose, then every 24 weeks (± 2 weeks) thereafter*	Scans every 12 weeks (± 1 week) for 3 years after first dose following re-initiation, then every 24 weeks (± 2 weeks) thereafter[a]

[a] Scans may continue every 12 weeks (± 1 week) if clinically indicated.

Notes: CT or MRI chest, abdomen, pelvis and all known sites of disease. Use same imaging method as was used at screening/baseline.
Subjects with a history of brain metastasis may have surveillance MRI approximately every 12 weeks from the date of first dose, or sooner if clinically indicated.

5.2 Study Materials

- NCI CTCAE version 4.0
- Nivolumab Investigator Brochure
- Ipilimumab Investigator Brochure
- BMS-986016 Investigator Brochure
- Daratumumab Investigator Brochure
- Pharmacy Binder
- Laboratory manuals for collection and handling of blood (including biomarker and immunogenicity) and tissue specimens
- Site manual for operation of interactive voice response system, including enrollment worksheets
- Manual for entry of local laboratory data
- Pregnancy Surveillance Forms
- RECIST 1.1 pocket guide

5.3 Safety Assessments

At baseline, a medical history will be obtained to capture relevant underlying conditions. The baseline examinations should include signs and symptoms, weight, height, ECOG Performance Status, BP, HR, and temperature, and they should be performed within 14 days prior to first dose except where noted in Table 5.1-1. Concomitant medications will also be collected within 14 days prior to first dose and through the study treatment period (See Table 5.1-1, Table 5.1-2 Table 5.1-3, Table 5.1-4, Table 5.1-5, and Table 5.1-6) and during the re-initiation period if applicable Table 5.1-8, Table 5.1-9, Table 5.1-10, Table 5.1-11 and Table 5.1-12.

Baseline local laboratory assessments should be done within 14 days prior to the first dose and include: CBC w/differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, TSH, Free T4, Free T3, and Hep B and C testing (HBV sAg and HCV RNA or Ab) (see Table 5.1-1). Pregnancy testing for WOCBP (done locally) should be done within 24 hours prior to first dose, and then every 4 weeks (±1 week) regardless of dosing schedule and during re-initiation period, as applicable, and at each safety follow-up visits after the original treatment phase and after re-initiated treatment.

Subjects will be evaluated for safety if they have received any study drug. Toxicity assessments will be performed continuously during the treatment phase and during re-initiated treatment if applicable. During the safety follow-up phase (Table 5.1-7 and Table 5.1-13), toxicity assessments should be done in person. Once subjects reach the survival follow-up phase, either in-person visits or documented telephone calls to assess the subject's status are acceptable.

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

On-study weight, ECOG Performance Status, and vital signs should be assessed at each on-study visit prior to nivolumab dosing. Vital signs should also be taken as per institutional standard of care prior to, during and after dosing. The start and stop time of the nivolumab, ipilimumab, BMS-986016, and daratumumab infusions should be documented. Physical examinations are to be performed as clinically indicated. If there are any new or worsening clinically significant changes since the last exam, report changes on the appropriate non-serious or serious adverse event page.

Additional measures, including non-study required laboratory tests, should be performed as clinically indicated or to comply with local regulations. Laboratory toxicities (eg, suspected drug inducted liver enzyme elevations) 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.

Some of the previously referred to assessments 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 Imaging Assessment for the Study

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

Collect any additional imaging that may demonstrate tumor response or progression (including scans performed at unscheduled time points and/or at an outside institution) for RECIST 1.1 tumor assessment and submit to the BICR.

5.4 Efficacy Assessments

- Study evaluations will take place in accordance with the flow charts in Section 5.1. Baseline assessments should be performed within 28 days prior to the first dose utilizing CT or MRI. In addition to chest, abdomen, and pelvis, all known sites of disease should be assessed at baseline. Subsequent assessments should include chest, abdomen, and pelvis, and all known sites of disease and should use the same imaging method as was used at baseline. Baseline MRI for brain should be done for known or suspected disease. Subjects with a history of brain metastasis should have surveillance MRI approximately every 12 weeks, or sooner if clinically indicated. Subjects will be evaluated for tumor response beginning 6 weeks (±1 week) from first dose and continuing every 6 weeks (± 1 week) for the first 24 weeks and every 12 weeks (±1 week) thereafter, until disease progression is documented or treatment is discontinued (whichever occurs later). Tumor imaging assessments for ongoing study treatment decisions will be completed by the investigator using RECIST (Response Evaluation Criteria in Solid Tumors) 1.1 criteria, Appendix 3. Confirmation of PR and/or CR is required after at least 4 weeks from the initial scan reporting response. Confirmation of progression is not required.

For re-initiated subjects, assessments will only be performed locally and the imaging vendor will collect scans. During Re-initiation, tumor imaging assessments should occur every 6 weeks from

the date of re-initiation of treatment (±1 week) for the first 24 weeks, then every 12 weeks (± 1 week) thereafter until disease progression or treatment is discontinued (whichever occurs later).

In order to help reduce unnecessary participant burden and help optimize participant safety by reducing the possible radiation exposure risk of a secondary malignancy, investigators should reduce scan frequency for participants having disease control at 3 years, per Table 5.1-14b. 3 years after the first dose or 3 years after re-initiation dose, as the case may be, the participant's tumor assessment schedule should be modified to every 24 weeks unless clinically indicated to continue tumor assessments every 12 weeks.

Immune-related response criteria using unidimensional measurements may be used to describe tumor shrinkage following disease progression.[107] This phenomenon has been described for ipilimumab as well as for nivolumab.

5.4.1 Primary Efficacy Assessment

The primary endpoint is ORR in all subjects as determined by investigators. ORR is defined as the number of subjects with a best overall response (BOR) of complete response (CR) or partial response (PR) divided by the number of treated subjects. The investigator assessed ORR will be further characterized by the investigator-determined duration of response (DOR) and the magnitude of reduction in tumor volume.

5.4.2 Secondary Efficacy Assessment

The secondary endpoint is ORR based on IRRC determination. IRRC-assessed ORR will be further characterized by IRRC-determined DOR.

5.5 Pharmacokinetic and Immunogenicity Assessments

Samples for PK and immunogenicity assessments will be collected for all subjects receiving nivolumab monotherapy, nivolumab combined with ipilimumab, nivolumab combined with BMS-986016, and nivolumab combined with daratumumab. All time points are relative to the start of study drug administration. All on-treatment time points are intended to align with days on which study drug is administered. If dosing occurs on a different day, the PK and immunogenicity sampling should be adjusted accordingly. Further details of sample collection, processing, and shipment will be provided in the laboratory procedures manual.

Samples for PK and immunogenicity assessments will not be collected for subjects who have re-initiated treatment following discontinuation at maximum clinical benefit.

All samples which have been collected prior to protocol revision 08 will be analyzed.

5.5.1 Pharmacokinetics and Immunogenicity Collection and Processing

A detailed schedule of PK and immunogenicity evaluations is provided in Table 5.5.1-1, Table 5.5.1-2, Table 5.5.1-3, Table 5.5.1-4, Table 5.5.1-5, and Table 5.5.1-6. All time points in nivolumab/ipilimumab and nivolumab/BMS-986016 combination cohorts are relative to the start of nivolumab infusion. In the nivolumab/daratumumab combination cohort, predose sample for daratumumab should be drawn before administration of daratumumab (window of -2 hours before the start of daratumumab dosing). Daratumumab post-dose samples should be drawn within

2 hours after the end of the infusion. PK samples will be analyzed for nivolumab, ipilimumab, BMS-986016, and daratumumab by validated assays. Immunogenicity samples will be analyzed for anti-nivolumab, anti-ipilimumab, and anti-BMS-986016, and anti-daratumumab antibodies by validated immunogenicity assays; samples may also be analyzed for neutralizing antibodies by validated methods. Serum samples may be analyzed by an exploratory method that measures these mAbs or anti-drug antibodies for technology exploration purposes; exploratory results will not be reported. Serum samples designated for PK or biomarker assessments may also be used for immunogenicity analysis if required (eg, insufficient volume for complete immunogenicity assessment or to follow up on suspected immunogenicity related AE). PK and immunogenicity samples after 2 years of treatment, and samples for post-treatment discontinuation follow-up visits (1 & 2), will not be collected.

Table 5.5.1-1: PK Sampling- Pharmacokinetic & Immunogenicity Sampling Schedule -Arm N+I (Nivolumab in combination with Ipilimumab

Study Day	Event	Time (Relative to Start of Infusion) Hour: Min	Nivolumab PK Blood Sample	Nivolumab Immunogenicity Sample	Ipilimumab PK Blood Sample	Ipilimumab Immunogenicity Sample
D1 Week 1	Predose[a]	00:00	X	X	X	X
D1 Week 4	Predose[a]	00:00	X	X	X	X
D1 Week 10	Predose[a]	00:00	X	X	X	X
D1 Week 13	Predose[a]	00:00	X	X	X	X
D1 Week 25	Predose[a]	00:00	X	X	X	X
Day 1 of every 24th week until discontinuation of study treatment or up to 2 years of treatment	Predose[a]	00:00	X	X		

[a] Predose samples should be collected just prior to the start of infusion on the day the study drug is administered

Table 5.5.1-2: PK Sampling-Pharmacokinetic & Immunogenicity Sampling Schedule - Arm N (Nivolumab monotherapy)

Study Day	Event	Time (Relative to Start of Infusion) Hour:Min	Nivolumab PK Blood Sample	Nivolumab Immunogenicity Sample
D1 Week 1	Predose[a]	00:00	X	X
D1 Week 5	Predose[a]	00:00	X	X
D1 Week 13	Predose[a]	00:00	X	X
D1 Week 25	Predose[a]	00:00	X	X
Day 1 of every 24th week until discontinuation of study treatment or up to 2 years of treatment	Predose[a]	00:00	X	X

[a] Predose samples should be collected just prior to the start of infusion on the day the study drug is administered

Table 5.5.1-3: PK Sampling- Pharmacokinetic & Immunogenicity Sampling Schedule for Cohort C3 (Nivolumab and Ipilimumab Sample Collections)

Study Day (1 Cycle =6 Weeks)	Event	Time (Relative to Start of Infusion) Hour: Min	Nivolumab PK Blood Sample	Nivolumab Immunogenicity Sample	Ipilimumab PK Blood Sample	Ipilimumab Immunogenicity Sample
D1 Week 1 (D1 Cycle 1)	Predose[a]	00:00	X	X	X	X
D1 Week 3 (D15 Cycle 1)	Predose[a]	00:00	X	X	X	X
D1 Week 9 (D15 Cycle 2)	Predose[a]	00:00	X	X	X	X
D1 Week 15 (D15 Cycle 3)	Predose[a]	00:00	X	X	X	X
D1 Week 21 (D15 Cycle 4)	Predose[a]	00:00	X	X	X	X
Day 1 of every 24th (4 cycles) week after week 21 until discontinuation of study treatment or up to 2 years of treatment	Predose[a]	00:00	X	X	X	X

[a] Predose samples should be collected just prior to the start of infusion on the day the study drug is administered.

Table 5.5.1-4: Pharmacokinetic and Immunogenicity Sampling Schedule (Nivolumab and BMS-986016 Combination, Cohort C5)

Study Day[a]	Event (Relative to Start of Infusion/Event)	Time (Relative to Start of Nivolumab Infusion) Hour:Min	PK Blood Sample for Nivolumab and BMS-986016	Immunogenicity Sample for Nivolumab and BMS-986016
Cycle 1 Day 1 (Week 1 Day 1)	Predose[b]	00:00	X	X
Cycle 5 Day 1(Week 9 Day 1)	Predose[b]	00:00	X	X
Cycle 7 Day 1(Week 13 Day 1)	Predose[b]	00:00	X	X
Day 1 of every 8th cycle (every 16 weeks) until discontinuation of study treatment or up to 2 years of treatment	predose[b]	00:00	X	X

[a] If BMS-986016 is discontinued and nivolumab continues, BMS-986016 PK and ADA should be collected only for the next 2 time points (corresponding to nivolumab sample collection) according to the PK table. If nivolumab is discontinued and BMS-986016 continues, nivolumab PK and ADA should be collected only for the next 2 time points (corresponding to BMS-986016 sample collection) according to the PK table.

[b] Pre-dose samples should be taken just prior to the start of infusion (preferably within 30 minutes). If the infusion is delayed and a pre-dose sample is already collected, there is no need to collect an additional pre-dose sample.

Table 5.5.1-5: Pharmacokinetic and Immunogenicity Sampling Schedule for Nivolumab (Nivolumab and Daratumumab Combination, Cohort C6)

Study Day (1 Cycle =4 weeks starting Week 25)	Event (Relative to Start of Infusion/Event)	Time (Relative to Start of Nivolumab Infusion) Hour:Min	PK Blood Sample for Nivolumab	Immunogenicity Sample for Nivolumab
Cycle 3 Day 1 (Week 3 Day 1)[a]	Predose[b]	00:00	X	X
Cycle 9 Day 1(Week 9 Day 1)	Predose[b]	00:00	X	X
Cycle 11 Day 1(Week 13 Day 1)	Predose[b]	00:00	X	X
Cycle 17 Day 1(Week 25 Day 1)[c]	Predose[b]	00:00	X	X
Day 1 of every 4th cycle (every 16 weeks) until discontinuation of study treatment or up to 2 years of treatment	Predose[b]	00:00	X	X

[a] Nivolumab will start at Week 3.

[b] Pre-dose samples should be taken just prior to the start of infusion (preferably within 30 minutes). If the infusion is delayed and a pre-dose sample is already collected, there is no need to collect an additional pre-dose sample.

[c] Starting from Week 25, nivolumab will be given 480 mg Q4W.

Table 5.5.1-6: Pharmacokinetic and Immunogenicity Sampling Schedule for Daratumumab (Nivolumab and Daratumumab Combination, Cohort C6)

Study Day	Event (Relative to Start of Daratumumab Infusion/Event)	Time (Relative to Start of Daratumumab Infusion) Hour:Min	PK Blood Sample for Daratumumab	Immunogenicity Assessment for Daratumumab (taken from Daratumumab PK sample)[a]
Week 1 Day 1	Pre-dose[b]	00:00	X	X
Week 1 Day 1	Post-dose	EOI	X	
Week 5 Day 1	Pre-dose	00:00	X	X
Week 5 Day 1	Post-dose	EOI	X	
Week 9 Day 1	Predose[b]	00:00	X	X
Week 13 Day 1	Predose[b]	00:00	X	X
Week 25 Day 1	Predose[b]	00:00	X	X
Week 41 Day 1	Predose[b]	00:00	X	
Week 57 Day 1	Predose[b]	00:00	X	X
Week 73 Day 1	Predose[b]	00:00	X	
Week 89 Day 1	Predose[b]	00:00	X	
Week 105 Day 1	Predose[b]	00:00	X	X

[a] Daratumumab immunogenicity will be assessed from an aliquot of the daratumumab PK blood sample – no additional blood draw is required.

[b] Daratumumab predose PK samples should be drawn before administration of either nivolumab or daratumumab (window of -2 hours before that start of dara dosing). Daratumumab post dose samples should be drawn within 2 hours after the end of the infusion.

5.6 Biomarker Assessments

Peripheral blood and tumor tissue will be collected prior to therapy and at selected time points on treatment. Residual sample material available after completion of the designated analyses may be used in the future for identification of additional pharmacodynamic or predictive markers or to enhance understanding of disease biology. If biomarker samples are drawn but study drug(s) is not administered, samples will be retained. A detailed description of each assay system is described below and a schedule of pharmacodynamic evaluations is provided in Table 5.6.8-1, Table 5.6.8-2, Table 5.6.8-3, Table 5.6.8-4, Table 5.6.8-5, and Table 5.6.8-6.

5.6.1 Serum

In this study, we plan to analyze serum samples collected at baseline, during, and after treatment from subjects enrolled on the trial to identify potential biomarkers with prognostic and predictive value for outcomes (response, PFS, OS, toxicity). Preliminary results from this study will inform estimates for the Phase II efficacy study. Soluble factors, such as cytokines, chemokines, soluble receptors, and antibodies to tumor antigens will be characterized and quantified by immunoassays in serum. Analyses may include, but not necessarily be limited to, soluble CD25, soluble PD-1, soluble LAG-3, and CXCL-9. Collected serum samples will also be used for the assessment of tumor antigen-specific responses elicited following treatment with monotherapy and combination therapy to explore which antitumor antibodies are most associated with clinical response. Antibody levels to cancer test antigens will be assessed by multiplex assays and enzyme-linked immunosorbent assay (ELISA).

5.6.2 Plasma

The presence of cell-free DNA in circulating blood is a well-documented phenomenon. Fragments of DNA are shed into the blood stream from dividing cells during cell proliferation or cell death. In subjects with cancer, a fraction of this DNA is tumor-derived and is termed circulating tumor DNA (ctDNA). Albeit small, fragments of DNA average between 180 to 200 base pairs, and specific genomic regions can be amplified with PCR. Moreover, several studies have detected mutations in ctDNA that exactly correspond to mutations from the parent tumor. Using tissue and plasma from subjects with known driver mutations in melanoma or head and neck cancer, BEAMing or similar technology will be utilized to count the frequency of mutations in circulation.

5.6.3 Immunophenotyping

The proportion of specific lymphocyte subsets and expression levels of T cell co-stimulatory markers in peripheral blood mononuclear cell (PBMC) and/or whole blood preparations will be quantified by flow cytometry. Analyses may include, but not necessarily be limited to, the proportion of T, B, MDSC, and NK cells, granulocytes, the proportion of memory and effector T cell subsets, and expression levels of PD-1, PD-L1, other B7 family members, ICOS, and Ki67. The proposed immunophenotyping by flow cytometry, along with peripheral blood gene expression analysis and T cell repertoire analysis would constitute the “immune monitoring” of the systemic immunity.

5.6.4 Ex vivo Functional Assays

To explore whether monotherapy and/or combination therapy will restore T cell activation and function, peripheral blood mononuclear cells (PBMCs) will be isolated and cryopreserved. Assays of the functional status of effector T cells will be performed, including but not limited to, assays for interferon-gamma (IFN-γ) and CD107.

5.6.5 Peripheral Blood Gene Expression

The expression level of genes related to response to nivolumab monotherapy and nivolumab combined with ipilimumab, BMS-986016, or daratumumab will be quantified molecular methods such as RNASeq, Affymetrix by microarray and/or quantitative reverse transcription polymerase

chain reaction (RT-PCR) analysis in whole blood samples. Analysis may include, but not necessarily be limited to, genes associated with immune-related pathways, such as T cell activation and antigen processing and presentation.

5.6.6 T Cell Repertoire Analysis

Low diversity of the peripheral T cell compartment has been shown to correlate with poor OS in metastatic breast cancer.[108] A standing theory in immuno-oncology suggests a diverse and activated immune environment is better adept at eradicating tumor compared to a skewed repertoire of naïve and tolerized T cells. In order to explore whether a diverse T cell repertoire is predictive of response to therapy, next generation, high-throughput, DNA sequencing will be performed on DNA isolated from peripheral blood and tumor tissue to quantitate the composition of the T cell repertoire prior to, and during, monotherapy and combination therapy.

5.6.7 Microbiome Analysis

Colorectal cancer may be associated with the gut microbiome through several mechanisms, including promotion of disease via induction of chronic inflammation or catabolism of polyamines on other carcinogenic digestible material. In addition, the innate and adaptive immune system activation state and repertoire may be altered based on local microbiota leading to differential activity of nivolumab and/or ipilimumab in colorectal cancer subjects.

DNA will be extracted from fecal samples taken prior to therapy and on-treatment. A gene-sequencing approach will be utilized to survey microbial species in the gut in order to define microbiota as a function of efficacy and safety. Overall changes in the gut microbiota will also be characterized in individual subjects that receive therapy.

5.6.8 Tumor Samples

Tumor-Based Biomarker Measures

Tumor biopsy specimens will be obtained from consenting subjects prior to and during treatment with nivolumab monotherapy, nivolumab combined with ipilimumab, nivolumab combined with BMS-986016, and nivolumab combined with daratumumab to characterize immune cell populations and expression of selected tumor markers. Biopsy collection is mandatory for subjects with accessible lesions prior to therapy and on-treatment biopsy samples are optional. For Cohorts C3, C5, and C6, tissue submitted will be assessed for quality with an H&E stain, and only those subjects who have met tissue quality thresholds can be assigned study drug.

Fresh biopsies will be provided for biomarker analysis if accessible and deemed safe by the investigator. An archived biopsy prior to therapy is acceptable if the fresh biopsy cannot be obtained and if the archived tissue meets the defined criteria as stated below.

- An archived biopsy (block or slides) must contain tumor tissue
- The subject has not received systemic therapy subsequent to archived biopsy and prior to screening
- If an archived block is not available, 30 or more slides containing tumor are available for exploratory use

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. Accordingly, all subjects must also have archive tumor tissue obtained prior to the last systemic therapy received in the metastatic setting or from an unresectable site of disease.

A biopsy sample of subjects that have confirmed progression is optional, but strongly encouraged for the purposes of understanding mechanisms of resistance to therapy.

Biopsy samples may be used for the following assessments:

Characterization of tumor infiltrating lymphocytes (TILs) and tumor antigens

Immunohistochemistry (IHC) will be used to assess the number and composition of immune infiltrates in order to define the immune cell subsets present within formalin-fixed, paraffin-embedded (FFPE) tumor tissue before and after exposure to therapy. These IHC analyses will include, but not necessarily be limited to, the following markers: CD4, CD8, CD45RO, FOXp3, PD-1, PD-L1, and PD-L2.

Characterization of T cell repertoire

As described above, DNA sequencing will be performed on pre- and post-treatment tumor tissue to assess the composition of the T cell repertoire. DNA will be isolated from either the FFPE tumor block or from RNAlater or equivalent preparations.

Gene expression profiling

Tumor biopsies that are collected in RNAlater or equivalent fixative will be examined for mRNA gene expression to detect expression of selected immune related genes.

Tumor sample collection details

Fresh biopsy:

Fresh biopsies at baseline should be prioritized over archived samples and are strongly encouraged on-treatment.

Tumor samples obtained from bone metastases are not considered acceptable for PD-L1 testing because the PD-L1 assay does not include a decalcification step. For any cases where the only tumor tissue available is from a bone metastasis lesion, please discuss further with the study Medical Monitor.

Biopsy samples should be excisional, incisional or core needle. Fine needle aspirates or other cytology samples are only allowed after discussion with the sponsor's biomarker expert.

It is recommended that samples be fixed in 10% Neutral-buffered formalin for 24-48 hours. Tumor tissue samples should not be shipped in formalin as the temperature and length of fixation cannot be controlled during shipping.

If slides are submitted, the recommended tissue section thickness is 4 microns and **the slides must be positively charged.** Slides should be shipped refrigerated at 2-8° C.

Sample shipments should include a completed requisition form containing collection date, collection method, primary/met, site, fixation conditions, and a copy of Pathology report, if available.

If a fresh biopsy is taken, up to 4 core biopsies are recommended. An assessment of biopsy quality by a pathologist is strongly encouraged at the time of the procedure. The tumor tissue that is obtained from these biopsies will be divided equally into FFPE samples and RNAlater.

The investigator, in consultation with the radiology staff, must determine the degree of risk associated with the procedure and find it acceptable. Biopsies may be done with local anesthesia or conscious sedation. Institutional guidelines for the safe performance of biopsies should be followed. Excisional biopsies may be performed to obtain tumor biopsy samples. Invasive procedures that require general anesthesia should not be performed to obtain a biopsy specimen. However, if a surgical procedure is performed for a clinical indication, excess tumor tissue may be used for research purposes with the consent of the subject.

For subjects who re-initiate treatment, biomarker sample collection should follow either Table 5.6.8-4, Table 5.6.8-5, or Table 5.6.8-6, depending on the cohort. Detailed instructions can be found in the lab manual.

Table 5.6.8-1: CA209142 Biomarker Sampling Schedule (Subjects Receiving Nivolumab Only)								
Collection Timing[a]	**Soluble Biomarkers**		**PBMC**		**Stool**	**Tumor**	**Whole Blood**	
Study Day	Serum	Plasma	Immuno-phenotyping	Ex vivo Functional Assay	Microbiome Analysis	Tumor Biopsy	Gene Expression	SNP
Screening						X[b]		
D1 Week 1	X	X	X	X	X		X	X
D1 Week 2[c]	X		X					
D1 Week 3	X		X					
D1 Week 5	X		X					
D1 Week 7	X		X	X	X	X[d]	X	
D1 Week 13	X		X					
D1 Week 15	X		X	X			X	
Upon Progression[e]	X		X	X	X	X[d]	X	

[a] All biomarker samples may be obtained ± 3 days from the indicated time.

[b] Tumor biopsy prior to therapy is mandatory during initial treatment period. If an archived biopsy (as defined in the protocol) is not available at screening, a fresh biopsy will be taken at any point prior to treatment..

[c] Day 1 Week 2 samples are optional, but strongly encouraged for biomarker analysis.

[d] Optional biopsies on-treatment and upon progression and can be taken ± 7 days at the discretion of the investigator.

[e] Samples from subjects that have confirmed progression although optional, are encouraged.

Table 5.6.8-2: Biomarker Sampling Schedule (Subjects Receiving Nivolumab + Ipilimumab Combination)

Collection Timing[a]	Soluble Biomarkers		PBMC		Stool	Tumor	Whole Blood	
Study Day	**Serum**	**Plasma**	**Immuno-phenotyping**	**Ex vivo Functional Assay**	**Microbiome Analysis**	**Tumor Biopsy**	**Gene Expression**	**SNP**
Screening						X[b]		
D1 Week 1	X	X	X	X	X		X	X
D1 Week 2[c]	X		X					
D1 Week 4	X		X					
D1 Week 7	X		X	X	X	X[d]	X	
D1 Week 13	X		X					
D1 Week 15	X		X	X			X	
Upon Progression[e]	X		X	X	X	X[d]	X	

[a] All biomarker samples may be obtained ± 3 days from the indicated time.

[b] Tumor biopsy prior to therapy is mandatory during initial treatment period. If an archived biopsy (as defined in the protocol) is not available at screening, a fresh biopsy will be taken at any point prior to treatment.

[c] Day 1 Week 2 samples are optional, but strongly encouraged for biomarker analysis.

[d] Optional biopsies on-treatment and upon progression and can be taken ± 7 days at the discretion of the investigator.

[e] Samples from subjects that have confirmed progression although optional, are encouraged.

Table 5.6.8-3: Biomarker Sampling Schedule (Cohorts C3, C5, and C6)

Collection Timing[a]	Soluble Biomarkers		PBMC		Stool	Tumor	Whole Blood	
Study Day	**Serum**	**Plasma**	**Immuno-phenotyping, T Cell Repertoire Analysis and Others**	**Ex vivo Functional Assay**	**Microbiome Analysis**	**Tumor Biopsy**	**Immune Monitoring (flow cytometry, gene expression analysis and other analysis)**	**SNP**
Screening						X[b]		
D1 Week 1	X	X	X	X	X		X	X
D1 Week 3	X	For Cohort 6 Only X	X	For Cohort 6 Only X	For Cohort 6 Only X		For Cohort 6 Only X	For Cohort 6 Only X
D1 Week 5	X		X			For Cohorts C5 Only X[c]	For Cohorts C5 and C6 Only X	
D1 Week 7	X	X	X	X	X	X[c]	X	
D1 Week 13	X	X						
D1 Week 17	X	X	X	X			X	
Upon Progression[d]	X		X	X	X	X[c]	X	

[a] All biomarker samples may be obtained ± 3 days from the indicated time.

[b] Tumor biopsy prior to therapy is mandatory during initial treatment period. If an archived biopsy (as defined in the protocol) is not available at screening, a fresh biopsy will be taken at any point prior to treatment.

[c] Optional biopsies on-treatment and upon progression and can be taken ± 7 days at the discretion of the investigator.

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

Table 5.6.8-4: Biomarker Sampling Schedules for Subjects in mStage 1/2 who Re-initiate Treatment

Collection Timing during Re-initiation (R)	Tumor Biopsy	Whole Blood	Serum	Plasma	PBMC
Screening (R)	X[a]				
D1 Week 1 (R)		X	X	X	X
D1 Week 5 (R)			X	X	X
Upon Progression			X	X	X

[a] Optional, but strongly encouraged.

Table 5.6.8-5: Biomarker Sampling Schedules for Subjects in cStage 1/2 and Cohort 3 who Re-initiate Treatment

Collection Timing during Re-initiation (R)	Tumor Biopsy	Whole Blood	Serum	Plasma	PBMC
Screening (R)	X[a]				
D1 Week 1 (R)		X	X	X	X
D1 Week 4 (R)			X	X	X
Upon Progression			X	X	X

[a] Optional, but strongly encouraged.

Table 5.6.8-6: Biomarker Sampling Schedule for Subjects in Cohort 5 who Re-initiate Treatment

Collection Timing during Re-initiation (R)	Tumor Biopsy	Whole Blood	Serum	Plasma	PBMC
Screening (R)	X[a]				
D1 Week 1 (R)		X	X	X	X
D1 Week 3 (R)			X	X	X

Table 5.6.8-6: Biomarker Sampling Schedule for Subjects in Cohort 5 who Re-initiate Treatment

Collection Timing during Re-initiation (R)	Tumor Biopsy	Whole Blood	Serum	Plasma	PBMC
D1 Week 5 (R)			X	X	X
Upon Progression			X	X	X

[a] Optional, but strongly encouraged.

5.7 Outcomes Research Assessments

Outcomes research data including health-related quality of life and patient-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 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 EORTC-QLQ C-30 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 EORTC 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 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety) and a visual analog rating scale (VAS). The utility data generated from the EQ-5D is recommended for and commonly used in cost effectiveness analysis.

The EQ-5D and the EORTC-QLQ C-30 will be collected for Cohort N, Cohort N + I, and Cohorts 3-6.

If exceptional circumstances preclude the continued administration of measures using planned modalities, then alternate administration methods may be required, after consultation with 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 and EORTC-QLQ C-30.

5.8 Results of Central Assessments

Not applicable.

6 ADVERSE EVENTS

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered an investigational (medicinal) product 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 investigational product, whether or not considered related to the investigational product.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or results from other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Note that abnormal lab tests or other safety assessments should only be reported as AEs if the final diagnosis is not available. Once the final diagnosis is known, the reported term should be updated to be the diagnosis. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose, as a verbatim term (as reported by the investigator), should not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae and should specify "intentional overdose" as the verbatim term
Events NOT Meeting the AE Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The casual 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 subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

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 subject 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 subject 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 drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 6.1.1 for reporting pregnancies).

Any component of a study endpoint that is considered related to study therapy (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported) should be reported as SAE (see Section 6.1.1 for reporting details).

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 anti-cancer therapy in the absence of any other SAEs

6.1.1 Serious Adverse Event Collection and Reporting

Following the subject'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 100 days of discontinuation of dosing. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

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

An SAE report should 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 should 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. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). When using paper forms, the reports 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. The paper forms should be used and submitted immediately, only in the event the electronic system is unavailable for transmission. 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 should 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, a follow-up SAE report should be sent within 24 hours to the BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

6.2 Nonserious Adverse Events

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

6.2.1 Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug. Nonserious 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 subjects.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 6.1.1). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic).

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

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 (paper or electronic) as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject 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).

6.4 Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study subject 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 (or designee) Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours and in accordance with the 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 subject safety).

In the rare event that the benefit of continuing study drug is thought to outweigh the risk, after consultation with BMS, the pregnant subject may continue study drug, after a thorough discussion of benefits and risk with the subject.

Protocol required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

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

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. Occurrences of overdose should be reported as an AE/SAE per Section 6 definitions, *Events Meeting the AE Definition, Events Not Meeting the AE Definition*).

6.6 Potential Drug Induced Liver Injury (DILI)

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

Potential drug induced liver injury is defined as:

1. ALT or AST elevation > 3 times upper limit of normal (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, 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

An IRRC will be utilized in this study for determination of IRRC-assessed ORR. Details of IRRC responsibilities and procedures will be specified in the IRRC charter.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

This study will consist of 5 cohorts: non-MSI-H safety cohort, MSI-H cohort (Cohort N and Cohort N+I), Cohort C3 (MSI-H subjects who have not had prior therapy for their metastatic disease), Cohort MSI-H C5, and Cohort non-MSI-H C6. All information pertaining to the C4 cohort was added via a site-specific Amendment 06. It is expected to treat up to approximately 96 subjects (up to 29 non-MSI-H and up to 67 MSI-H) for the initial non-MSI-H and MSI-H cohorts. It is expected to treat approximately 30 subjects in cohort C3. It is expected to treat approximately 40 MSI-H subjects in C5 Cohort and 40 non-MSI-H subjects C6 Cohort.

Sample size determination for the non-MSI-H safety Cohort and MSI-H Cohort:

The MSI-H cohort will include subjects who are defined as MSI-H based on standard diagnostic testing documented in the subject's medical history and prospectively confirmed in the current study by repeat testing using a PCR test.

The non-MSI-H cohort will include all subjects testing non-MSI-H by the repeat PCR test, including those who were MSI-H by medical history but not confirmed by repeat testing.

For the non-MSI-H safety cohort, sample size is not based on power considerations and will depend on the observed toxicity.

For the MSI-H cohort, a Simon optimal two-stage design will be used to test the null hypothesis that the true ORR is $\leq$ 30% (not considered clinically compelling) with either nivolumab monotherapy or the combination of nivolumab/ipilimumab. In the first stage (mStage 1), 19 subjects will be treated with nivolumab monotherapy. If there are 2 or fewer responses in these first 19 treated subjects, the protocol will be closed to further enrollment. If there are more than 2 but less than 7 responses in the first 19 treated subjects, accrual to the monotherapy arm will be stopped, and the combination arm will be opened for accrual. Otherwise, if there are 7 or more responses in the first 19 treated subjects, approximately 29 additional subjects will be accrued to the monotherapy arm (mStage 2) to target a total of 48 treated subjects.

If accrual to the combination arm is opened to the MSI-H cohort as specified above, stage I of the Simon two-stage design will be initiated in the combination arm with 19 treated subjects (cStage 1). If there are 6 or fewer responses in these first 19 treated subjects, accrual to the combination arm will be stopped. Otherwise, approximately 29 additional subjects will be accrued to the combination arm (cStage 2) to target a total of 48 subjects treated with combination therapy.

Subjects whose repeat testing does not confirm MSI-H status will be replaced in order to obtain the required number of subjects in each stage of the Simon design. Note that because of the delay in obtaining the centrally evaluated MSI status, more than 48 subjects may be treated with monotherapy and combination therapy in these initial cohorts.

The null hypothesis will be rejected if 20 or more responses are observed in 48 treated subjects in the open arm (nivolumab monotherapy and/or nivolumab/ipilimumab combination). Within a

given treatment arm, this design yields a one-sided type I error rate of 5% and power of 90% when the true response rate is 52%.

Sample size determination for Cohort C3:

The sample size determination for Cohort C3 was not based on power consideration but to provide precision on estimation of ORR. Saltz and coworkers reported ORR of 49% and 38% in chemotherapy group, per investigator assessment and per independent response review committee assessment, respectively, in this patient population.[42] Table 8.1-1 presents the 95% CI for ORR ranging from 45% to 65%, which are considered meaningful clinical outcome, with a sample size of 30 subjects.

Table 8.1-1: Interval Estimation and Coverage Probability -Clopper-Pearson Method (95% Confidence Interval)

Sample size	Number of responses	Response rate	Confidence interval
30	13	0.43333	(0.2546, 0.6257)
30	14	0.46667	(0.2834, 0.6567)
30	15	0.50000	(0.3130, 0.6870)
30	16	0.53333	(0.3433, 0.7166)
30	17	0.56667	(0.3743, 0.7454)
30	18	0.60000	(0.4060, 0.7734)
30	19	0.63333	(0.4386, 0.8007)
30	20	0.66667	(0.4719, 0.8271)

Sample size determination for Cohort C5:

The sample size determination for Cohort C5 was not based on power consideration but to provide precision on estimation of ORR. Table 8.1-2 shows the precision of the estimation of ORR based on the two-sided 95% exact CI using Clopper Pearson methods based on 4, 8, 12, 16, and 20 responders out of 40 subjects. With 40 subjects, the 95% CI of observed 16 responders will be (24.9%, 56.7%), which has the lower bound excluding the 23% background ORR from previous interim results.

Table 8.1-2: Two-sided 95% exact CI using Clopper-Pearson method based on the number of observed responses out of 40 subjects (For C5 Cohort)

The number of observed responses	4	8	12	16	20
Observed Response Rate	4/40 (10.0%)	8/40 (20.0%)	12/40 (30.0%)	16/40 (40.0%)	20/40 (50.0%)

Table 8.1-2: Two-sided 95% exact CI using Clopper-Pearson method based on the number of observed responses out of 40 subjects (For C5 Cohort)

The number of observed responses	4	8	12	16	20
95% exact CI	(2.8%, 23.7%)	(9.1%, 35.6%)	(16.6%, 46.5%)	(24.9%, 56.7%)	(33.8%, 66.2%)

Sample size determination for Cohort C6:

The sample size determination for Cohort C6 was not based on power consideration but to provide precision on estimation of ORR. Table 8.1-3 shows the precision of the estimation of ORR based on the two-sided 95% exact CI using Clopper Pearson methods based on 6, 7, 8, 9, and 12 responders out of 40 subjects. With 40 subjects, the 95% CI of observed 6 responders will be (5.7%, 29.8%), which has the lower bound excluding the 5% background ORR.

Table 8.1-3: Two-sided 95% exact CI using Clopper-Pearson method based on the number of observed responses out of 40 subjects (For C6 Cohort)

The number of observed responses	6	7	8	9	12
Observed Response Rate	6/40 (15.0%)	7/40 (17.5%)	8/40 (20.0%)	9/40 (22.5%)	12/40 (30.0%)
95% exact CI	(5.7%, 29.8%)	(7.3%, 32.8%)	(9.1%, 35.6%)	(10.8%, 38.5%)	(16.6%, 46.5%)

8.2 Populations for Analyses

- The following definitions will apply to all cohorts except where otherwise specified:
- The MSI-H cohort will include subjects who are defined as MSI-H based on standard diagnostic testing documented in the subject's medical history (MSI-H per local testing) including those prospectively confirmed in the current study by repeat testing using a PCR test. Subjects in this cohort will be referred to as 'confirmed MSI-H subjects.' Similarly, the non-MSI-H cohort will include all subjects testing non-MSI-H by the repeat PCR test or standard diagnostic testing documented in the subject's medical history.
- All Treated Subjects: All subjects who received at least one dose of study medication within a cohort. This is the primary population for safety and efficacy analysis in any cohort.
- All response evaluable subjects: All treated subjects within a given cohort who have baseline and at least one on-study evaluable tumor measurement.
- PK subjects: All subjects with available serum time-concentration data from subjects dosed with study drug.
- Immunogenicity subjects: all treated subjects with available immunogenicity data.

- PD-L1 measurable subjects: all treated subjects with a measurable PD-L1 expression result.
- Biomarker subjects: All treated subjects with available biomarker data.
- Outcomes Research Subjects: all treated subjects who have an assessment at baseline (Visit 1 assessment prior to administration of drug) and at least 1 subsequent assessment (for EORTC QLQ-C30 and EQ-5D separately).
- All Re-initiation Treated Subjects: All subjects who received at least one dose of study medication following re-initiation of treatment.

8.3 Endpoints

8.3.1 Primary Endpoint(s)

The primary objective will be measured by the primary endpoint of investigator-assessed ORR in each cohort. It is defined as the number of subjects with a best overall response (BOR) of confirmed CR or PR, according to RECIST 1.1 criteria, divided by the number of treated subjects in the related cohort. The final analysis of the primary endpoint will occur at least 6 months after the last enrolled subject'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 v1.1 or the date of subsequent therapy, whichever occurs first. For subjects without documented progression or subsequent therapy, all available response designations will contribute to the BOR determination. For purposes of analysis, if a subject receives one dose and discontinues the study without assessment or receives subsequent therapy prior to assessment, this subject will be counted in the denominator (as non-respondent.)

The investigator-assessed ORR will be further characterized by the investigator assessed duration of response (DOR) and rate of complete response (CR). DOR is defined as the time from first confirmed response (CR or PR) to the date of the first documented tumor progression as determined using RECIST 1.1 criteria or death due to any cause, whichever occurs first. For subjects who neither progress nor die, the DOR censoring will be the same as PFS censoring (see Section 8.3.3). In each cohort, DOR will be computed for subjects with a BOR of PR or CR.

8.3.2 Secondary Endpoint(s)

The secondary objective will be measured by the secondary endpoint of IRRC-assessed ORR in each cohort. It is defined as the number of subjects with a best overall response (BOR) of confirmed CR or PR, according to RECIST 1.1 criteria, divided by the number of treated subjects in the related cohort. The final analysis of the secondary endpoint will occur the time of the primary endpoint analysis. 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 v1.1 or the date of subsequent therapy, whichever occurs first. For subjects without documented progression or subsequent therapy, all available response designations will contribute to the BOR determination. For purposes of analysis, if a subject receives one dose and discontinues the study without assessment or receives subsequent therapy prior to assessment, this subject will be counted in the denominator (as non-respondent).

The IRRC-assessed ORR will be further characterized by the IRRC-assessed duration of response (DOR) and rate of CR. DOR is defined as the time from first confirmed response (CR or PR) to the date of the first documented tumor progression as determined using RECIST 1.1 criteria or death due to any cause, whichever occurs first. For subjects who neither progress nor die, the DOR censoring will be the same as PFS censoring (see Section 8.3.3). In each cohort, DOR will be computed for subjects with a BOR of PR or CR.

Investigator-assessed and IRRC-assessed DCR will be reported. Disease control rate (DCR) is defined as the number of subjects with a BOR of confirmed CR or PR or SD lasting at least 12 weeks divided by the number of treated subjects.

8.3.3 Exploratory Endpoint(s)

Exploratory safety objectives will include safety and tolerability of nivolumab monotherapy (mStage 1 and 2) or nivolumab in combination with ipilimumab (cStage 1 and 2 and the cohort C3) in subjects with metastatic MSI-H CRC, nivolumab in combination with anti-LAG-3 antibody (BMS-986016, Cohort C5) in subjects with metastatic dMMR/MSI-H mCRC, or nivolumab in combination with daratumumab (Cohort C6) in subjects with metastatic non-MSI-H (pMMR) mCRC, as measured by the incidence of adverse events and specific laboratory abnormalities (worst grade) in each treatment arm. In addition, the safety and tolerability of nivolumab in combination with ipilimumab in subjects with metastatic non-MSI-H CRC will also be evaluated. Toxicities will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Exploratory efficacy objectives will be measured by exploratory endpoints of PFS (using investigator and IRRC assessments) and OS in all treated subjects with metastatic CRC within each cohort. PFS is defined as the time from first dosing date to the date of the first documented progression, or death due to any cause, whichever occurs first. Subjects who die without a reported prior progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment. Subjects who did not have any on-study tumor imaging assessments and did not die will be censored on the first dosing date. Subjects who started any subsequent anti-cancer therapy without a prior reported progression, including death, will be censored at the last evaluable assessment prior to initiation of the subsequent anti-cancer therapy.

OS is defined as the time from first dosing date to the date of death. A subject who has not died will be censored at their last known date alive. OS will be followed continuously while subjects are on the study drug and every 3 months via in-person or phone contact after subjects discontinue the study drug.

The PK objective will be measured from serum concentration. Samples will be collected to characterize pharmacokinetics of nivolumab monotherapy, PK of nivolumab, ipilimumab, BMS-986016, and daratumumab when combined, and to explore exposure-response relationships (Section 5.5).

The discordance rate between repeat MSI testing and prior MSI testing will be characterized using test results from both MSI-H and non-MSI-H cohorts (mStage1/2 and cStage1/2).

Other exploratory endpoints for immunogenicity, pharmacogenomics, and outcomes research are discussed in detail in Sections 5.5, 5.6, and 5.7, respectively.

For the evaluation of clinical activity of nivolumab monotherapy or combination treatment re-initiation, new endpoints will be considered: BOR-re-initiation (BOR-R), ORR-re-initiation (ORR-R), DCR-re-initiation (DCR-R), TTR-re-initiation (TTR-R), DOR-re-initiation (DOR-R), PFS-re-initiation (PFS-R) and OS-re-initiation (OS-R). These endpoints will be defined similarly as the original ones but using the new re-initiation start date or new baseline evaluations as reference, where apply. Detailed definition of these endpoints will be provided in the SAP.

8.4 Analyses

Analysis methodologies presented in this section will apply to all cohorts except otherwise specified. Each cohort will be analyzed separately and interdependently but pooling of certain cohorts may be performed.

8.4.1 Demographics and Baseline Characteristics

Demographic and baseline laboratory results will be summarized for all treated subjects by cohort (MSI-H, non-MSI-H, C3, C4, C5, and C6) and treatment (monotherapy and combination therapy, if applicable) using descriptive statistics.

8.4.2 Efficacy Analyses

8.4.2.1 Primary Endpoint Methods

The investigator-assessed ORR will be summarized by cohort and by treatment (monotherapy and combination therapy, if applicable). A response rate estimate and corresponding two-sided exact CI will be provided. For the reporting following a 2-stage design, the method proposed by Atkinson and Brown will be used to estimate a 90% CI. This confidence interval takes into account the group sequential nature of the two-stage Simon design, where applicable. Otherwise, the method of Clopper-Pearson will be used to estimate a 95% CI, regardless of the study design, if more subjects were treated beyond the sample size per the original Simon's 2-stage design.

Within each cohort, ORR will be further characterized by the DOR and rate of CR. DOR will be summarized for subjects who achieve confirmed PR or CR using the Kaplan-Meier (KM) product-limit method. Median values of DOR, along with two-sided 95% CI (based on the log-log transformation), will also be calculated. Investigator-assessed CR will be summarized by cohort and by treatment (monotherapy and combination therapy, if applicable). An estimate of complete response rate (CRR) and corresponding two-sided 95% exact CI will be provided using Clopper-Pearson method.

8.4.2.2 Secondary Endpoint Methods

ORR based on IRRC assessment will be summarized similarly as above and will be characterized by IRRC-assessed DOR and IRRC-assessed CRR similarly as above.

8.4.2.3 Exploratory Endpoint Methods

PFS and OS will be summarized descriptively for each cohort using the KM product-limit method. Median values of PFS and OS, along with two-sided 95% CI (based on the log-log transformation), will also be calculated.

8.4.3 Safety Analyses

Safety analyses will be performed in all treated subjects by cohort (MSI-H, non-MSI-H independent safety cohort, and C3, C4, C5, and C6) and treatment (monotherapy and combination therapy, if applicable). Descriptive statistics of safety will be presented using NCI CTCAE version 4.0. All on-study AEs, drug-related AEs, SAEs, and drug-related SAEs 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.

8.4.4 Pharmacokinetic Analyses

The nivolumab, ipilimumab, BMS-986016, and daratumumab concentration data obtained in this study may be combined with data from other studies in the clinical development programs to develop or refine a population PK model. These models may be used to evaluate the effects of intrinsic and extrinsic covariates on the PK of nivolumab or other compounds and to determine measures of individual exposure. In addition, model determined exposures may be used for exposure-response analyses. If performed, results of population PK and exposure response-analyses will be reported separately.

8.4.5 Biomarker Analyses

Methodology for exploratory biomarker analyses, including characterization of discordant rates for MSI testing, is described in the statistical analysis plan.

8.4.6 Outcomes Research Analyses

EQ 5D

Subject's overall health state on a visual analog scale (EQ-VAS) at each assessment time point will be summarized using descriptive statistics, for each cohort assessed, by treatment (monotherapy and combination therapy, if applicable). The proportion of subjects reporting problems for the 5 EQ-5D dimensions at each assessment time point will be summarized by level of problem each cohort by treatment (monotherapy and combination therapy, if applicable). Percentages will be based on number subjects assessed at assessment time point.

A by-subject listing of EQ-5D 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), and EQ-VAS will be provided.

EORTC QLQ C-30

The analysis of EORTC QLQ C-30 will be performed in all treated subjects in each cohort who have an assessment at baseline and at least one follow-up assessment.

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. EORTC QLQ C-30 global health status/QoL composite scale data and the remaining EORTC QLQ C-30 scale data will be summarized by time point using descriptive statistics for each cohort assessed.

8.4.7 Other Analyses

8.4.7.1 Immunogenicity Analyses

Immunogenicity may be reported for ADA positive status (such as persistent positive, transient positive, only last sample positive, baseline positive) and ADA negative status, relative to baseline. In addition, presence of neutralizing antibody may be reported, if applicable. Effect of immunogenicity on safety/efficacy and biomarkers and PK may be explored.

8.4.7.2 Analyses of Re-initiation Treated Subjects

The same methodologies as used for the primary, secondary and exploratory efficacy endpoints will be used to analyze the specific endpoints defined to evaluate the clinical activity of nivolumab monotherapy or combination treatment after re-initiation.

Selected safety analyses will be repeated using the new re-initiation start date or new baseline evaluations as reference, to evaluate the safety of nivolumab monotherapy or combination treatment re-initiation.

All these analyses will be using the population of All Re-initiation Treated Subjects and will be presented by cohort.

In addition, time from initial discontinuation to re-initiation will be described. The detailed of these analyses will be provided in the SAP.

8.5 Interim Analyses

For each treatment arm in the MSI-H cohort (mStage 1 monotherapy and combination therapy, if applicable), one interim analysis of investigator-assessed ORR will be performed on the first 19 treated subjects with confirmed MSI-H CRC. If there are 6 or fewer responses in these first 19 treated subjects, accrual to the corresponding treatment arm will be stopped. Otherwise, approximately 29 additional confirmed MSI-H subjects will be accrued into the corresponding treatment arm to target a total of 48 treated subjects in that arm.

Subjects in mStage 1 or cStage 1 who remain on treatment should complete a 24-week follow up for an assessment of ORR. The final analyses of these initial MSI-H cohort will take place after sufficient follow-up has been achieved for most or all of the subjects (eg, 6 months of treatment for the monotherapy cohort and 9 months of treatment for the combination therapy cohort).

Anticipating a different enrollment rate in cohorts C3-C6, these cohorts will be analyzed independently. Interim analyses will be conducted approximately 6 months after the last subject treated in the corresponding cohort.

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

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 subjects.

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 subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

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

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.

9.1.3 Investigational Site Training

Bristol-Myers Squibb will provide quality investigational staff training prior to study initiation and prior to implementation of any significant protocol revision. 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.

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 investigational product (those supplied by BMS) is maintained at each study site where study drug are inventoried and dispensed. 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 subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage
- nonstudy disposition (eg, lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to BMS
- retain samples for bioavailability/bioequivalence, 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 paper or electronic SAE form and Pregnancy Surveillance form, respectively. 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 subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

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

The completed CRF, including any paper or electronic SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form .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

Clinical Study Report:

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

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

- Subject recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design

Publications:

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

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

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

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

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

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

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

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.

10 GLOSSARY OF TERMS

Term	Definition
Adverse Reaction	An adverse event that is considered by either the investigator or BMS as related to the investigational product
Unexpected Adverse Reaction	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, Investigator Brochure for an unapproved investigational product)
Serious Adverse Event	Serious adverse event defined as any untoward medical occurrence that at any dose: results in death; is life threatening (defined as an event in which the subject 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; 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 subject 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.). For reporting purposes only, BMS also considers the occurrence of pregnancy, overdose (regardless of association with an AE), and cancer as important medical events.

11 LIST OF ABBREVIATIONS

Term	Definition
ADA	antidrug antibody
ADL	activities of daily living
AE	adverse event
ACLS	advanced cardiac life support
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
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANOVA	analysis of variance
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AT	aminotransaminases
AUC	area under the concentration-time curve
AUC(INF)	area under the concentration-time curve from time zero extrapolated to infinite time
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
A-V	atrioventricular
β-HCG	beta-human chorionic gonadotrophin
BA/BE	bioavailability/bioequivalence
%BE	percent biliary excretion
BID, bid	bis in die, twice daily
BLQ	below limit of quantification
BMI	body mass index
BMS	Bristol-Myers Squibb

Term	Definition
BOR-R	best overall response-re-initiation phase
BP	blood pressure
BRt	total amount recovered in bile
%BRt	total percent of administered dose recovered in bile
BSA	body surface area
BUN	blood urea nitrogen
C	celsius
C12	concentration at 12 hours
C24	concentration at 24 hours
Ca++	calcium
Cavg	average concentration
Cavgss	average serum concentration at steady state
Cavg28	average serum concentration at Day 28
CBC	complete blood count
Cexpected-tau	expected concentration in a dosing interval
CFR	Code of Federal Regulations
CI	confidence interval
C1-	chloride
CLcr	creatinine clearance
CLD	dialysate clearance of drug from plasma/serum
CLNR	nonrenal clearance
CLR	renal clearance
CLT	total body clearance
CLT/F (or CLT)	apparent total body clearance
CLT/F/fu or CLT/fu	apparent clearance of free drug or clearance of free drug (if IV)
cm	centimeter
Cmax, CMAX	maximum observed concentration
Cmin, CMIN	trough observed concentration
CNS	central nervous system
COVID-19	coronavirus disease 2019

Term	Definition
CRC	colorectal cancer
CRF	Case Report Form, paper or electronic
Ct	expected concentration at a certain time, usually at the end of an expected future dosing interval (eg, concentration at 24 hours, concentration at 12 hours, etc.)
Ctau	concentration in a dosing interval (eg, concentration at 24 hours, concentration at 12 hours, etc.)
Ctrough	trough observed plasma concentration
CR	complete response
CT	computed tomography
cTnI	cardiac troponin I
cTnT	cardiac troponin T
CV	coefficient of variation
CYP	cytochrome p-450
D/C	discontinue
dL	deciliter
dMMR	deficient mismatch repair
DOR-R	duration of response-re-initiation phase
DRt	total amount recovered in dialysate
%DRt	total percent of administered dose recovered in dialysate
DSM IV	Diagnostic and Statistical Manual of Mental Disorders (4th Edition)
EA	extent of absorption
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	electronic data capture
EEG	electroencephalogram
eg	exempli gratia (for example)
ESR	Expedited Safety Report
F	bioavailability
Fb	fraction of bound drug
FDA	Food and Drug Administration
FI	fluctuation Index ([Cmax-Ctau)/Cavg])

Term	Definition
FRt	total amount recovered in feces
%FRt	total percent of administered dose recovered in feces
FSH	follicle stimulating hormone
%FE	percent fecal excretion
fu	fraction of unbound drug
fT4	free thyroxine
g	gram
G	grade
GC	gas chromatography
GCP	Good Clinical Practice
G criteria	adjusted R2 value of terminal elimination phase
GGT	gamma-glutamyl transferase
GFR	glomerular filtration rate
h	hour
H&E	hematoxylin and eosin
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCO3-	bicarbonate
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
I-O	immuno-oncology
IAT	indirect antiglobulin test
IC	informed consent form
ICD	International Classification of Diseases
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ID	infectious disease
ie	id est (that is)
IEC	Independent Ethics Committee
IMP	investigational medicinal products

Term	Definition
IND	Investigational New Drug application
IRB	Institutional Review Board
IRRC	independent radiology review committee
IU	international unit
IV	intravenous
IVIG	intravenous immunoglobulin
IVRS	Interactive Voice Response System
K	slope of the terminal phase of the log concentration-time curve
K3EDTA	potassium ethylenediaminetetraacetic acid
K+	potassium
kg	kilogram
λz	terminal disposition rate constant
L	liter
LC	liquid chromatography
LDH	lactate dehydrogenase
LFT	liver function tests
ln	natural logarithm
LVEF	left ventricular ejection fraction
Lz_Start	the time point starting the log-linear elimination phase defining the terminal half life
Lz_End	the time point ending the log-linear elimination phase defining the terminal half life
Lz_N	number of time points in the log-linear elimination phase defining the terminal half life
mg	milligram
Mg++	magnesium
MIC	minimum inhibitory concentration
min	minute
mL	milliliter
mmHg	millimeters of mercury
MMR	mismatch repair (of DNA)
MR_AUC(0-T)	ratio of metabolite AUC(0-T) to parent AUC(0-T), corrected for molecular weight

Term	Definition
MR_AUC(INF)	ratio of metabolite AUC(INF) to parent AUC(INF), corrected for molecular weight
MR_AUC(TAU)	ratio of metabolite AUC(TAU) to parent AUC(TAU), corrected for molecular weight
MR_Cmax	ratio of metabolite Cmax to parent Cmax, corrected for molecular weight
MR_Ctau	ratio of metabolite Ctau to parent Ctau, corrected for molecular weight
MRI	magnetic resonance imaging
MRT	mean residence time
MS	mass spectrometry
MSI	microsatellite instability
MSI-H	microsatellite instability-high
MTD	maximum tolerated dose
MUGA	multiple-gated acquisition
µg	microgram
N	number of subjects or observations
Na+	sodium
N/A	not applicable
ng	nanogram
NIMP	non-investigational medicinal products
NSAID	nonsteroidal anti-inflammatory drug
ORR-R	overall response rate-re-initiation phase
pAUCe	extrapolated partial AUC from last quantifiable concentration to infinity
Pb	percent of bound drug
PD	pharmacodynamics
PFS-R	progression-free survival-re-initiation phase
PK	pharmacokinetics
pMMR	proficient mismatch repair
PO	per os (by mouth route of administration)
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time

Term	Definition
Pu	percent of unbound drug
QC	quality control
QD, qd	quaque die, once daily
Q2W	every 2 weeks
Q3W	every 3 weeks
Q4W	every 4 weeks
Q6W	every 6 weeks
R2	coefficient of determination
RBC	red blood cell
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCCHN	squamous cell carcinoma of the head and neck
SD	standard deviation
SMT	safety management team
SOP	standard operating procedures
sp.	species
Subj	subject
t	temperature
T	time
TAO	Trial Access Online, the BMS implementation of an EDC capability
T. bili	total bilirubin
T-HALF	half life
T-HALFeff_AUC	effective elimination half life that explains the degree of AUC accumulation observed
T-HALFeff_Cmax	effective elimination half life that explains the degree of Cmax accumulation observed)
TID, tid	ter in die, three times a day
Tmax, TMAX	time of maximum observed concentration
TR_AUC(0-T)	AUC(0-T) treatment ratio
TR_AUC(INF)	AUC(INF) treatment ratio
TR_Cmax	Cmax treatment ratio
TSH	thyroid stimulating hormone
TTE	transthoracic echocardiogram

Term	Definition
TTR-R	time to response-re-initiation phase
ULN	upper limit of normal
UR	urinary recovery
%UR	percent urinary recovery
URt	total amount recovered in urine
%URt	total percent of administered dose recovered in urine
UV	ultraviolet
Vss/F (or Vss)	apparent volume of distribution at steady state
Vz	volume of distribution of terminal phase (if IV and if multi-exponential decline)
W	washout
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential
x g	times gravity

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APPENDIX 1 MANAGEMENT ALGORITHMS

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.

25-Jun-2019

Renal Adverse Event Management Algorithm

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

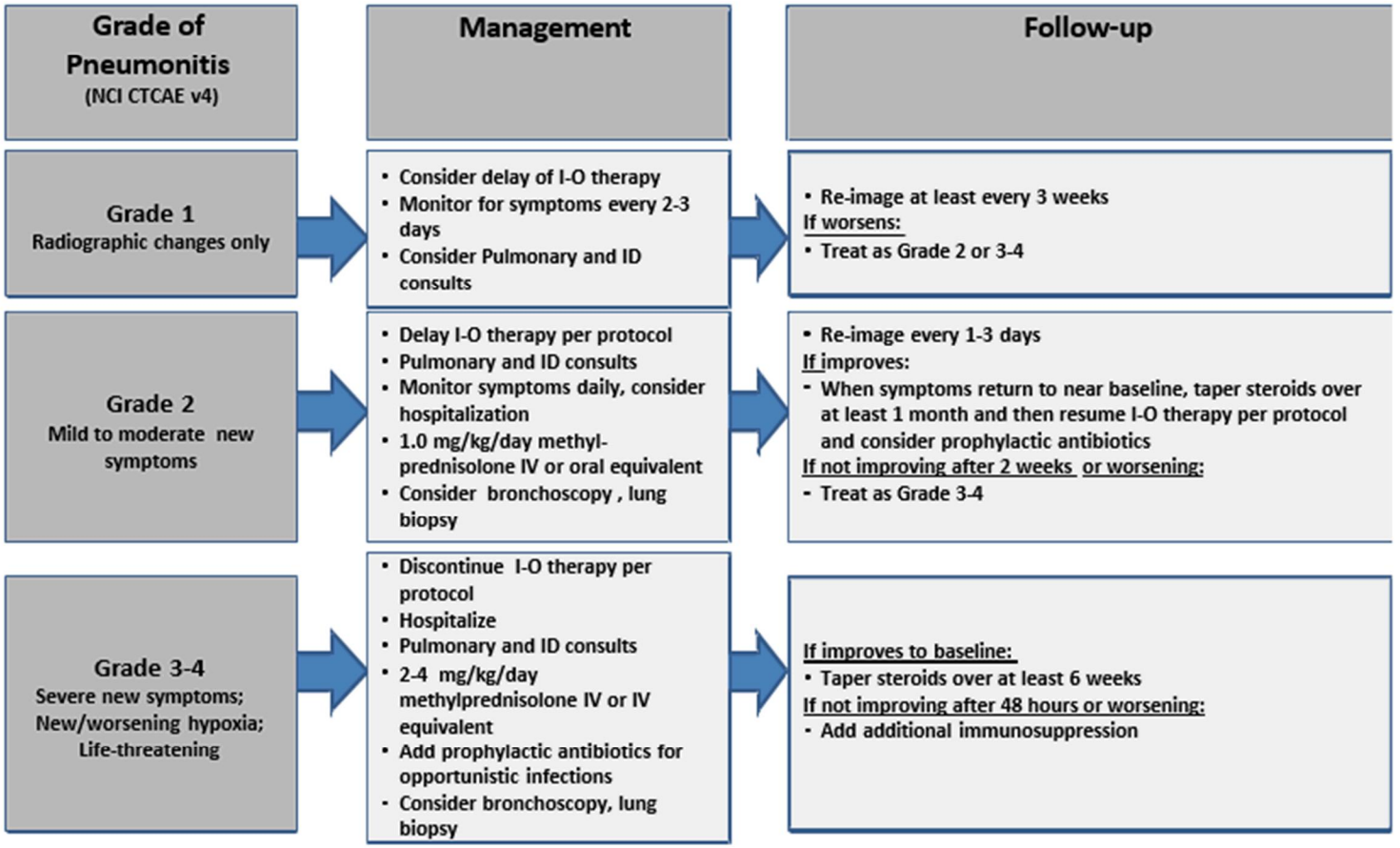
Grade of Creatinine Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 Creatinine > ULN and > than baseline but ≤ 1.5x baseline	• Continue I-O therapy per protocol • Monitor creatinine weekly	<u>If returns to baseline:</u> •Resume routine creatinine monitoring per protocol <u>If worsens:</u> •Treat as Grade 2 or 3/4
Grade 2-3 Creatinine > 1.5x baseline to ≤ 6x ULN	• Delay I-O therapy per protocol • Monitor creatinine every 2-3 days • 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent • Consider renal biopsy with nephrology consult	<u>If returns to Grade 1:</u> •Taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy and routine creatinine monitoring per protocol <u>If elevations persist > 7 days or worsen:</u> •Treat as Grade 4
Grade 4 Creatinine > 6x ULN	• Discontinue I-O therapy per protocol • Monitor creatinine daily • 1.0-2.0 mg/kg/day methylprednisolone IV or IV equivalent • Consult nephrologist • Consider renal biopsy	<u>If returns to Grade 1</u> : Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections

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.

25-Jun-2019

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.

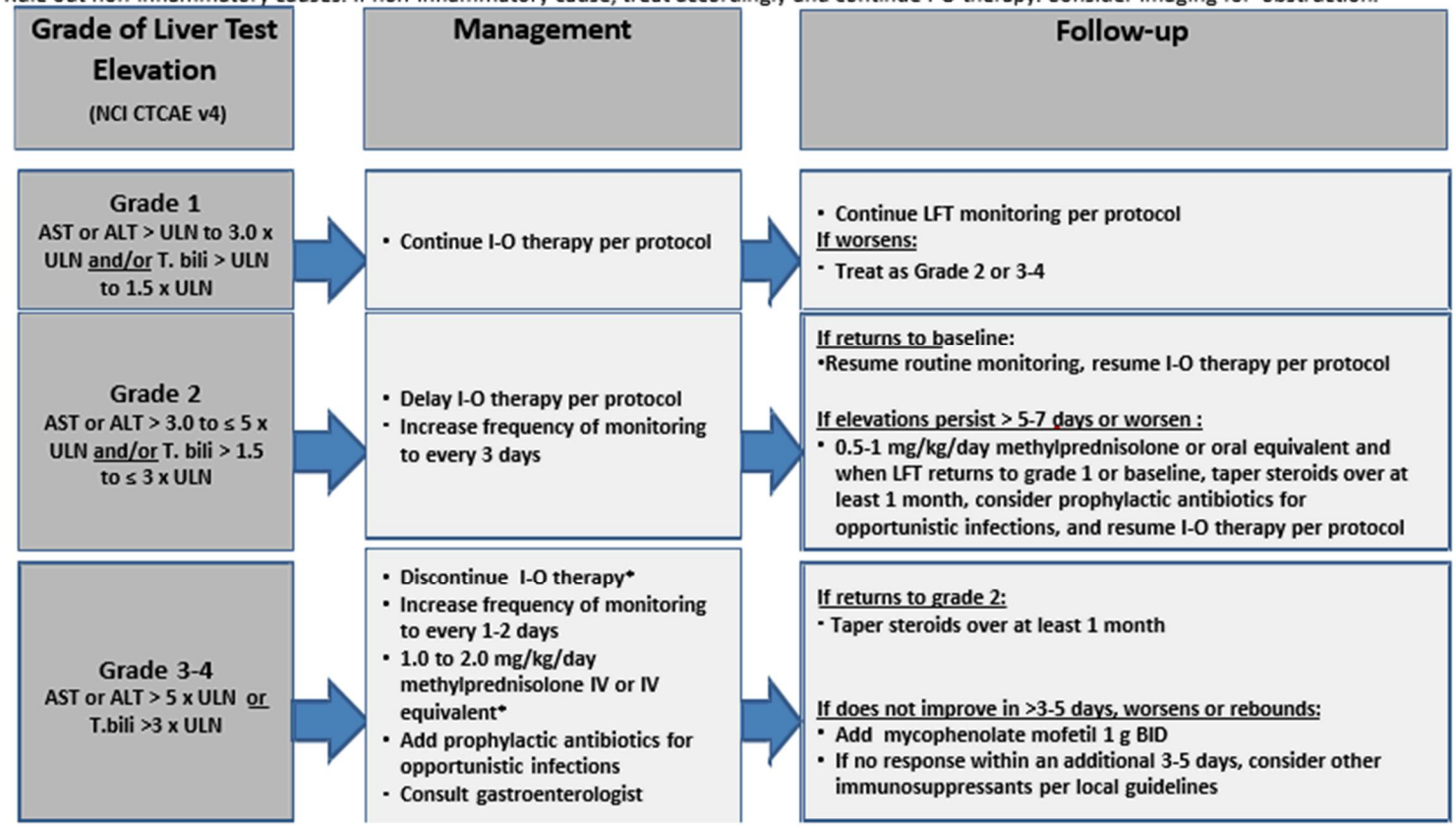


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

25-Jun-2019

Hepatic Adverse Event Management Algorithm

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



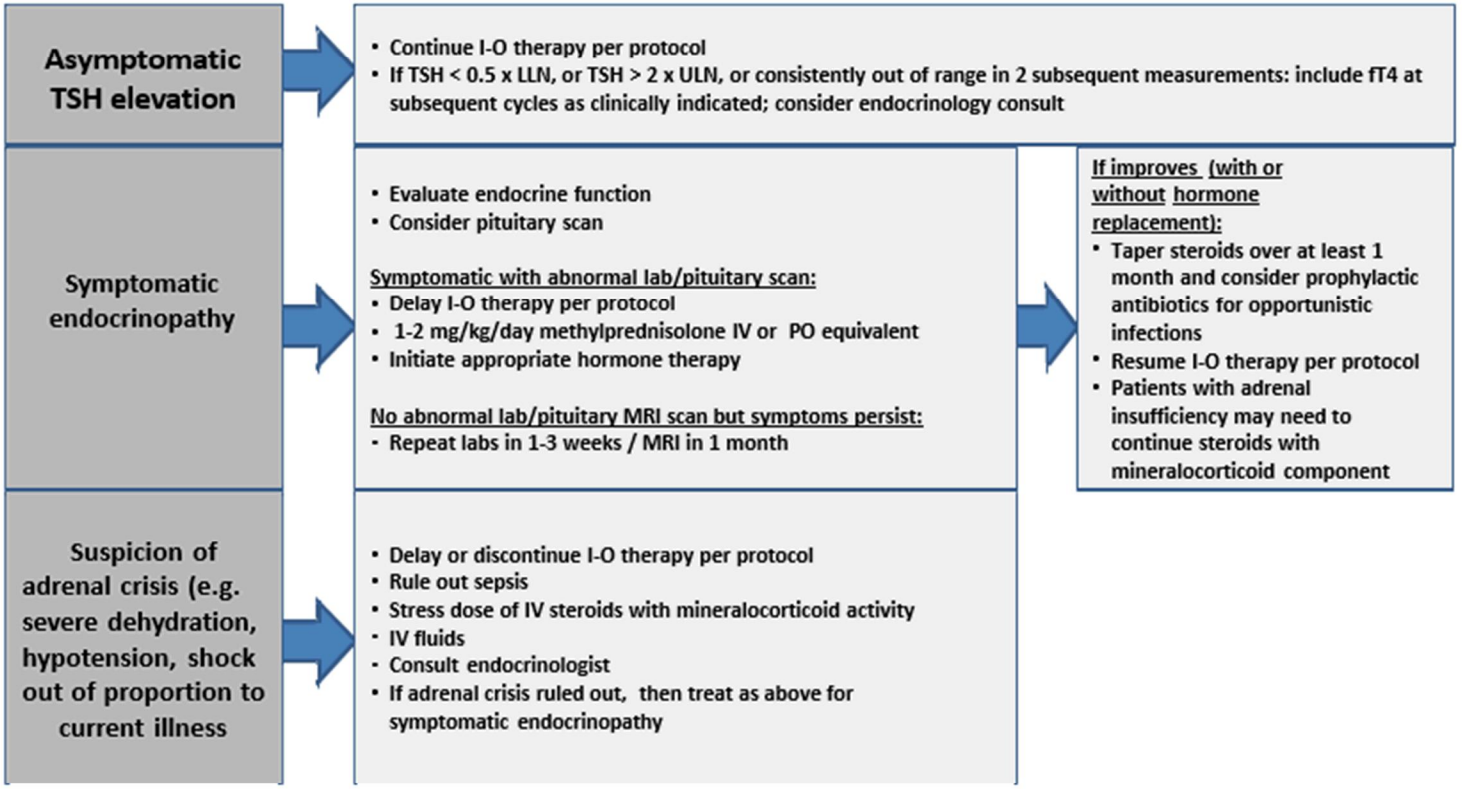
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

*The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

25-Jun-2019

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.

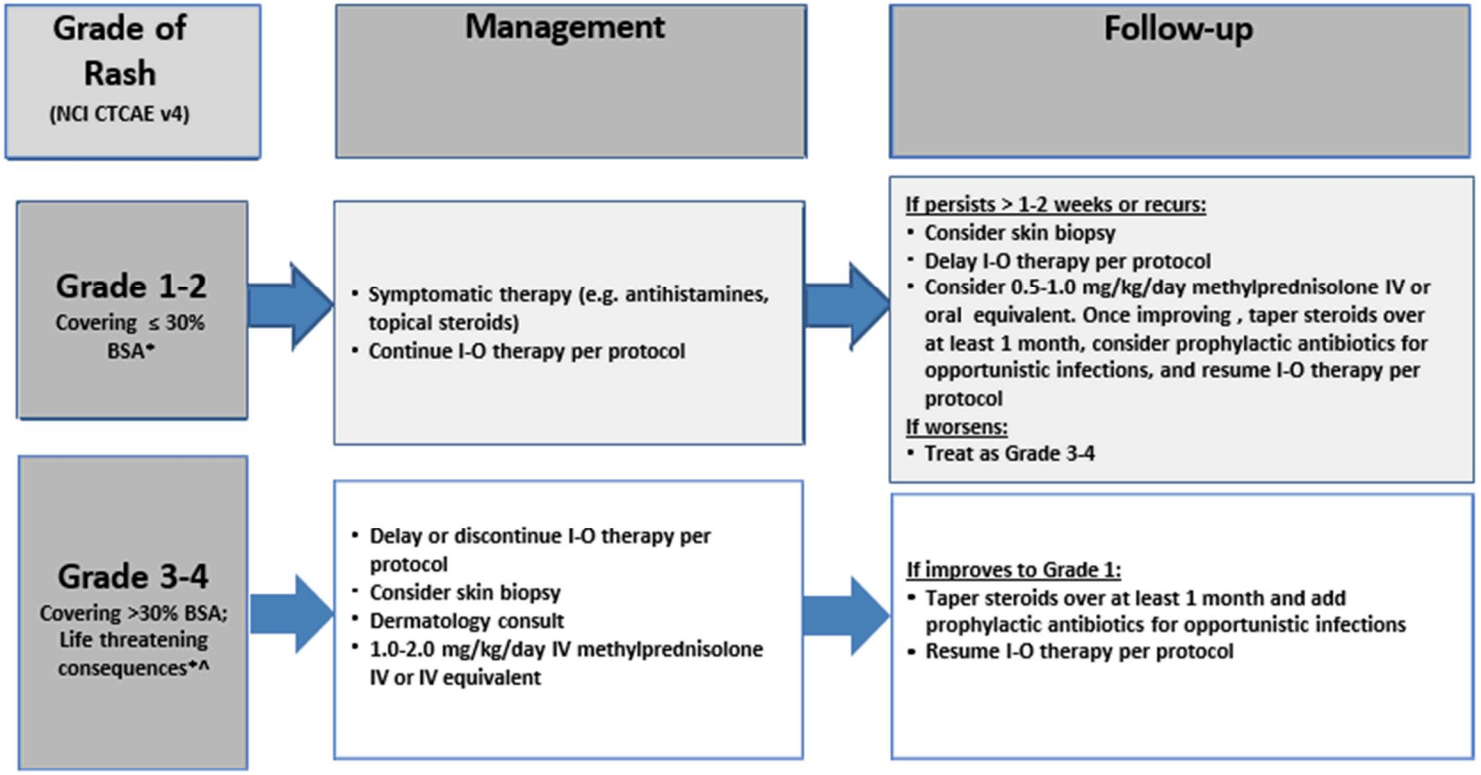


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

25-Jun-2019

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.

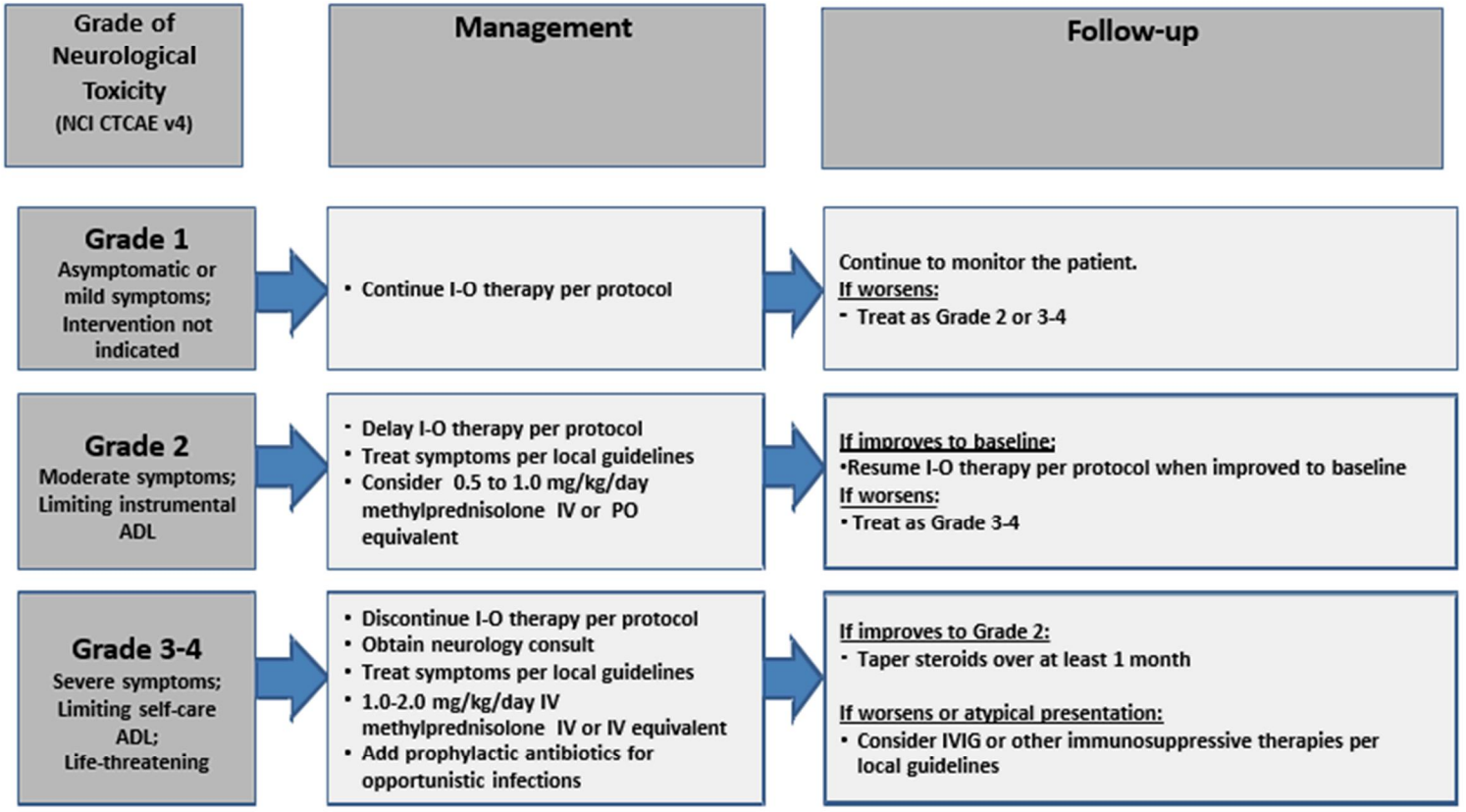
*Refer to NCI CTCAE v4 for term-specific grading criteria.

^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.

25-Jun-2019

Neurological Adverse Event Management Algorithm

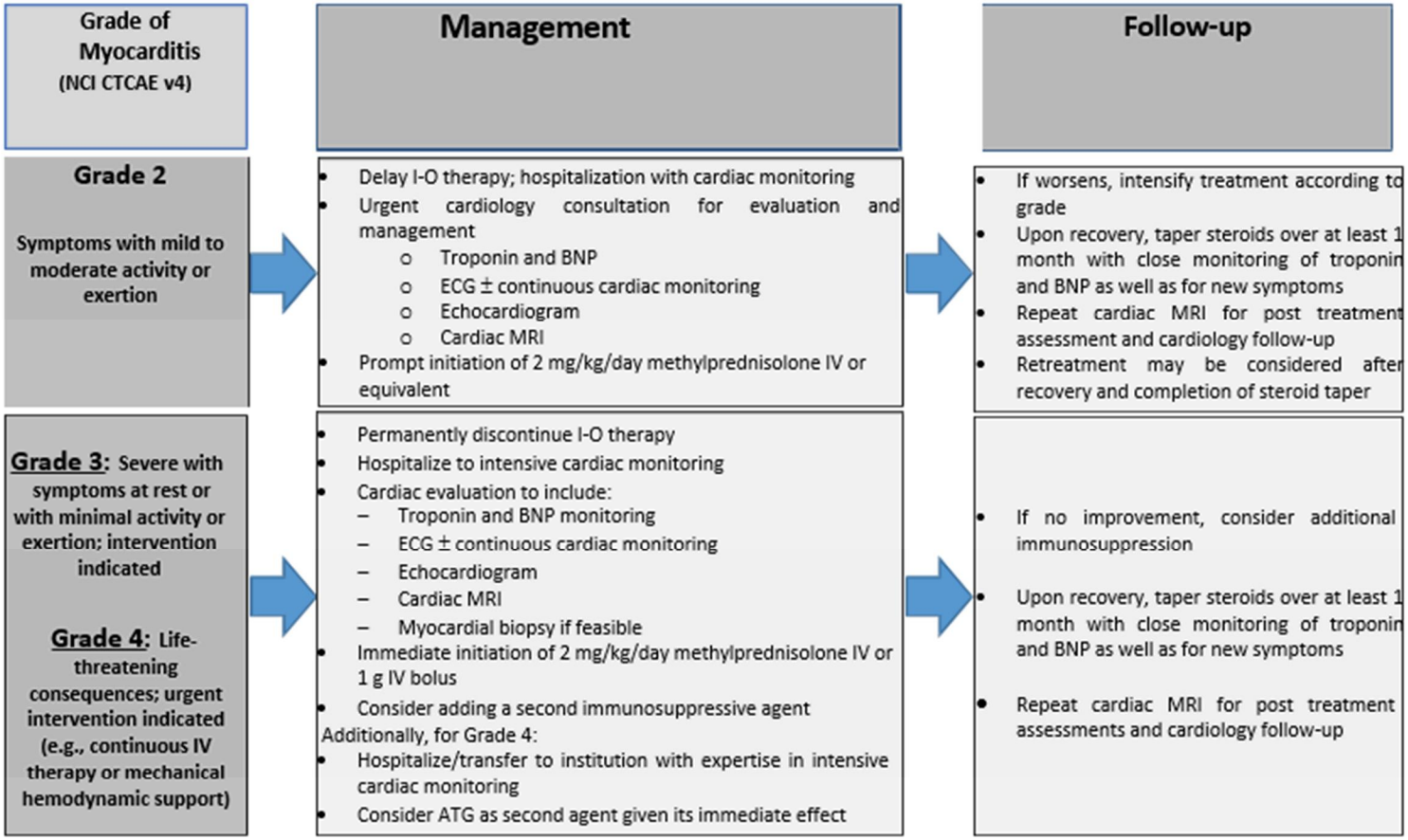
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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.

25-Jun-2019

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

25-Jun-2019

APPENDIX 2 ECOG PERFORMANCE STATUS

These scales and criteria are used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. They are included here for health care professionals to access.

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 selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours**
3	**Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours**
4	**Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair**
5	**Dead**

* As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

The ECOG Performance Status is in the public domain therefore available for public use. To duplicate the scale, please cite the reference above and credit the Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

How to contact ECOG:

Revised: July 27, 2006

APPENDIX 3 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 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 the measurement to be recorded) with a minimum size of:

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

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

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

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

1.2 Non-measurable

All other lesions are considered non-measurable, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that in 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 or plain films are ***not*** considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with *identifiable soft tissue components*, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the *soft tissue component* meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

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

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

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

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

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

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

2. RESPONSE CRITERIA

2.1 Evaluation of Target lesions

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

2.1.1 Special Notes on the Assessment of Target Lesions

2.1.1.1 Lymph nodes

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

2.1.1.2 Target lesions that become 'too small to measure'

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

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

2.1.1.3 Lesions that split or coalesce on treatment

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

2.2 Evaluation of Non-target lesions

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

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

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

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

2.2.1.1 When the patient also has measurable disease

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

2.2.1.2 When the patient has only non-measurable disease

This circumstance arises in some trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change

in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include, an increase in lymphangitic disease from localized to widespread, or may be described as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore the increase must be substantial.

2.2.2 New Lesions

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

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

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

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

at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

2.3 Response Assessment

2.3.1 Evaluation of Best Overall Response

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

2.3.2 Time Point Response

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

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

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

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

Table 2.3.2-2: Time Point Response: Patients with Non-target Disease Only

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

Table 2.3.2-2: Time Point Response: Patients with Non-target Disease Only		
Non-Target Lesions	**New Lesions**	**Overall Response**
Unequivocal PD	Yes or No	PD
Any	Yes	PD
CR = complete response, PD = progressive disease and NE = inevaluable		

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

2.3.3 Best Overall Response

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

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

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

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

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**
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE
CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable		

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

2.3.4 Confirmation Scans

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

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

REFERENCES

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

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APPENDIX 4 MSI STATUS TESTING

TESTING PANEL DESCRIPTIONS (PCR AND IHC)

Bethesda method (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-β-RII
  - ACTC (635/636)
- 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 markers 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 markers with instability
- **MSI-L:** not evaluable with this technique

Prioritization of Tumor Tissue Samples for MSI Testing

1) Archive tissue (Preferred)
   a) For MSI status confirmation
   b) Archived tissue is required for all subjects. See main protocol and protocol Administrative Letter 02 dated 22Jan2015 for more information.
2) Fresh biopsy
   a) For biomarker evaluations
   b) For MSI status confirmation (if archive tissue is determined not suitable for testing by BMS-contracted Lab)

Important Reminders:

- Refer to Central Lab Flow Chart and protocol for specific sample requirements
- A normal control ACD whole blood sample is required as well as tumor tissue
- Please contact BMS or The Central Lab if there are any questions.

APPENDIX 5 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

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

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

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

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. The duration of the washout period below are suggested guidelines and the investigators should use their judgement in checking serum FSH levels.

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

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

End of Relevant Systemic Exposure

- End of relevant systemic exposure is the time point where the IMP or any active major metabolites has 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 (NOAEL) or the time required for 5 half-lives of the IMP to pass.

METHODS OF CONTRACEPTION

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

Highly Effective Contraceptive Methods That Are <u>User Dependent</u> *Failure rate of <1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation and/or implantation (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol)[b] – oral (birth control pills) – intravaginal (vaginal birth control suppositories, rings, creams, gels) – transdermal • Combined (estrogen-and progestogen-containing) hormonal contraception must begin at least 30 days prior to initiation of study therapy
• Progestogen-only hormonal contraception associated with inhibition of ovulation (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol)[b] – oral – injectable • Progestogen-only hormonal contraception must begin at least 30 days prior to initiation of study therapy
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation and/or implantation (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol)[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol)[b,c] • Bilateral tubal occlusion
• Vasectomized partner 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 5.
- 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, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception for this study.

NOTES:

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

[b] Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized.

[c] Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness

Less Than Highly Effective Contraceptive Methods That Are User Dependent

Failure rate of >1% per year when used consistently and correctly.

- Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously
- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal Sponge with spermicide
- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action (This method of contraception cannot be used by WOCBP participants in studies where hormonal contraception is prohibited)

Unacceptable Methods of Contraception

- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus).
- Spermicide only

- Lactation amenorrhea method (LAM)

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 6.4 and the Appendix for Adverse Events and Serious Adverse Events Definitions and procedures for Evaluating, Follow-up and Reporting.

APPENDIX 6 REVISED PROTOCOL SUMMARY OF CHANGE HISTORY

Overall Rationale for Revised Protocol 08, 08-Jun-2020

In this protocol revision, the study follow-up period is extended to obtain at least 5 years of data, to enable better characterization of the long-term efficacy of the study treatment. Nivolumab pharmacokinetics (PK) and immunogenicity (IMG) properties have been well characterized across the entire nivolumab program. Sufficient PK and IMG data have been collected in CA209142, therefore these sample collections beyond 2 years have been removed from Arm N, Arm N+I, Cohort C3, and Cohort C6. In these same arms and cohorts, PK and IMG collection during Follow-up Visits 1 & 2 have also been removed. All samples which have been collected prior to revision 08 will be analyzed.

Summary of key changes for Revised Protocol 08		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	Changed Medical Monitor from Ajlan Atasoy to Sandzhar Abdullaev Added Jing Yang as Study Director	To report important personnel changes
Synopsis, Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Products 1.1.4.8 Rationale for Shorter Nivolumab and Ipilimumab Infusion Times 4.1.3.1 BMS-936558 Nivolumab 4.1.3.2 Ipilimumab	Nivolumab infusion duration reduced to 30 minutes for Arms N and N+I	To align with current nivolumab and ipilimumab program standards

Summary of key changes for Revised Protocol 08		
Section Number & Title	**Description of Change**	**Brief Rationale**
Synopsis, Study Design Schematic Figure 3.1-1 Study Design Schematic 3.1.9.1 Follow-up for all Cohorts After Initial Study Treatment Table 5.1-7 Follow-Up Period (All treatment groups, CA209142) Table 5.1-13 Follow-Up (MSI-H Cohorts at Discontinuation of Re-initiated Treatment, CA209142)	Revised text to increase Survival Follow-up from a maximum of 3 years to a minimum of 5 years	The study follow-up is extended to have at least 5 years of data. The longer time frame will enable better characterization of the long-term efficacy of the study treatment.

Summary of key changes for Revised Protocol 08		
Section Number & Title	**Description of Change**	**Brief Rationale**
3.1.9.1 Follow-up for all Cohorts After Initial Study Treatment Table 5.1-7 Follow-Up Period (All treatment groups, CA209142) 5.5.1 Pharmacokinetics and Immunogenicity Collection and Processing Table 5.5.1-1 PK Sampling-Pharmacokinetic & Immunogenicity Sampling Schedule -Arm N+I (Nivolumab in combination with Ipilimumab) Table 5.5.1-2 PK Sampling-Pharmacokinetic & Immunogenicity Sampling Schedule - Arm N (Nivolumab monotherapy) Table 5.5.1-3 PK Sampling-Pharmacokinetic & Immunogenicity Sampling Schedule for Cohort C3 (Nivolumab and Ipilimumab Sample Collections) Table 5.5.1-6 Pharmacokinetic and Immunogenicity Sampling Schedule for Daratumumab (Nivolumab and Daratumumab Combination, Cohort C6)	Removed PK and IMG collection during Survival Follow-up Visits 1 & 2 collection	Removed collection during survival follow-up to align with current BMS standards
3.1.10 End of Study Definition	Added new subsection	To provide definition of end of study, to align with current BMS standards

Summary of key changes for Revised Protocol 08		
Section Number & Title	**Description of Change**	**Brief Rationale**
4.3.3 Dose Delay Criteria	Added that nivolumab and BMS-986016 (C5 Cohort treatment) administration should be delayed for elevated troponin and Grade 2 myocarditis	To align with current BMS-986016 and nivolumab program standards
4.3.3.1 Management Algorithms for Immuno-Oncology Agents	Add Myocarditis algorithm	Provided Myocarditis algorithm per recent Nivolumab Investigator Brochure update
4.3.6 Discontinuation Criteria	Added details to Grade 4 drug-related adverse events or laboratory abnormalities Revised consultation to re-initiate dosing after a dosing interruption to include Medical Monitor "or designee" Added text regarding any adverse event, laboratory abnormality, or intercurrent illness that the Investigator judges to presents a substantial clinical risk to the subject	To align with current nivolumab program standards
4.3.8 Treatment Beyond Disease Progression	Specified a minimum of 5 mm absolute increase to definition of further progression Added that treatment should be discontinued permanently upon documentation of further progression Added criteria to determine progression for treatment discontinuation	To align with current nivolumab program standards
5.5 Pharmacokinetics and Immunogenicity Assessments	Added that all samples which have been collected prior to revision 08 will be analyzed (see below)	For clarity

Summary of key changes for Revised Protocol 08		
Section Number & Title	**Description of Change**	**Brief Rationale**
5.5.1 Pharmacokinetics and Immunogenicity Collection and Processing Table 5.5.1-1 PK Sampling-Pharmacokinetic & Immunogenicity Sampling Schedule -Arm N+I (Nivolumab in combination with Ipilimumab Table 5.5.1-2 PK Sampling-Pharmacokinetic & Immunogenicity Sampling Schedule - Arm N (Nivolumab monotherapy) Table 5.5.1-3 PK Sampling-Pharmacokinetic & Immunogenicity Sampling Schedule for Cohort C3 (Nivolumab and Ipilimumab Sample Collections)	Add that PK and immunogenicity samples after 2 years of treatment will not be collected	Nivolumab PK and IMG properties have been well characterized across the entire nivolumab program. Sufficient PK and IMG data have been collected in CA209142, therefore samples beyond 2 years will no longer be collected in Arm N, Arm N+I, Cohort C3, and Cohort C6.
6 Adverse Event	Updated information on events meeting and not meeting the adverse events definition	Updated per BMS standard
6.5 Overdose	Revised overdose reporting instructions	To align with updated information on events meeting and not meeting the adverse events definition in Section 6 (above)
9.3 Clinical Study Report and Publications	Revised to include greater detail regarding publications	To align with current BMS standards
Appendix 1 Management Algorithms	Added Myocarditis algorithm; revised date of the other algorithms	Provided Myocarditis algorithm per recent Nivolumab Investigator Brochure update
All	Minor typographical changes or clarifications	Minor, so not noted

Overall Rationale for Revised Protocol 07, 05-Feb-2019

Clinical study CA209-142 was originally designed to continue nivolumab monotherapy and nivolumab combination treatments until progression or toxicity in all cohorts. The optimal duration of immunotherapy still remains an important question and continues to be investigated. At the time of Revised Protocol 07, some subjects with MSI-H metastatic colorectal cancer have experienced durable clinical benefit and have remained on study treatment for longer than 24 months. Accumulating data suggest that 24 months of PD-1 checkpoint inhibitor treatment may be sufficient for long term benefit. Per Revised Protocol 07, because a strict stopping rule was not considered ideal for CA209-142, the option to stop treatment in case of maximum clinical benefit as assessed by the Investigator has been incorporated into the study. To minimize the potential risk of disease recurrence as a result of premature treatment discontinuation, all MSI-H/dMMR subjects who achieve objective response within the second year of treatment will be required to continue to receive study therapy for an additional 12 months before they have the option to discontinue for maximum clinical benefit (Section 3.1.4.1). A minimum of 24 months of treatment along with other protocol defined criteria (Section 3.1.4.1) are required for eligibility for discontinuation at maximum clinical benefit. In addition, Revised Protocol 07 allows for the re-initiation of study treatment for subjects in MSI-H/dMMR cohorts who progress within 1 year (≤52 weeks) after treatment discontinuation at maximum clinical benefit. Eligibility for re-initiation of treatment for subjects in MSI-H cohorts has been included in Section 3.1.4.8 and Section 4.3.9.

Evaluation of clinical activity and safety of nivolumab monotherapy or combination treatment re-initiation has been added as an exploratory objective.

Administrative Letters 07, 06, and 05 as specified in the document history presented on the previous page have been incorporated and are not listed below.

Summary of key changes for Revised Protocol 07		
Section Number & Title	**Description of Change**	**Brief Rationale**
Synopsis: Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s): Section 3.1 Study Design and Duration	For each MSI-H cohort, text and section references to modifications made to treatment durations have been added.	Supports modification in treatment duration for MSI-H subjects

Summary of key changes for Revised Protocol 07		
Section Number & Title	**Description of Change**	**Brief Rationale**
Synopsis: Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s): Section 4.3.1 Re-initiation of Dose Schedules	New Section: Re-initiation dose and schedules are presented. Treatment duration after re-initiation will be a maximum of 24 months, except for subjects who achieve CR after re-initiation. Subjects who achieve CR will be permitted to stay on therapy until progressive disease if clinically indicated per Investigator.	Details of dosing during re-initiation of treatment.
Synopsis Study Design	MSI-H cohorts updated to include reference to modified treatment duration section.	Supports modification in treatment duration for MSI-H subjects
Section 1.1.4.6 Dose and Scheduling Rationale (Nivolumab and Ipilimumab)	On the basis of modification of treatment duration for MSI-H cohorts, text was modified.	Text modified to reflect new treatment duration options
Section 1.1.4.7 Rationale for Treatment Duration and Introducing Re-Initiation in MSI-H/dMMR Cohorts	New Section: Text added to support modification of treatment duration and introduction of treatment re-initiation for subjects in MSI-H cohorts	Describes rationale for introducing the option to discontinue treatment for maximum clinical benefit following a minimum treatment duration and the option for re-initiation
Section 1.1.4.10 Rationale for Nivolumab Dose 480 mg Q4W during Re-initiation Treatment	New Section: Text added to support nivolumab dose during re-initiation of treatment.	Nivolumab 480 mg Q4W dose during re-initiation is supported by pharmacokinetic data.
Section 1.3.3, Exploratory Objectives	Clinical activity and safety of nivolumab monotherapy or combination treatment re-initiation will be evaluated as an exploratory objective.	Evaluation of re-initiation treatment is exploratory.

Summary of key changes for Revised Protocol 07		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 1.5 Overall Risk/Benefit Assessment	Text added to support modification of treatment duration in MSI-H cohorts	The option to discontinue for maximum clinical benefit after a minimum of 24 months of treatment does not affect the risk/benefit assessment.
Section 3.1.4.1, Study Treatment Duration (MSI-H Cohorts Only)	This section specifies duration of treatment for these cohorts and includes criteria which define maximum clinical benefit.	Supports modification in treatment duration for MSI-H subjects
• Section 3.1.4.2, MSI-H Nivolumab Monotherapy (Arm N): mStage 1 and 2 • Section 3.1.4.3MSI-H Nivolumab + Ipilimumab(Arm N+I): cStage 1 and 2 • Section 3.1.4.5MSI-H, C3 Cohort (No Prior Treatment in Metastatic Setting, Nivolumab + Ipilimumab) • Section 3.1.4.6 MSI-H C5, Cohort (2L in Metastatic Setting, Nivolumab + BMS-986016)	These sections have been renumbered and updated to include references to modified treatment duration section.	Required update for change in treatment duration for MSI-H subjects
Section 3.1.4.8: Treatment Options Upon Progression after Treatment Discontinuation For Maximum Benefit	New Section.	Text added to specify treatment options after progression based on time of progression and treatment duration

Summary of key changes for Revised Protocol 07		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 3.4.1 Prohibited and/or Restricted Treatment	Live/attenuated vaccines (eg, varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella [MMR]) are prohibited during the study.	Updated per program wide standard for Nivolumab
Section 4.1 Study Treatment Table 4.1-1 Product Description Treatment Period	Throughout this section and table, content and data have been updated to drug supply standards.	Update per BMS standard
Section 4.2 Method of Assigning Subject Identification	Text added to support subjects who re-initiate treatment.	
Section 4.3 Selection and Timing of Dose for Each Subject Tables 4.3-1, 4.3-3, 4.3-4 and 4.3-5. Section 5.1 Flow Chart/Time and Events Schedules Tables 5.1-2 Tables 5.1-3 Table 5.1-4	Note added to each table as reference for modification of treatment duration for these cohorts.	Supports changes in treatment duration for MSH-I cohorts
Section 4.3.3, Dose Delay Criteria	Text updated	Updated per program wide standard for Nivolumab
Section 4.3.6 Discontinuation Criteria	Grade 3 drug myocarditis, of any duration has been added to drug-related adverse events that require discontinuation	
Section 4.3.8 Treatment Beyond Disease Progression	The treatment administered beyond progression to re-initiated subjects will be the treatment received during re-initiation.	Section aligned with option to re-initiate treatment for eligible MSI-H subject

Summary of key changes for Revised Protocol 07		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 4.3.9 Treatment Re-initiation: MSI-H Cohorts	Section added to specify eligibility requirements for re-initiation of treatment for MSI-H subjects who progress within 1 year (≤ 52 weeks) of discontinuation at Maximum Clinical Benefit	Section was added to align with option to re-initiate treatment for eligible MSI-H subjects.
Section 4.7 Retained Samples for Bioavailability / Bioequivalence	Paragraph deleted: not applicable to the study.	Correction
Section 5.1 Flow Chart/Time and Events Schedules Table 5.1-8 through 5.1-11	Schedule of Procedures during re-initiation of treatment have been added for each MSI-H cohort. Note: during re-initiation there will be no collection of samples for PK/immunogenicity;	• Assessments during re-initiation are included for each MSH-I cohort. • Additional data collection of PK/immunogenicity are not necessary. • Optional tumor biopsy material will support analysis of biomarker evolution and potentially to identify characteristics of subjects who benefit from re-initiation.
Section 5.1, Table 5.1-5 Short-term Procedural Outline for C5 Cohort [Nivolumab (BMS-936558) + Anti-Lag-3 (BMS-986016)]: MSI-H Row: Dispense Study Drug row	Text in note column that was not applicable to this combination was deleted.	Correction.
Section 5.4. Efficacy Assessments.	Text added to specify imaging during re-initiation.	Efficacy section update to align with change in study design

Summary of key changes for Revised Protocol 07		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.6.8 Tumor Samples Table 5.6.8-1, Table 5.6.8-2 Table 5.6.8-3	New tables added to support biomarker sampling for those MSI-H subjects who re-initiate treatment.	Tumor biopsy at re-initiation is optional due to the exploratory nature of analysis. Change in MSI status is not expected. Biopsy material will support analysis of biomarker evolution and, potentially, to identify characteristics of subjects who benefit from re-initiation
Section 8.2 Population for Analyses Section 8.3.3 Exploratory Endpoints Section 8.4.7.2 Analyses of Re-initiation Treated Subjects	These sections have been updated or added (Section 8.4.7.2) to address re-initiation of treatment for subject in MSI-H cohorts.	Aligned with changes in study design
Section 9.1.3 Investigational Site Training	Added text to include training of sites prior to implementation of significant protocol revisions	Text added to align with site training practices for protocol revisions.
Appendix 1: Hepatic Adverse Event Management Algorithm	Deletion of footnote stating I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN	Updated per BMS standard for all studies with nivolumab
Throughout the protocol	Minor editorial corrections and clarifications with no impact on protocol content.	